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Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA1/2*-Related Cancer in Women: A Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Pathogenic mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* increase risks for breast, ovarian, fallopian tube, and peritoneal cancer in women; interventions reduce risk in mutation carriers.

Purpose: To update the 2013 U.S. Preventive Services Task Force review on benefits and harms of risk assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women.

Data Sources: Cochrane libraries; MEDLINE, PsycINFO, EMBASE (January 1, 2013 to March 6, 2019 for updates; January 1, 1994 to March 6, 2019 for new key questions and populations); reference lists.

Study Selection: Discriminatory accuracy studies, randomized controlled trials (RCTs), and observational studies of women without recently diagnosed *BRCA1/2*-related cancer.

Data Extraction: Data on study methods; setting; population characteristics; eligibility criteria; interventions; numbers enrolled and lost to followup; outcome ascertainment; and results were abstracted. Two reviewers independently assessed study quality.

Data Synthesis (Results): 103 studies (110 articles) were included. No studies evaluated the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing incidence and mortality of *BRCA1/2*-related cancer. Fourteen studies of 10 risk assessment tools to guide referrals to genetic counseling demonstrated moderate to high accuracy (area under the receiver operating characteristic curve 0.68 to 0.96). No studies determined optimal ages, frequencies, or harms of risk assessment.

Twenty-eight studies indicated genetic counseling is associated with reduced breast cancer worry, anxiety, and depression; increased understanding of risk; and decreased intention for testing. A RCT showed that population-based testing of Ashkenazi Jews detected more *BRCA1/2* mutations than family-history based testing, while measures of anxiety, depression, distress, uncertainty, and quality of life were similar between groups; clinical outcomes were not evaluated. Twenty studies indicated breast cancer worry and anxiety were higher after testing for women with positive results and lower for others, and understanding of risk was higher.

No RCTs evaluated the effectiveness of intensive screening for breast or ovarian cancer in mutation carriers. In observational studies, false-positive rates, additional imaging, and benign biopsies were higher with MRI than mammography. In eight RCTs, tamoxifen (risk ratio [RR], 0.69; 95% confidence interval [CI], 0.59 to 0.84; 4 trials), raloxifene (RR, 0.44 95% CI, 0.24 to 0.80; 2 trials), and aromatase inhibitors (RR, 0.45 95% CI, 0.26 to 0.70; 2 trials) were associated with lower risks of invasive breast cancer compared with placebo; results were not specific to mutation carriers. Adverse effects included venous thromboembolic events for tamoxifen and raloxifene; endometrial cancer and cataracts for tamoxifen; and vasomotor, musculoskeletal, and other symptoms for all medications. In observational studies, mastectomy was associated with 90 to 100 percent reduction in breast cancer incidence and 81 to 100 percent reduction in breast

cancer mortality; oophorectomy or salpingo-oophorectomy was associated with 69 to 100 percent reduction in ovarian cancer; complications were common with mastectomy.

Limitations: Including only English-language articles and studies applicable to the United States; varying number, quality, and applicability of studies; and few studies of untested women previously treated for *BRCA1/2*-related cancer.

Conclusions: Risk assessment, genetic counseling, and genetic testing to reduce *BRCA1/2*-cancer incidence and mortality as a prevention service has not been directly evaluated by current research. Risk assessment with familial risk tools accurately identifies high-risk women for genetic counseling. Genetic counseling reduces breast cancer worry, anxiety, and depression; increases understanding of risk; and decreases intention for mutation testing, while testing improves accuracy of understanding of risk. The effectiveness of intensive screening is not known, but it increases false-positive results and procedures. Risk-reducing medications and surgery are associated with reduced breast and ovarian cancer, but also have adverse effects. Evidence gaps relevant to prevention remain and additional studies are needed to better inform clinical practice.

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Chapter 1. Introduction and Background

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update the 2013 recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA1/2*-related cancer in women. The target population for screening includes women with unknown *BRCA1/2* mutation status who have either not been previously diagnosed with breast or ovarian cancer or have completed treatment and are considered cancer-free. Women with previously treated breast or ovarian cancer were not included in previous USPSTF reviews. This report focuses on *BRCA1/2* mutations because they are more prevalent and penetrant than other types, estimates of cancer risk are available, and interventions to reduce risk for carriers have been studied.[1-3]

Condition Background

Condition Definition

Pathogenic mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* are associated with increased risks for breast, ovarian, fallopian tube, and peritoneal cancer in women, breast cancer in men, and to a lesser degree, pancreatic and early onset prostate cancer;[4-9] *BRCA2* is also associated with melanoma.[6,7] *BRCA1/2* mutations cluster in families, exhibiting an autosomal dominant pattern of transmission in either the maternal or paternal lineage. Penetrance, the probability of developing cancer in *BRCA1/2* mutation carriers, is variable and many carriers never develop cancer.

Breast cancer is a malignancy that develops in tissues of the breast. Ductal carcinoma is the most common invasive histology, followed by lobular carcinoma.[10,11] Ovarian, fallopian tube, and peritoneal carcinomas are overlapping epithelial malignancies in which the designation of the three primary sites is often arbitrary. For the purpose of this review, the three disease sites will be collectively referred to as ovarian carcinoma.

Prevalence and Burden of Disease/Illness

Excluding nonmelanoma skin cancer, breast cancer is the most common cancer in women in the United States and the second leading cause of cancer death in women after lung cancer.[12] In 2018, an estimated 266,120 women developed breast cancer in the United States and 40,920 died from the disease.[13] Ovarian cancer is the fifth leading cause of cancer death among women in the United States with an estimated 22,240 new cases and 14,070 deaths in 2018.[13]

The 5-year relative survival rate for all stages of breast cancer in the United States is 91 percent. Rates are 99 percent for localized, 85 percent for regional, and 27 percent for distant disease.[14] The 5-year relative survival rate for ovarian cancer in the United States is 47 percent overall, and

92 percent for early stages.[15] However, up to 79 percent of women with ovarian cancer have non-localized disease at the time of diagnosis. Five-year relative survival rates for women with regional and distant disease are 73 percent and 29 percent, respectively.[15]

Etiology and Natural History

Pathogenic mutations in *BRCA1* and *BRCA2* are associated with increased risks for breast, ovarian, fallopian tube, and peritoneal cancer in women, breast cancer in men, pancreatic and early onset prostate cancer,[4-9] and melanoma.[6,7] Although all of these types of cancer are considered during familial risk assessment, studies of male breast cancer, pancreatic cancer, prostate cancer, and melanoma are otherwise outside the scope of this review.

Pathogenic *BRCA1/2* mutations are estimated to occur in 1 in 300 to 500 in the general population[16-19] and account for 5 to 10 percent of breast and 15 percent of ovarian cancer.[16,20] Specific *BRCA1/2* mutations, known as founder mutations, are clustered among certain groups including Ashkenazi Jews,[21-23] specific populations of blacks[24] and Hispanics,[25,26] and among families in the Netherlands,[27] Iceland,[28,29] and Sweden,[30] among others.

Specific cancer phenotypes are associated with *BRCA1/2* mutations, even in the absence of family history, including triple negative breast cancer and high-grade ovarian or fallopian tube cancer.[31-36] Pathologic and clinical characteristics of tumors also differ by the type of mutation. In a series of 3797 cases of breast cancer among *BRCA1* carriers, 78 percent were estrogen receptor (ER) negative, 79 percent progesterone receptor (PR) negative, 90 percent human epidermal growth factor receptor 2 (HER2) negative, and 69 percent triple negative.[37] The proportion of ER negative cases decreased with increasing age. In a series of 2392 cases of breast cancer among *BRCA2* carriers, 23 percent were ER negative, 36 percent PR negative, 87 percent HER2 negative, and 16 percent triple negative.[37] These receptor characteristics are important in determining cancer treatment and prognosis.

Several additional mutations not included in this review are also associated with hereditary susceptibility to breast and ovarian cancer, such as *CDH1, PTEN, STK11, TP53, ATM, CHEK2, PALB2*, but they are less prevalent or penetrant than *BRCA1/2* mutations.[1,7,38,39] For example, in addition to the *BRCA1/2* mutations, the National Comprehensive Cancer Network (NCCN) identifies two other genes with "known high-penetrance mutations:" *TP53* (Li-Fraumeni syndrome) and *PTEN* (Cowden syndrome).[1] However, these mutations are rare, and the associated syndromes vary and generally affect individuals at young ages. The population prevalence is estimated at 1 in 5,000 to 20,000 for Li-Fraumeni syndrome,[40] and 1 in 200,000 for Cowden syndrome.[41]

Risk Factors

In the general population, lifetime risks of developing cancer are 12 percent for breast cancer and 1.3 percent for ovarian cancer.[42] These risks are higher for *BRCA1/2* mutation carriers and women with family histories of these cancer types regardless of carrier status. Approximately 5 to 10 percent of women with breast cancer have a mother or sister with breast cancer, and up to 20 percent have either a first-degree or a second-degree relative with breast cancer.[43-47] Although

most of these women do not have *BRCA1/2* mutations, some women report family history patterns that suggest their presence. In general, breast cancer risk increases to 45 to 65 percent by age 70 years for pathogenic mutations in either *BRCA1/2* genes;[48,49] ovarian, fallopian tube, or peritoneal cancer risk increases to 39 percent for mutations in *BRCA1* and 10 to 17 percent in *BRCA2*.[48,4948,49]

Rationale for Screening/Screening Strategies

Genetic risk assessment, counseling, and *BRCA1/2* mutation testing involve determining risk for pathogenic *BRCA1/2* mutations followed by mutation testing of high-risk individuals. Mutation testing of appropriate candidates could lead to increased awareness of cancer risk and effective use of interventions to reduce *BRCA1/2*-related cancer incidence and mortality, as well as reduced interventions for individuals and their family members who are not mutation carriers.

Family history of *BRCA1/2*-related cancer is important in estimating individual risk for a pathogenic *BRCA1* or *BRCA2* mutation in a woman without cancer or known family mutation. Although *BRCA1/2* mutation probability is linked to family history, this only partially explains familial aggregation of breast cancer and hereditable variance in risk in a population. [4550]Decisions about referral, testing, and risk-reducing interventions are often based on self-reports of family histories that include types of cancer, relationships within the family, and ages of onset. Appropriate decisions rely on family histories that are accurately reported by women and correctly obtained by clinicians.

The accuracy of family cancer history information was evaluated in studies that validated self-reported family histories with medical records. In one study, a report of breast cancer in a first-degree relative of a healthy individual had a sensitivity of 82 percent, specificity of 91 percent, positive likelihood ratio of 8.9 (95% CI, 5.4 to 15.0), and negative likelihood ratio of 0.20 (95% CI 0.08, to 0.49).[51] A population-based study in the United States indicated the accuracy of self-reported breast cancer history in a first-degree relative as 64.9 percent sensitivity and 99.0 percent specificity.[52] In this study, the accuracy for first-degree relatives was higher than for second-degree. A report of ovarian cancer in a first-degree relative had a sensitivity of 50 percent, specificity of 99 percent, positive likelihood ratio of 34.0 (95% CI, 5.7 to 202.0), and negative likelihood ratio of 0.51 (95% CI, 0.13 to 2.10).[51]

Referral guidelines have been developed by health maintenance organizations (HMOs),[53] professional organizations,[54] cancer programs,[55,56] State and National health programs,[57-59] and researchers[60] to assist non specialists in genetics in identifying women at potentially increased risk for pathogenic *BRCA1/2* mutations. Most guidelines are intended to lead to referrals for more extensive risk assessment and counseling, not directly to testing. The effectiveness of referral guidelines in improving cancer clinical outcomes has not been evaluated. Although specific items vary, most guidelines include questions about personal and family history of *BRCA1/2* mutations, types of cancer, age of diagnosis, bilateral breast cancer, and Ashkenazi Jewish ancestry.[56]

Genetic counseling is the process of identifying and advising individuals with potential inherited cancer susceptibility and is recommended before and after *BRCA1/2* mutation testing.[54,56,61]

Services include comprehensive assessment of familial risk for inherited disorders using kindred analysis and models to estimate risk that are based on logistic regression,[62] Bayesian analysis,[49,63,64] and other methods.[65] Genetic counseling also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing to facilitate decision making, interpretation of results after testing, discussion of management options, and psychosocial counseling and support. Some genetic counseling programs offer their services by telephone and other telemedicine technology. Providers of genetic counseling may be genetic counselors,[66-68] specifically trained physicians and nurse educators,[69,70] or other health professionals with comparable skills.[71] Accreditation standards from specialty groups specifically outline essential training and skills for genetics professionals.[72]

The NCCN provides specific criteria for genetic testing in their genetic/familial high-risk assessment breast and ovarian cancer guidelines[56] These guidelines recommend that mutation testing begin with a relative with known *BRCA1/2*-related cancer, including male relatives, to determine if a pathogenic mutation is segregating in the family before testing individuals without cancer.[56] If an affected family member is not available, then the relative with the highest probability of mutation should be tested. Ideally, results of the initial test will guide testing decisions of other family members. However, the optimal candidate may not be available for testing, limiting the interpretation of results. Individuals without cancer meeting NCCN criteria for testing include those from families with known *BRCA1*/*2* mutations or from families with extensive cancer history.

The type of mutation analysis required depends on family history. A small number of pathogenic *BRCA1/2* mutations have been found repeatedly in different families, such as the three founder mutations detected in the Ashkenazi Jewish population. However, most identified pathogenic mutations have been found in only a few families.[73] Individuals from families with known mutations, or from groups with common mutations, can be tested specifically for them. Several clinical laboratories in the United States test for specific mutations or sequence specific exons. The sensitivity and specificity of analytic techniques are determined by the laboratories and are not generally available.

Individuals without linkages to families or groups with known mutations undergo different types of testing. Testing options have recently changed since the U.S. Supreme Court ruling in 2013 that determined human genes are not patentable (*Association for Molecular Pathology et al. v. Myriad Genetics*).[74] Up to this point, most *BRCA1/2* mutation testing in the United States was conducted by Myriad Genetics Inc. Currently, a search of the GeneTests™ database shows 82 multi-gene panels that include *BRCA1* offered by multiple U.S. laboratories, and 97 panels that include *BRCA2*.[75] The specific genes analyzed in multi-gene panels vary and include moderate-risk genes that may be difficult to interpret and are not clinically actionable. The U.S. Food and Drug Administration (FDA) does not currently regulate laboratory-developed tests (i.e., those "designed, manufactured, and used within a single laboratory"). However, tests manufactured in kits marketed to other laboratories are FDA-regulated as devices, and approval requires evidence of efficacy and safety. For example, in 2017, the FDA authorized Memorial Sloan Kettering Cancer Center's (MSK) IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) tumor profiling test.[76]

The interpretation of mutation testing is complicated by the terminology used to report results. Guidelines from the American College of Medical Genetics and Genomics (ACMG) updated in 2015 recommend new standard terminology for reporting sequence variants identified by genetic tests that apply to *BRCA1/2* mutations.[77] Guidelines include a 5-tier system using the terms pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. The ACMG also defines criteria for translating results from published studies, population and disease databases, and the patient's clinical and family history into pathogenic and benign categories. The category of variant of uncertain significance (VUS) used in both current and previous classifications either does not fulfil these criteria or represents conflicting results regarding pathogenicity. The ACMG states that a VUS should not be used in clinical decision making, and categories indicating pathogenic and benign designations should be used to inform patient management.

Interventions/Treatment

Interventions to reduce risk for cancer in *BRCA1/2* mutation carriers include earlier, more frequent, or intensive cancer screening; use of risk-reducing medications; and risk-reducing surgery. The NCCN recommends that *BRCA1/2* mutation carriers be aware of breast changes beginning at age 18 years; have clinician breast examinations every 6 to 12 months beginning at age 25 years; and have annual mammography and breast magnetic resonance imaging (MRI) beginning at age 25 years or based on family history when breast cancer is diagnosed in a relative before age 30 years.[56] The NCCN also recommends risk-reducing mastectomy and salpingo-oophorectomy; monitoring with transvaginal ultrasound (TVUS) and cancer antigen-125 (CA-125) levels at the provider's discretion for women not undergoing salpingo-oophorectomy; and risk-reducing medications.

Tamoxifen and raloxifene (selective estrogen receptor modulators [SERMs]) and exemestane and anastrozole (aromatase inhibitors) reduce primary breast cancer in women at increased risk in placebo-controlled trials.[78-87] However, these medications also have adverse effects, including thromboembolism (tamoxifen and raloxifene), endometrial cancer and cataracts (tamoxifen), and vasomotor and other symptoms.[78,79,88,89] While SERMS are FDA approved for breast cancer risk reduction, aromatase inhibitors are approved only for breast cancer treatment. None of these trials reported results specifically for *BRCA1/2* mutation carriers and it is unclear whether efficacy differs.

Risk-reducing mastectomy and salpingo-oophorectomy reduce risk for breast and ovarian cancer in *BRCA1/2* mutation carriers.[90-93] Bilateral total simple mastectomy with or without reconstruction and with or without nipple preservation is currently the most common approach.[94,95] This procedure provides more complete removal of breast tissue than the previously used subcutaneous mastectomy, although, no procedure completely removes all breast tissue[96] and breast cancer can still occur postmastectomy.[97] Bilateral oophorectomy reduces risk for both breast and ovarian cancer.[98-100] Recognition of the importance of the fallopian tube as a site of cancer origin has led to including salpingectomy in addition to oophorectomy. The role of hysterectomy to reduce cancer risk remains controversial.

Current Clinical Practice/Recommendations of Other Groups

Guidelines recommend testing for cancer susceptibility mutations when 1) an individual has personal or family cancer history suggestive of inherited cancer susceptibility; 2) the test can be adequately interpreted; and 3) results will aid in management.[54,101] However, [56]actual practices for *BRCA1/2* testing in the United States are unclear. The lack of screening effectiveness trials, differing interpretations of existing research among specialties, variability of insurance coverage, and direct-to-consumer advertising targeting patients, physicians, and health systems[102-106] have resulted in highly variable clinical practices.

Chapter 2. Methods

Key Questions and Analytic Framework

Using methods developed by the USPSTF,[107] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework outlining the key questions and the patient populations, interventions, and outcomes included in the review (**Figure 1**).

The target population for screening includes women with unknown *BRCA1/2* mutation status who have either not been previously diagnosed with breast or ovarian cancer or have completed treatment and are considered cancer-free. The USPSTF recommendations are intended for routine preventive health care in predominantly primary care settings in which cancer survivors often receive care after cancer treatment. The inclusion of women with previously treated breast or ovarian cancer is new for this update and is intended to address *BRCA1/2* mutation testing among women who were not evaluated for testing at the time of diagnosis, but could benefit from prevention interventions. For example, a woman with previously treated breast cancer may consider risk-reducing salpingo-oophorectomy if her test indicates a pathogenic mutation. Important subpopulations specifically considered for this update include non-white women, premenopausal women, and women with co-morbidities. The conditions of interest are *BRCA1/2* mutation carrier status and *BRCA1/2*-related cancer (predominantly breast, ovarian, fallopian tube, and peritoneal).

Key questions for this update are similar to the 2013 review except that a question on the clinical validity of mutation testing, which is established, has been replaced by a question on optimal testing approaches (Key Question 2c).

Key Questions

1. In women with unknown *BRCA1/2* mutation status, does risk assessment, genetic counseling, and genetic testing result in reduced incidence of *BRCA1/2*-related cancer and cause-specific and all-cause mortality?

2a. What is the accuracy of familial risk assessment for *BRCA1/2*-related cancer when performed by a nonspecialist in genetics in a clinical setting? What are the optimal ages and intervals for risk assessment?

2b. What are the benefits of pre-test genetic counseling in determining eligibility for genetic testing for *BRCA1/2*-related cancer? (Includes improved accuracy of risk assessment and pretest probability for testing and improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes.)

2c. What are optimal testing approaches to determine the presence of pathogenic *BRCA1/2* mutations in women at increased risk for *BRCA1/2*-related cancer? (Includes testing other high-risk family members, including men, before testing the index patient and using specific types of tests or multigene panels.)

2d. What are optimal post-test counseling approaches to interpret results and determine eligibility for interventions to reduce risk of *BRCA1/2*-related cancer? (Includes improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes.)
3. What are adverse effects of a) risk assessment, b) pre-test genetic counseling, c) genetic testing, and d) post-test counseling for *BRCA1/2*-related cancer? (Includes inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse effects on the patient's family relationships; overdiagnosis and overtreatment; false reassurance; incomplete testing; misinterpretation of test results; anxiety; cancer worry; and ethical, legal, and social implications.)
4. Do interventions reduce the incidence of *BRCA1/2*-related cancer and mortality in women at increased risk? (Includes intensive screening [earlier and more frequent screening; use of additional screening methods], use of risk-reducing medications [aromatase inhibitors; tamoxifen; raloxifene], and risk-reducing surgery [mastectomy; salpingo-oophorectomy; other procedures] when performed for prevention purposes.)
5. What are adverse effects of interventions to reduce risk for *BRCA1/2*-related cancer? (Includes immediate and long-term harms associated with screening, risk-reducing medications, and risk-reducing surgery and ethical, legal, and social implications.)

Search Strategies

A research librarian searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PsycINFO, and EMBASE for relevant English-language studies, systematic reviews, and meta-analyses. Searches included studies published in January 1, 2013 to March 6, 2019 to update previous key questions; and studies published since January 1, 1994 (when *BRCA1/2* genes were discovered) for new key questions and to include women with previously treated breast or ovarian cancer. Studies published before 2013 were identified from prior systematic reviews for the USPSTF.[108,109] Search strategies are listed in **Appendix A1**. Search terms for existing systematic reviews and meta-analyses included "*BRCA1/2*," "breast cancer," "genetic counseling," "risk assessment," and "genetic testing," among other terms. Investigators also reviewed reference lists of relevant articles to identify studies.

Study Selection

Selection criteria for studies were developed for each key question based on the patient populations, interventions, comparisons, outcome measures, and types of evidence (**Appendix A2**). Investigators reviewed abstracts and full-text articles using prespecified eligibility criteria.[107] second reviewer independently confirmed results of the initial review and discrepancies were resolved by consensus with a third reviewer if needed. Study selection is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Randomized clinical trials (RCTs), systematic reviews, prospective and retrospective cohort

studies, case-control studies, and diagnostic accuracy evaluations that addressed Key Questions were eligible. These included studies of the accuracy of risk assessment tools (Key Question 2a), outcomes of genetic counseling and testing (Key Questions 1, 2bcd), and effectiveness studies of interventions to reduce risk of *BRCA1/2*-related cancer among mutation carriers (Key Question 4). Interventions include intensive screening (e.g., earlier and more frequent mammography, breast MRI, TVUS), risk-reducing medications (e.g., tamoxifen, raloxifene, aromatase inhibitors), and risk-reducing surgery (e.g., mastectomy, salpingo-oophorectomy).

Risk assessment tools were included only if they were intended for use by nonspecialists in genetics to guide referrals and were applicable to U.S. primary care clinical settings (i.e., brief, nontechnical, did not require special training to administer or interpret). Evaluation of complex models used in genetic counseling was outside the scope of this review. Only studies reporting discriminatory accuracy of the tools were included. Discriminatory accuracy is a measure of how well the tool can correctly classify individuals at higher risk from those at lower risk and is measured by the tool's concordance statistic or c-statistic. The c-statistic is determined by the area under the receiver operating characteristic curve (AUC), a plot of sensitivity (true-positive rate) versus 1 – specificity (false-positive rate). Perfect discrimination is a c-statistic of 1.0, whereas a c-statistic of 0.5 would result from chance alone. An acceptable level of discrimination is between 0.70 and 0.79, excellent is between 0.80 and 0.89, and outstanding is 0.90 or greater,[110] although these thresholds vary depending on the clinical condition and purpose of the test. Studies of individual risk factors, laboratory tests, or models designed primarily to evaluate risk for breast or ovarian cancer rather than risk for pathogenic mutation were excluded.

Studies of any design were included to describe potential harms of risk assessment, genetic counseling, mutation testing, and risk-reducing interventions (Key Questions 3 and 5). Potential adverse effects include inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; false reassurance; incomplete testing; misinterpretation of the test result; anxiety; cancer worry; immediate and long-term harms associated with breast imaging, among others.

Studies that included women with histories of breast or ovarian cancer were excluded completely from the 2013 review. For this update, these women were included because they may also benefit from genetic risk assessment, counseling, and testing, and, if indicated, further risk-reducing interventions. Only studies that included women who were diagnosed with breast or ovarian cancer at least 5 years before enrollment and completed cancer treatment were included in order to assure that genetic testing was intended for risk reduction rather than treatment purposes. Studies that did not report the time since breast or ovarian cancer diagnosis were excluded.

Data Abstraction and Quality Rating

For included RCTs and observational studies, investigators abstracted the following data: study design; setting; population characteristics (age, ethnicity, and diagnosis); eligibility criteria; interventions (dose and duration); numbers enrolled and lost to followup; method of outcome ascertainment; and results for each outcome. For studies of risk assessment, investigators abstracted: study design; population characteristics; eligibility criteria; reference standards; risk

factors included in the models; and performance measures. A second investigator reviewed accuracy of abstracted data.

Two investigators independently applied criteria developed by the USPSTF[107] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process.

Data Synthesis

For all key questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[107] Evidence was rated good, fair, or poor, based on study quality, consistency of results between studies, precision of estimates, study limitations, risk of reporting bias, and applicability; and summarized in a table.[107] No statistical meta-analysis was performed.

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners and was posted for public comment from February 19, 2019 to March 18, 2019.

Chapter 3. Results

103 studies (110 articles) were included;[66-69,71,98-100,111-212] 14 discriminatory accuracy studies; 15 RCTs; 59 cohort studies; 2 case-control studies; 12 before and after studies; and 1 systematic review. These include 31 new studies, 70 studies from the 2013 review,[108,213] and one new publication of followup results of a study included in the 2013 review. [108,213]**Appendix A3** shows the results of the literature search and selection process and **Appendix A4** lists the excluded full-text papers. Included studies and quality ratings are described in **Appendix B Tables**.

Key Question 1. In Women With Unknown *BRCA1/2* Mutation Status, Does Risk Assessment, Genetic Counseling, and Genetic Testing Result in Reduced Incidence of *BRCA1/2*-Related Cancer and Cause-Specific and All-Cause Mortality?

No studies addressed Key Question 1.

Key Question 2a. What Is the Accuracy of Familial Risk Assessment for *BRCA1/2*-Related Cancer When Performed by A Nonspecialist in Genetics in A Clinical Setting? What Are the Optimal Ages and Intervals for Risk Assessment? Key Question 3a. What Are the Potential Adverse Effects of Risk Assessment?

Summary

Fourteen discriminatory accuracy studies of eight risk assessment tools met inclusion criteria (**Table 1**)[111-124] including four new studies that evaluated existing tools.[115,117,120,124] No studies evaluated optimal ages and intervals for risk assessment and no studies described harms. Most studies used results of mutation testing as reference standards, although two studies included in the 2013 review used clinical criteria that involved risk estimates from more complex models as reference standards (e.g., BRCAPRO, BOADICEA).[112,114]

The new studies further evaluated existing tools including the Manchester Scoring System (MSS),[120] Pedigree Assessment Tool (PAT),[124] International Breast Cancer Intervention Study (IBIS) risk model (also known as Tyrer-Cuzick),[117] and brief versions of BRCAPRO, a complex model typically used by genetic counselors.[115] Results indicated that a revised version of the MSS that integrated pathology data of the family member diagnosed with cancer had higher sensitivity than the original model.[120] In new validation studies, AUC values were 0.71 for the PAT[124] and 0.74 (95% CI, 0.71 to 0.77) for IBIS,[117] and were comparable to other more complex tools that were also evaluated. Another study demonstrated that the accuracy of brief versions of

BRCAPRO were comparable to the full BRCAPRO and a sequential approach did not improve accuracy over BRCAPRO alone (i.e., brief version followed by the full BRCAPRO if indicated).[115]

Results of the four new studies were consistent with the 10 studies of eight familial risk assessment tools included in the 2013 review.[108,213] In these studies, results generally indicated moderate to high diagnostic accuracy (AUC 0.68 to 0.96) in predicting *BRCA1/2* mutations in individuals when compared against results of mutation testing or clinical criteria. However, results varied across studies and some tools were only evaluated in single studies. No studies in the 2013 review addressed harms of risk assessment.

Evidence

Familial risk prediction tools that address this key question are primarily intended for use by nonspecialists in genetics to guide patient referrals to genetic counselors for more comprehensive evaluations. These tools specifically predict familial risk of genetically related cancer risk, and do not include tools that predict the overall probability of developing breast cancer, such as the Gail model. Risk tools generally include variations of key risk factors including *BRCA1/2* mutations previously detected in relatives; Ashkenazi Jewish heritage; numbers, ages, and types of relatives affected with breast or ovarian cancer; and presentations of cancer that are highly suggestive of *BRCA1/2* mutations, such as male or bilateral breast cancer, breast and ovarian cancer in the same person, and young age at cancer onset (<50 years old). Several tools have been developed and evaluated in patients, including the Ontario Family History Assessment Tool (FHAT), FHS-7 (7-question Family History Screening), MSS, PAT, and Referral Screening Tool (RST).

Four new fair-quality studies describing performance characteristics of existing tools met inclusion criteria for this update[115,117,120,124] in addition to 10 studies of eight tools included in the 2013 review (**Table 1** and **Appendix C**).[111-114,116,118,119,121-123] All studies met criteria for fair- or good-quality (**Appendix B Table 1**). Most studies used results of mutation testing as reference standards, although two studies included in the 2013 review used clinical criteria that involved risk estimates from more complex models as reference standards (e.g., BRCAPRO, BOADICEA).[112,114] Overall, risk tools demonstrated moderate to good discriminatory accuracy in predicting the probability of familial *BRCA1/2*-related cancer risk in individuals (AUC 0.68 to 0.96). Details of each tool are further described below.

Ontario Family History Assessment Tool (FHAT)

The FHAT is a 17-question instrument developed to assist Canadian clinicians in selecting patients for referral to genetic counseling.[118] The referral threshold is equivalent to doubling of the general population lifetime risk for breast or ovarian cancer (22%). With FHAT, points are assigned according to the number of relatives, third-degree or closer, diagnosed with breast, ovarian, colon, or prostate cancer; age at diagnosis; and type and number of primary cancers. Patients with scores of 10 or more points meet the referral threshold.

In a study of 184 women with incident familial and non-familial breast cancer, the sensitivity and

specificity of FHAT for a pathogenic *BRCA1/2* mutation were 94 and 51 percent, respectively.[118] This compares with sensitivity and specificity of 74 and 79 percent using BRCAPRO, and 74 and 54 percent using Claus methods. The 2013 review included three additional studies of FHAT that replicated its accuracy.[121-123]

Manchester Scoring System (MSS)

The MSS was developed in the United Kingdom for use in clinical practice to predict *BRCA1/2* mutations at the 10 percent threshold for mutation probability,[116] a level often used clinically.[101] Points are assigned depending on type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis. The tool provides scores for *BRCA1* and *BRCA2* mutations separately and combined.

A new fair-quality study validated the MSS by testing models with and without pathology information in 9,390 families in the German Hereditary Breast and Ovarian Cancer Consortium.[120] Mutation analysis for *BRCA1/2* was performed for each index patient as the reference standard. Three different models of the MSS were evaluated. The original model, MSS-2004, included 12 components representing the numbers of breast, ovarian, pancreatic, and prostate cancers identified at different ages among relatives in the pedigree, with specific sub scores for each *BRCA1/2* mutation. The MSS-2009 was similar to the MSS but included histology and hormone receptor status from the breast cancer of the index case in a family. The MSS-recal was a recalibrated model using logistic regression to assess whether the components of the MSS were significantly predictive in the validation population and how the weights of the components compared with the original scores.

The use of pathological parameters in high-risk families' histories increased predictive performance and recalibration improved specificity (MSS-2004, AUC, 0.77; 95% CI, 0.75 to 0.79; MSS-2009, AUC, 0.80; 95% CI, 0.78 to 0.82; MSS-recal, AUC, 0.82; 95% CI, 0.80 to 0.83). Methodologic limitations of this study include unclear exclusion criteria, incomplete pathology information for some index patients, and limited applicability resulting from selective sampling conditions of the cohort.

In the 2013 review, the MSS was evaluated in five studies in the United Kingdom and Canada and compared with other existing tools.[111,113,116,121,122] In these studies, the MSS (for combined *BRCA1/2*) had 58 to 93 percent sensitivity, 33 to 71 percent specificity, and AUC values of 0.75 to 0.80, comparing well with the other tools tested.[111,113,116,121,122] Importantly, the MSS is not designed to assess families with Ashkenazi Jewish ancestry, and may have more limited applications in clinical settings in the United States.

Referral Screening Tool (RST)

The RST was developed to help primary care clinicians make appropriate referrals for genetic counseling in response to the USPSTF's 2005 recommendation.[114,214] The RST uses a checklist of risk information, including breast cancer at age 50 or younger in self or relatives; ovarian cancer at any age in self or relatives; two or more breast cancer cases at age older than 50 on the same side of the family; male breast cancer; and Jewish ancestry. The referral threshold of 10

percent or higher mutation probability is reached with two or more positive responses. It was designed for simplicity and is the least complicated model to administer for screening purposes.

In an evaluation study in the 2013 review, the RST was administered to 2,464 unselected women undergoing screening mammography in a U.S. healthcare system.[114] Results were compared against a reference standard that included detailed four-generation cancer pedigrees analyzed using four established hereditary risk models (BRCAPRO, Myriad II, BOADICEA, FHAT), with a 10 percent or higher *BRCA1/2* mutation probability or a FHAT score of 10 or more as the definition of "high-risk." The RST demonstrated sensitivity 81 percent, specificity 92 percent, and AUC 0.87. A revised model (B-RST) was further refined and is available on a website.[114,214] In a followup analysis using the same risk data from participants of the original study, the revised tool demonstrated increased sensitivity and slightly decreased specificity when compared against the other tools (BRCAPRO, Myriad II, BOADICEA, FHAT) and had an overall AUC of 0.90 (95% CI, 0.85 to 0.95). [214]

Pedigree Assessment Tool (PAT)

The PAT was specifically designed to identify women at increased risk for *BRCA1/2*-related cancer in U.S. primary care settings.[119] The PAT uses a point scoring system based on information from first, second, and third-degree relatives regarding breast cancer onset at ages younger or older than 50 years; ovarian cancer at any age; male breast cancer; and Ashkenazi Jewish ancestry. The referral threshold is 8 or more points indicating 10 percent or higher mutation probability.

A new fair-quality study evaluated PAT scores using results of mutation testing as the reference standard.[124] Participants were identified retrospectively through a high-risk clinic for cancer genetic counseling in the United States. Using the referral threshold score of 8 or more and mutation probability of 10 percent, PAT had sensitivity 96 percent and specificity 20 percent, with an AUC value of 0.705, comparable to Myriad II and Penn II models that were also evaluated. Methodologic limitations include uncertain applicability in the general population and enrollment methods using retrospective data collection from chart reviews.

In the 2013 review, a study of the performance characteristics of PAT using Myriad II as the reference standard indicated sensitivity of 100 percent, specificity of 93 percent, and AUC 0.96.[119]

FHS-7 (7-Question Family History Screening)

The FHS-7 is a 7-question instrument about family history of breast, ovarian, and colorectal cancer.[112] It was developed as a simple instrument for primary care settings for screening and referral purposes. The questions include first-degree relatives with breast or ovarian cancer; and any relatives with breast cancer age 50 and younger, bilateral breast cancer, breast and ovarian cancer in the same person, male breast cancer, two or more relatives with breast and/or ovarian cancer, and two or more relatives with breast and/or colon cancer. A single positive response is the threshold for referral.

An evaluation of the FHS-7 was included in the 2013 review. The FHS-7 was administered to 9,218 women during routine visits to primary care clinics in Brazil. The reference standard was based on clinical criteria for hereditary breast cancer syndrome involving an evaluation with pedigree analysis, lifetime risk estimates from established models (Claus; Gail; Tyrer-Cuzick; PennII), American Society of Clinical Oncology criteria, and review by two clinical geneticists. In this study, the FHS-7 had a sensitivity of 88 percent, specificity of 56 percent, and AUC value of 0.83.[112]

International Breast Cancer Intervention Study (IBIS)

The IBIS instrument was developed from eligibility criteria for the IBIS-I placebo-controlled trial of tamoxifen to reduce risk for primary breast cancer. It includes personal history information (current age, age at menopause, menarche, childbirth history, menopausal status, use of menopausal hormone therapy), personal breast history (breast density [optional], prior breast biopsy, history of breast or ovarian cancer), genetic testing, Ashkenazi Jewish ancestry, and information about relatives (breast or ovarian cancer, age at diagnosis, genetic testing). IBIS uses information from female index patients only, and incorporates information from female first and second-degree relatives and affected cousins and half-sisters.

In a new fair-quality study, the IBIS instrument was compared with more comprehensive risk assessment models in a large study of 7,352 families using mutation testing results as the reference standard.[117] Families were recruited through health centers participating in a high-risk consortium (German Consortium for Hereditary Breast and Ovarian Cancer) with eligibility based on risk for heredity cancer. IBIS had a sensitivity of 77 percent, specificity of 56.5 percent, and AUC of 0.749 (95% CI 0.735 to 0.763). These results were similar to more comprehensive models including BOADICEA (sensitivity 82.1%, specificity 56.8%, AUC, 0.791; 95% CI, 0.779 to 0.804), BRCAPRO (sensitivity 84.3%, specificity 55%, AUC, 0.796; 95% CI, 0.784 to 0.808), and eClaus (sensitivity 98%, specificity 9.6%, AUC, 0.745; 95% CI, 0.732 to 0.759).

BRCAPRO-LYTE, PLUS, SIMPLE

BRCAPRO is a statistical model that uses software to assess the probability that an individual carries *BRCA1/2* mutations based on family history of breast and ovarian cancer. The full BRCAPRO model is complex and generally used for genetic counseling. Brief variations of BRCAPRO were developed to use as screening tools prior to genetic counseling as part of a two-stage approach to genetic risk assessment in primary care.[115]

The basic BRCAPRO-LYTE version uses information on the numbers and types of first and second-degree relatives, which relatives are affected with breast or ovarian cancer, and ages of diagnosis. BRCAPRO-LYTE-Plus includes factors in the basic version, but imputes the ages of unaffected relatives (i.e., a value is calculated to provide an estimate). BRCAPRO-LYTE-Simple collects the least amount of data (age and relationships of each person with cancer) and imputes information on the numbers of each type of relative including age.

The accuracy of the brief BRCAPRO variations was evaluated in a new fair-quality study.[115] Participants were enrolled from high-risk families in the United States referred from three

different cancer centers for genetic counseling. Results of mutation testing served as the reference standard and data were analyzed retrospectively. BRCAPROLYTE had higher sensitivity but lower specificity than the other models (sensitivity 57%, specificity 56%); BRCAPRO-LYTE-Plus (sensitivity 39%, specificity 83%); BRCAPROLYTE-Simple (sensitivity 43%, specificity 79%).

The sensitivity and specificity of the two stage approaches (i.e. brief version followed by the full BRCAPRO for those at high risk on the initial instrument) were similar to BRCAPRO alone (46% and 75%). In this study, BRCAPRO-LYE overestimated risk of mutation; BRCAPRO-LYTE-Plus underestimated risk; and the Simple version provided the closest estimate and was the most stable across varying cutoffs.

Key Question 2b, 3b. What Are the Benefits and Adverse Effects of Pre-Test Genetic Counseling in Determining Eligibility for Genetic Testing for *BRCA1/2*-Related Cancer?

Summary

Twenty-eight studies (in 30 publications) were included,[66-69,71,125-149] including one new before and after study.[125] This study showed that agreement between a woman's understanding of her breast cancer risk and her genetic counselor's appraisal decreased 1 year after counseling compared with immediately after (49% agreement vs. 35%) among 89 women in the Netherlands. In the 2013 review, 16 of 23 studies indicated improved patient understanding of level of risk after genetic counseling. [125]

Twenty-seven studies included in the 2013 review reported additional outcomes related to genetic counseling. Seventeen of 18 studies indicated that genetic counseling is associated with decreases in measures of breast cancer worry or is not associated with breast cancer worry. Of 13 studies reporting anxiety outcomes and seven reporting depression, none indicated increased measures after genetic counseling. Of five studies evaluating genetic counseling's association with intention for mutation testing, one showed increased intention in black, but not white women; while four showed decreased intention.

Evidence

Twenty-eight studies (in 30 publications) met inclusion criteria, including one published since the 2013 review[125] and 27 included previously[66-69,71,126-149] (**Table 2** and **Appendix B Tables 2-7**). No studies included women treated for breast or ovarian cancer. Studies reported measures of breast cancer worry, anxiety, and depression associated with genetic counseling for *BRCA1/2*-related cancer. Additional outcomes included intention for genetic testing and women's understanding of their levels of risk. Overall, results indicated that genetic counseling was associated with decreased breast cancer worry, anxiety, and depression; increased understanding of risk; and decreased intention for inappropriate mutation testing.[66-69,71,126-149]

Across all studies, enrollment ranged from 64 to 1,971 women with family histories of breast and ovarian cancer who were seeking genetic counseling and interested in receiving genetic testing for *BRCA1/2* mutations. Several studies compared different types of genetic counseling[130,133,134,136,146] and genetic counseling versus no counseling,[126,129,142-144] while others compared outcomes before and after genetic counseling.[125,127,128,132,135,138,139,145] The types of genetic counseling services varied across studies and are summarized in **Table 3**.

Studies used various measures including the Cancer Worry Scale (CWS) and the State-Trait Anxiety Inventory (STAI) to measure breast cancer worry; the Hospital Anxiety and Depression Scale (HADS), Impact of Events Scale (IES), General Health Questionnaire (GHQ), and Visual Analogue Scale (VAS) to measure anxiety and depression; and general Likert scales to measure intention for genetic testing and understanding of risk. These measures are described in **Table 4**.

Breast Cancer Worry/Distress

Of 17 studies evaluating breast cancer worry, one reported increased measures after genetic counseling, but only in women at high-risk;[131] eight reported decreases;[127,130,132-134,136,138,144] and eight reported no associations.[67,69,71,129,137,140,148,149] Some studies showed mixed results that varied by subgroup or type of counseling.[69,128,131,132]

Most studies compared genetic counseling with no counseling, or changes before and after counseling.[69,127-129,131-133,137,138,140,144,149] A fair-quality prospective cohort study found that cancer-specific distress of high-risk women undergoing counseling decreased more from baseline to 1 year post-counseling (from 52 to 41% of women) than high-risk women without genetic counseling (from 41 to 35% of women), or a random sample of women from the general population without counseling (from 32 to 30%).[144] Similarly, two before and after studies, using a modified CWS, reported reductions in cancer worry after genetic counseling compared with baseline.[132,138 138132]Cancer worry also decreased after genetic counseling in a before and after study using the IES,[127,128] and a fair-quality RCT of women at moderate- or high-risk.[134]

Some studies compared different types of genetic counseling.[67,71,130,134,136,148] A fair-quality RCT reported that women who received either in-person or telephone counseling had decreased CWS worry scores 3 months after counseling compared with a control group that did not receive counseling.[136] More women in the in-person counseling group felt they could discuss their concerns during counseling sessions compared with women who received telephone counseling (77.4 vs. 67.3%, respectively, $p<0.05$). A fair-quality RCT reported decreases in cancer worry 6 months after both group and individual genetic counseling compared with a noncounseling control group.[130] Another study comparing a computer intervention with an in-person counseling session reported decreased worry in both groups 3 months after counseling, with no differences between groups.[133]

Anxiety and Depression

Of 13 studies evaluating anxiety associated with genetic counseling, none reported increases, five reported decreases,[71,131,133,145,146] and eight reported no associations.[68,127,137,138,141,144,148,149] Seven studies of depression also showed no increases in measures of depression, while one study

indicated decreases,[146] and six reported no associations.[68,71,127,141,144,148]

Results were consistent regardless of the type of counseling provided,[68,71,148] as demonstrated in a good-quality RCT that compared enhanced services with usual care.[146] In this study, women receiving genetic counseling from a nurse specialist in addition to resources about informing at-risk relatives, a pamphlet, and a videotape were compared with women receiving genetic counseling with no additional resources. Both groups reported significant decreases in mean anxiety and depression scores, as measured by the HADS, at 2 weeks and 8 months after counseling, with no significant differences between groups. None of the mean scores reached the clinical threshold (score of 8 or more) for diagnosing either anxiety or depression.

Understanding of Risk

Of 22 studies evaluating genetic counseling's association with women's understanding of their level of cancer risk, 14 reported increased understanding,[67,71,130,131,133-137,140,142,145,146,148] one reported decreased understanding,[139] six reported no associations,[125,129,138,141,143,149] and one reported mixed results.[68] Only one study assessed risk for ovarian cancer and found that women underestimated their risks by 5 percent at 6 months after counseling.[139] Most studies measured women's understanding of risk by comparing a woman's perceived risk of cancer (higher risk vs. same or lower than other women their age) with an objective measure; or agreement of a woman's understanding of risk with the genetic counselor's appraisal.

The new before and after study of 89 women in the Netherlands showed that agreement of a woman's understanding of breast cancer risk with her genetic counselor's appraisal decreased 1 year after counseling compared with immediately after (49% agreement vs. 35%).[125] However, this study did not describe details of the counseling intervention, and may not be applicable to U.S. practice.

In the 2013 review, a fair-quality systematic review included 19 studies published before February 2007 of women's understanding of risk after genetic counseling.[147] In these studies, outcomes were measured by changes in the proportion of women who accurately perceived their risk, and by the degree of overestimation or underestimation of risk. Overall, the proportion of women who accurately perceived their risk increased from an average of 42 percent before to 58 percent after counseling. Women who overestimated their risks did so by approximately 18 percent (range 6 to 40%) after counseling, which was an improvement from 25 percent before counseling. Seven studies indicated counseling that delivered information about family history, heredity, and personal risk estimates improved understanding of risk. Improvement was also measured in three of five studies that included education about heredity; and in three of six studies when counseling facilitated informed decision making and adaptation to personal risk.

Intent to Participate in Genetic Testing

Five studies in the 2013 review evaluated genetic counseling's associations with intention for genetic testing; one study reported increased intention,[69] four reported decreased intention,[67,130,131,136] and none reported no associations. A study comparing telephone counseling versus in-person counseling versus no counseling determined that participants' intentions to

pursue genetic testing were similar between groups at baseline.[136] Three months after genetic counseling, intention scores increased for the control group, but decreased for the two counseling groups. Three fair-quality RCTs reported decreased interests in genetic testing 6 months after group and/or individual counseling.[66,67,130] Interest in testing for women randomized to counseling decreased more than those in the control group in two of the studies.[67,130] The third study showed decreases in all groups at 6 months followup.[66] One fair-quality RCT reported increased interests in genetic testing 1 month after individual counseling among black women, but not for white women who had decreased interests in genetic testing.[69]

Key Question 2c. What Are Optimal Testing Approaches to Determine the Presence of Pathogenic *BRCA1/2* Mutations in Women at Increased Risk for *BRCA1/2*-Related Cancer? Key Question 3c. What Are Adverse Effects of Genetic Testing?

Summary

One new good-quality RCT evaluated outcomes of different testing approaches. This study indicated that population-based testing detected more *BRCA1/2* mutations than family-history based testing among Ashkenazi Jews, however, it did not determine health outcomes related to increased detection.[164] Measures of anxiety, health anxiety, depression, distress, uncertainty, and quality of life were similar between groups.

Five new studies reported adverse effects of genetic testing for *BRCA1/2* mutations[150,157,161,163,170] including two studies not included in the 2013 review because they enrolled women previously treated for breast or ovarian cancer or men. In one study, women who chose to receive their test results experienced decreased breast cancer related worry over the subsequent 12 months regardless of carrier status. Of two new studies of generalized anxiety after genetic testing, one showed higher generalized anxiety for mutation carriers compared with noncarriers after testing, while one did not. Another study found that men and women who declined testing after initial pre-test counseling sessions did so because of fear of the psychological impact of the test results.

The new studies are generally consistent with the 2013 review indicating genetic testing is associated with increased distress in the short-term. In these studies, breast cancer worry and anxiety increased for women with positive results and decreased for others, although results varied across studies. Women's understanding of their risk generally improved after receiving test results.

Evidence

Seven new studies[150,157,161,163,164,170,172] (**Table 5** and **Appendix B Table 8**) and 14 observational studies (in 16 publications) in the 2013 review[151-156,158-160,162,165-169,171] met inclusion criteria for these key questions. One study evaluated approaches to testing for *BRCA1/2*-related cancer, and

the others determined psychological benefits and harms of genetic testing for *BRCA1/2*-related cancer measured as changes in worry, anxiety, depression, and understanding of risk. Two studies were not included in the 2013 review because they enrolled women previously treated for breast or ovarian cancer or men.[150,170] No studies described other adverse effects of testing, such as the impact of false-positive or negative results or use of additional risk-reducing interventions.

Of the six new studies, four met criteria for good-quality[157,161,164,170] and two for fair.[150,163] One poor-quality study is not discussed further in this report.[172] Of eight cohort studies included in the 2013 review, five met criteria for good-quality,[155,156,159,165,167,171] two for fair,[154,162] and one for poor.[160] The remaining studies include a fair-quality case-control study,[152,169] and five studies with before and after designs for which quality rating criteria are not available.[151,153,158,166,168] Limitations include unclear enrollment information,[154,160,162] high loss to followup,[162] and differences between groups at baseline or lack of reporting of baseline characteristics of participants.[154,160,162]

Fourteen studies (in 16 publications) from the 2013 review, including cohort, case-control, and before and after designs, reported breast cancer worry and anxiety and women's understanding of risk related to *BRCA1/2* testing. In these studies, breast cancer worry and anxiety increased for women with positive results and decreased for others, although results varied across studies. Understanding of risk generally improved after receiving genetic test results. Limitations of studies included lack of studies with comparison groups, variations in methodology and enrollment criteria, and high loss to followup (**Appendix B Tables 2-5**).

Studies used a variety of metrics to measure worry related to genetic testing. These included the Cancer Related Worry (CRW) Scale and CWS-R (CWS-Revised), STAI, HADS, IES, GHQ, Swedish Short Form 36-item (SF-36) Health Survey, Short Form 12-question (SF-12) Health Survey including the Physical Health Component Scale (PCS) and Mental Health Component Scale (MCS) of the SF-12, Health Anxiety Inventory (HAI) scale, Coping Orientation to Problems Experienced Scale, Emotional Approach Coping Scale (COPE), Beck Depression Inventory (BDI), Post-Traumatic Growth Inventory (PTGI), Miller Behavioral Style Scale (MBSS), Multidimensional Impact of Cancer Risk Assessment (MICRA) scale, Multidimensional Fatigue Symptom Inventory-Short Form (MSFI-SF), Beck Hopelessness Scale (BHS), Brief Symptom Inventory (BSI), Perceived Personal Control (PPC) scale, Satisfaction With Decision (SWD) Instrument, and Center for Epidemiologic Studies-Depression Scale (CES-D). These measures are described in **Table 4**. Studies also used general Likert scales to measure perceived personal control, knowledge of breast cancer testing, satisfaction with health decisions, and general satisfaction with the decision to undergo testing, as well as qualitative methods to understand reasoning behind choices to not pursue testing.

Genetic Testing Approaches

A large, good-quality trial in the United Kingdom randomized 691 women and 343 men of Ashkenazi Jewish ancestry to population-based *BRCA1/2* mutation testing versus family history-based testing.[164] The study evaluated the prevalence of mutations identified, psychological outcomes, and quality of life for each testing approach. Volunteers with self-reported Ashkenazi Jewish ancestry (4 grandparents) were recruited through community charities, religious groups,

pharmacy chains, and a website. Those with known *BRCA1/2* mutations, previous *BRCA1/2* testing, or first-degree relatives with *BRCA1/2* mutations were excluded.

All participants received structured, nondirective pretest genetic counseling. After genetic counseling, those who decided to undergo testing were randomized to testing groups. Genetic testing was performed on all participants randomized to population-based testing, and only on participants meeting criteria for high-risk randomized to family-history based testing. Testing involved sequencing analysis of *BRCA1* exons 1 and 20 and a segment of *BRCA2* exon 11 for three Jewish founder mutations performed by a National Health Service (NHS) clinical genetics laboratory. Mutation carriers were notified in person and advised to seek referral to an NHS regional genetics clinic for confirmatory testing and risk-management services. Mutation-negative volunteers who met family history criteria for high-risk were also referred to genetic clinics.

The detected prevalence of *BRCA1/2* mutations among participants was 2.45 percent overall, with 13 *BRCA1/2* carriers identified by population testing and 9 by family history. However, over 3 years of followup, 210 of the 438 family history negative participants opted to complete testing. This subsequent testing identified an additional five carriers among family history negative participants. Thus, a family history based testing approach would miss 56 percent of carriers in the population (15 of 27 carriers).[164] However, whether detection of *BRCA1/2* carriers in families without cancer history leads to improved clinical outcomes, such as reduced cancer incidence and mortality, was not evaluated in this study.

This study used the MICRA scale to assess distress, uncertainty, and experience after genetic testing; and the MCS and PCS subscales of the SF-12 to measure quality of life. Measures of anxiety, health anxiety, depression, distress, uncertainty, and quality of life were similar between family history and population testing groups at 7 days and 3 months after testing.[164]

Breast Cancer Worry/Distress

Of nine studies evaluating breast cancer worry, seven reported increases after genetic testing,[152,161,163,165,166,170,171] particularly for mutation carriers; two reported decreases;[150,154] and none reported no associations.

Two studies that were not part of the 2013 review because they included women previously treated for breast or ovarian cancer or men were included in this update.[150,170] A study of 60 Ashkenazi Jewish women in the United Kingdom (10 with previous breast or ovarian cancer and 50 without) who received risk assessment and counseling about advantages and disadvantages of genetic testing assessed breast cancer worry, depression, and anxiety outcomes over 12 months of followup.[150] Forty-three women chose to learn their testing results and 79 percent of them returned a 12-month followup questionnaire. Women without previous breast or ovarian cancer who chose to receive their results had a statistically significant decrease in breast cancer worry at 12 months regardless of their carrier status.[150]

A good-quality cohort study of 212 members of an established Utah-based *BRCA1* kindred (K2082 has more than 750 living adult members) demonstrated that male and female mutation

carriers experienced more distress than noncarriers.[170] Also, female carriers had more distress than female noncarriers and male carriers or noncarriers. Short-term (1 week) reactions to results of genetic testing varied by gender and were influenced by the results of siblings, including whether siblings had been tested and were carriers.

A fair-quality cohort study of 103 women with family histories of breast and ovarian cancer in a genetics clinic assessed understanding and psychological outcomes after *BRCA1/2* mutation testing.[163] Satisfaction with the decision to undergo testing did not differ between women identified with positive (pathogenic *BRCA1/2* mutations), VUS, or negative (no mutation) results. Distress measured by MICRA and IES was highest among women with positive versus VUS or negative results. Women with positive or VUS results had higher positive experience MICRA subscale scores than women with negative results.

Six studies from the 2013 review reported breast cancer-related worry after receiving *BRCA1/2* test results;[152,154,158,165,166,171] five reported increased worry. In a good-quality prospective cohort study, women with positive results had increased worry compared with women with true negative or uninformative results 1 and 7 months after disclosure of results.[171] A fair-quality case-control study found no differences in worry between carriers and noncarriers with high family history risk after a mean of 8 years since receiving test results as measured by the CRW scale.[152] However, carriers and high-risk noncarriers had higher levels of worry than low-risk women who were not tested (p=0.022). In a study of 17 mutation carriers, breast cancer worry increased from baseline to 1 year after disclosure of genetic test results and decreased at 2 years, though scores remained in the mild distress range (IES 5.2 vs. 23.8 vs. 17.2; p=0.05).[166] Two additional cohort studies indicated higher levels of breast cancer distress for carriers compared with noncarriers or women not tested, 1 year[165] and 3 years or more after genetic testing. [158] A decrease in breast cancer worry for both carriers and noncarriers from baseline to 3 years after disclosure of genetic test results was reported in one study (CRW-R scale mean decrease of 1.3 and 2.2 respectively).[154]

Anxiety

Of 13 studies evaluating anxiety, four reported increases after genetic testing;[154,161,162,171] two reported higher anxiety scores for women who did not get tested compared with those tested;[155,156,165] two reported decreases after genetic testing;[151,165] and six reported no associations.[150,152,153,164,167,168]

Three new studies evaluated generalized anxiety after genetic testing,[150,161] including the RCT of population versus risk-based testing described previously.[164] A prospective cohort study of 1,771 Ashkenazi Jews enrolled through clinic recruitment and self-referral reported higher generalized anxiety for carriers compared with noncarriers 6 months after testing (STAI-6 score 12.6 for carriers vs. 9.9 for noncarriers, p=0.016; IES 19.9 for carriers vs. 4.9 for noncarriers, p<0.001).[161] Another new study found no changes in anxiety 1 year after genetic testing for either carriers or noncarriers, regardless of whether they had a personal history of *BRCA1/2*-related cancer.[150]

In the 2013 review, studies were inconsistent regarding whether anxiety increases after genetic

testing for carriers and noncarriers. The largest study, a good-quality prospective cohort study, reported higher anxiety scores in women with family histories of breast cancer who were not tested compared with tested women 6 weeks after receiving positive results (HADS mean 5.3 vs. 4.2, respectively, $p<0.05$).[155,156] However, there were no differences between groups in the prevalence of HADS-defined anxiety (24% in both groups). In a good-quality cohort study, noncarriers, compared with carriers and women who did not get tested, had lower anxiety scores at 7 to 10 days followup (STAI mean 31.6 vs. 38.5 vs. 36.8, respectively, $p=0.024$), though all scores indicated high anxiety.[165] Three additional studies reported increased anxiety among carriers 6 months [171] and 8 years after testing,[162] and among both carriers and noncarriers 3 years after testing.[154]

Four studies reported no differences in anxiety either over time[153,168] or between carriers, noncarriers, and age-matched controls,[152,167] with all scores below the case cutoff threshold. A small study reported decreased anxiety scores 1 year after women received results compared with pretest evaluations regardless of carrier status (HADS mean 5.6 pretest vs. 4.2, $p<0.001$).[151]

Depression

Of eight studies evaluating depression, none reported increases after genetic testing; one reported decreases;[165] one reported higher depression scores for untested versus tested women;[156] and six reported no associations.[150-152,164,167,168] Two new studies reported no changes in measures of depression after testing for carriers, noncarriers, and women with previous breast or ovarian cancer,[150] and for those tested based on family-history or Ashkenazi Jewish ancestry.[164]

In the 2013 review, a good-quality prospective cohort study reported higher depression scores in untested women with family histories of breast cancer compared with tested women 6 weeks after receiving positive results (HADS mean 2.9 vs. 1.7, respectively, $p<0.05$), though scores did not reach the threshold for clinical depression.[156] Four studies reported no differences in depression over time[151,168] or between carriers, noncarriers, and age-matched controls,[152,167] with all measures below the case cutoff threshold. In a good-quality cohort study, noncarriers, compared with carriers and untested women, had lower depression scores at 4 months followup (BDI mean 3.6 vs. 6.2 vs. 6.4, respectively, $p=0.024$), though scores did not reach the threshold for clinical depression.[165]

Other Psychological Responses

A new good-quality prospective cohort study described reasons for declining *BRCA1/2* mutation testing using qualitative analysis of comments.[157] In this study, 1,220 men and women from 385 high-risk families were offered testing, 886 received results, and 364 withdrew either before or after genetic testing. Most who withdrew stated that they were afraid of the psychological impacts of testing and saw no advantage to genetic counseling or testing, despite many having family members with known mutations.[157]

From the 2013 report, a fair-quality case-control study reported more subjective sleep problems in *BRCA1/2* mutation carriers compared with noncarriers and age-matched controls 8 years after testing (Pittsburgh Sleep Quality Index mean 7.29 vs. 3.94 vs. 4.21, respectively, $p=0.013$).[169]

However, actual sleep duration, latency, and wakefulness, as measured by a wrist monitor, showed no differences between groups.

Understanding of Risk

A fair-quality prospective cohort study assessed risk perception among 103 women with mutation positive, VUS, or mutation negative results.[163] Of women with positive results, 80 percent interpreted their result as indicating higher risk of breast cancer, and none interpreted results as indicating certainty of breast cancer. Most of the mutation negative group (67%) interpreted their negative result to mean they had lower risk of developing breast cancer. However, 19 percent with negative results indicated that their results did not clarify their perceived risk, and 4 percent interpreted the negative result as indication that they had no risk of breast cancer. Seven of the 20 patients with VUS results indicated that their result was likely to impact their decision to have additional or more frequent screening.

In a good-quality prospective cohort study of 246 women from the 2013 review, the number perceiving their risk of breast cancer as high or very high increased 18 percent 5 years after receiving a positive result compared with before receiving results ($p=0.016$).[159] The number of noncarriers perceiving their risk as high or very high decreased 47 percent ($p<0.001$). Also, 20 percent more mutation carriers perceived their risk of ovarian cancer as high or very high ($p=0.007$) while 27 percent of noncarriers perceived their risk to be low ($p<0.001$).

Key Question 2d. What Are Optimal Post-Test Counseling Approaches to Interpret Results and Determine Eligibility for Interventions to Reduce Risk of *BRCA1/2*-Related Cancer? Key Question 3d. What Are Adverse Effects of Post-Test Genetic Counseling?

No studies were identified that specifically addressed post-test counseling. Several studies included for Key Question 2b and 3b included discussion of management options as part of the pre-test counseling process, although none of them discussed testing results or evaluated benefits or harms of counseling conducted after receiving test results.

Key Question 4. Do Interventions Reduce the Incidence of *BRCA1/2*-Related Cancer and Mortality for Women With Increased Risk?

Summary

No effectiveness trials of intensive screening for breast or ovarian cancer in *BRCA1/2* mutation carriers that report cancer or mortality outcomes have been published. Studies of performance characteristics of intensive screening may be useful in clinical decision making, but these studies

do not directly address this key question. In two studies including 1,364 total *BRCA1/2* mutation carriers, sensitivity of screening for breast cancer was 63 to 69 percent for MRI, 25 to 62 percent for mammography, and 66 to 70 percent for combined; specificity was 91 percent or higher for either modality alone or combined. In a study of 459 *BRCA1/2* mutation carriers, sensitivity of screening for ovarian cancer was 43 percent for TVUS, 71 percent for CA-125, and 71 percent for combined; specificity was 99 percent for either modality alone or combined.

No trials of risk-reducing medications report results specifically for *BRCA1/2* mutation carriers. A systematic review and meta-analysis of placebo-controlled RCTs of tamoxifen, raloxifene, and aromatase inhibitors anastrozole and exemestane, and a head-to-head trial of tamoxifen versus raloxifene provide efficacy outcomes for women at various risk levels.[78,79] Trials are clinically heterogeneous and data are not available to compare doses, duration, and timing of use. Tamoxifen, raloxifene, and aromatase inhibitors reduced invasive breast cancer after 3 to 5 years of use compared with placebo; tamoxifen had a greater effect than raloxifene in the head-to-head trial. Risks for invasive cancer were reduced in all subgroups evaluated based on family history of breast cancer. Reduction was significant for ER positive, but not ER negative breast cancer. Noninvasive breast cancer and mortality were not significantly reduced and did not differ between medications.

Six observational studies reported outcomes of risk-reducing mastectomy, two of salpingo-oophorectomy, and seven of oophorectomy. Risk-reducing bilateral mastectomy was associated with 90 to 100 percent reduction in breast cancer incidence for high-risk women and *BRCA1/2* mutation carriers. Breast cancer-specific mortality was reduced by 81 to 100 percent after risk-reducing mastectomy in one study. Newer studies of oophorectomy or salpingo-oophorectomy that control for biases did not show associations between surgery and breast cancer risk, though some studies showed reduced risk among younger women after surgery. Oophorectomy was associated with 69 to 100 percent reduction in ovarian cancer risk in two studies, but no differences in all-cause mortality.

Evidence

Intensive Screening

Although searches identified multiple studies of intensive screening that included women with *BRCA1/2* mutations, none reported changes in clinical outcomes (cancer incidence or mortality) attributable to screening. Most studies described performance characteristics of intensive screening, such as sensitivity and specificity that are relevant to screening decisions, however, these studies do not directly address this key question. These include three new studies of breast[215] and ovarian cancer screening;[216,217] and five observational studies (six publications) in the 2013 review.[198,201,203,204,218,219] In these studies, prevalent cases were defined as cancer detected on the first round of screening, and incident cases were those detected on subsequent rounds (**Table 6** and **Appendix B Table 9**).

Breast Cancer

A new retrospective study included 471 *BRCA1* and 299 *BRCA2* mutation carriers screened at a

single academic hospital in the Netherlands with annual breast MRI beginning at age 25 years, and annual mammography beginning at age 30 years.[215] Diagnoses among *BRCA1/2* carriers included 62 screen-detected breast cancers (invasive cancer and ductal carcinoma in situ), 11 symptomatic interval cancers, and 19 occult cancers detected at risk-reducing mastectomy. For *BRCA1* carriers, sensitivity was 45 percent for mammography, 63 percent for MRI, and 66 percent for combined modalities. For *BRCA2* carriers, sensitivity was 36 percent for mammography, 67 percent for MRI, and 70 percent for combined modalities. For all *BRCA1/2* carriers, specificity was 94 percent or higher with either single or combined modalities.

Included in the 2013 review, the Dutch MRI Screening Study (MRISC), a prospective study including 594 *BRCA1/2* mutation carriers, evaluated performance characteristics of biannual clinical breast examinations and annual concurrent contrast enhanced MRI and mammography.[219] Digital mammography replaced film during the study period. The average age of participants at study entry was 40 years, and they were followed for a mean of 4 years. For *BRCA1* mutation carriers diagnosed with breast cancer, sensitivities were 67 percent for MRI versus 25 percent for mammography (p=0.0129); for *BRCA2* mutation carriers, sensitivities were 69 percent for MRI versus 62 percent for mammography (p=1.0).

The Magnetic Resonance Imaging Breast Screening (MARIBS) study, a prospective multicenter study conducted in the United Kingdom, evaluated screening of high-risk women including 120 *BRCA1/2* mutation carriers using annual contrast enhanced MRI and mammography.[203] Median age at entry of 40 years and duration of followup varied, but each woman completed at least two annual screens. For *BRCA1* mutation carriers or women related to carriers, sensitivity of MRI alone (92%) or combined with mammography (92%) was higher than mammography alone (23%), but less specific (79% MRI vs. 74% combined modalities vs. 92% mammography). For *BRCA2* carriers or women related to carriers, sensitivity of MRI combined with mammography (92%) was higher than either method alone (MRI 58%, mammography 50%); specificity of mammography alone (94%) was higher than MRI alone (82%) or combined modalities (78%).

Two additional studies were limited by small numbers of participants. A retrospective chart review of 73 *BRCA1/2* mutation carriers or first-degree relatives at a high-risk cancer clinic in the United States evaluated outcomes after screening with MRI alternating with mammography every 6 months in addition to 6-monthly clinical breast examinations.[204] Women had at least two screening cycles and were followed for a median of 2 years. All 11 screen-detected cancers were found on MRI (92% sensitivity, 87% specificity), and estimates for mammography could not be calculated. A prospective study including 48 *BRCA1/2* mutation carriers in Italy evaluated screening with mammography, ultrasound, and clinical breast examinations.[218] However, only four mutation carriers developed breast cancer in this study.

Ovarian Cancer

A new study in the United Kingdom reported performance measures of an ovarian cancer screening protocol combining CA-125 and TVUS.[217] Among 804 *BRCA1/2* mutation carriers, 14 invasive ovarian, tubal, or peritoneal cancers were identified (nine screen-detected and five occult cancers at risk-reducing surgery in screen-negative women). Sensitivity of combined CA-

125 and TVUS ranged from 64 to 100 percent depending how occult tumors were classified, with 99 percent specificity.

Included in the 2013 review, a prospective European study evaluated annual CA-125 measurement and TVUS in 459 *BRCA1/2* mutation carriers.[198] Seven ovarian cancers were diagnosed (excluding occult cancers found at surgery) indicating 71 percent sensitivity for CA-125, 43 percent for TVUS, and 71 percent for combined modalities. Corresponding specificities were 99 percent for each modality alone and combined. An additional study of TVUS screening in 1,601 women with family histories of ovarian cancer provided limited data indicating only that 6 of 61 women with abnormal scans had ovarian cancer.[188]

Risk-Reducing Medications

No new studies and no studies in the 2013 review evaluated the benefits of risk-reducing medications specifically in mutation carriers, although the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) trial of tamoxifen described results for 288 mutation carriers who developed breast cancer during the trial.[220] Of the eight women with breast cancer who had *BRCA1* mutations, five received tamoxifen and three placebo (RR 1.67, 95% CI, 0.32 to 10.70). Of 11 women with breast cancer and *BRCA2* mutations, three received tamoxifen and eight placebo (RR 0.38, 95% CI 0.06 to 1.56). Also, 86 percent (6/7) of women with *BRCA1* mutations had ER negative breast cancer, and 67 percent (6/9) with *BRCA2* mutations had ER positive. Tamoxifen is only effective in reducing risk for ER positive breast cancer.

Although no RCTs evaluated risk-reducing medications specifically in *BRCA1/2* mutation carriers, several RCTs of women at various levels of risk have been published and summarized in meta-analyses for the USPSTF.[78,79] Most trials enrolled women with increased risk for breast cancer including unidentified *BRCA1/2* mutation carriers.

Four placebo-controlled trials of tamoxifen include the NSABP P-1 trial,[221] Royal Marsden trial,[222] Italian Randomized Tamoxifen Prevention Trial,[223] and the International Breast Cancer Intervention Study (IBIS-I).[224] Placebo-controlled trials of raloxifene include the Raloxifene Use for the Heart Trial (RUTH)[84] and Multiple Outcomes of Raloxifene Evaluation (MORE) trial with its followup study, the Continuing Outcomes Relevant to Evista (CORE).[225] The Study of Tamoxifen And Raloxifene (STAR)[226] is a head-to-head trial that compared raloxifene with tamoxifen. New studies added to a USPSTF updated meta-analysis include long term results from the placebo-controlled IBIS-I trial of tamoxifen[227] and two placebo-controlled trials of aromatase inhibitors, IBIS-II of anastrozole[87,228,229] and the Mammary Prevention.3 (MAP.3) trial of exemestane.[86,230]

Results of the updated meta-analysis[78,79] indicated clinically significant reductions in invasive breast cancer for tamoxifen (RR, 0.69; 95% CI, 0.59 to 0.84; 7 fewer cases per 1,000 women over 5 years of use [95% CI, 4 to 12]; 4 trials), raloxifene (RR, 0.44; 95% CI, 0.24 to 0.80; 9 fewer cases [95% CI 3 to 15]; 2 trials), and aromatase inhibitors (RR, 0.45; 95% CI, 0.26 to 0.70; 16 fewer cases [95% CI, 8 to 24]; 2 trials) (**Table 7**). Tamoxifen reduced invasive breast cancer more than raloxifene in the STAR head-to-head trial (RR, 1.24; 95% CI, 1.05 to 1.47). Effects did not differ by age of initiation (before or after age 50 years), or duration of use (3 to 5 years)

although this effect was not directly compared. Risk reduction persisted at least 8 years after discontinuation in the two tamoxifen trials providing long-term followup data. All medications reduced ER positive, but not ER negative invasive breast cancer; tamoxifen reduced noninvasive cancer in two trials. Breast cancer specific and all-cause mortality were not reduced.

Although no trials evaluated breast cancer incidence specifically for *BRCA1/2* mutation carriers, all trials evaluated breast cancer incidence by family history, except the IBIS-I trial, in which 97 percent of participants reported some degree of family history.[224] Trials defined a positive family history as breast cancer in any first-degree relative, except the Royal Marsden trial that also included second-degree relatives.[222] Risks for invasive breast cancer were reduced in all subgroups evaluated based on family history of breast cancer. No trials evaluated breast cancer or all-cause mortality outcomes based on familial risk.

Risk-Reducing Surgery

Mastectomy

Six studies met inclusion criteria, four from the 2013 review (in five publications)[98,173,175,176,183] and two from updated searches[174,177] (**Table 8** and **Appendix B Table 10**). Overall, studies indicate that risk-reducing bilateral mastectomy is associated with reduced breast cancer incidence for high-risk women and mutation carriers. However, studies are observational and limited by small sizes, selection bias, comparability of control groups, ascertainment of outcomes, and inadequate followup.

In a new fair-quality retrospective study in the United States, none of the 38 women undergoing risk-reducing mastectomy developed breast cancer, compared with 5 of the 36 women under surveillance.[174] Similarly, in another new study of 570 Dutch women with *BRCA1/2* mutations and no cancer history, none of 212 women undergoing bilateral risk-reducing mastectomy developed breast cancer over 6 years following surgery.[177] Of 358 women under surveillance for 4 years, 57 developed breast cancer. Very few women in this study died, and reductions in all-cause and breast cancer specific mortality were not statistically significant.

The 2013 review included a retrospective study based on data from medical records of 639 Mayo Clinic patients.[175,176] Among women who underwent risk-reducing mastectomy, breast cancer incidence was lower by 92 percent for high-risk women compared with sister controls, and by 89.5 percent for moderate-risk women compared with expected population rates.[176] Postmastectomy breast cancer related deaths were lower by 81 percent for high-risk women compared with sister controls, and by 100 percent for moderate-risk women compared with expected population rates.[175] When the high-risk group was evaluated for *BRCA1/2* status, none of the 18 mutation carriers developed postmastectomy breast cancer compared with the 4.5 (low-penetrance model) and 6.1 (high-penetrance model) cases expected.[176]

A fair-quality study included in the 2013 review included 2,482 women with *BRCA1/2* mutations from 22 North American and European centers; 1,458 without previous breast cancer.[98] During 2.7 years of followup, no women with risk-reducing mastectomies were diagnosed with breast cancer compared with 34 of 585 (5.8%) women without mastectomies. In a good-quality study of

mutation carriers in Denmark, 3 of 96 (0.8% per person-year) women who underwent mastectomy were diagnosed with breast cancer versus 16 of 211 (1.7% per person-year) who did not, although this difference was not statistically significant.[183] Another study compared observed with expected breast cancer cases in women with *BRCA1/2* mutations or otherwise considered high-risk. Results indicated that none of the 307 women who had bilateral mastectomies were diagnosed with breast cancer, while 21.3 were expected.[173]

Salpingo-Oophorectomy or Oophorectomy

Nine studies met inclusion criteria; four from the 2013 review[98-100,184] and five from updated searches.[178-182] These include two studies of risk-reducing salpingo-oophorectomy[98,178] and seven of oophorectomy alone[99,100,179-182,184] (**Table 8** and **Appendix B Table 10**). One poor-quality study included in the 2013 review[184]is not discussed in this update.

Five new fair-quality cohort studies estimated associations between risk-reducing surgery and breast cancer incidence in *BRCA1/2* carriers;[178-182] none reported mortality outcomes. The newer studies advance understanding of the relationship between risk-reducing salpingo-oophorectomy or oophorectomy and breast cancer by considering potential biases of observational methods in their analysis of outcomes. As a result, these studies indicate either no or weaker associations.

The Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON) study evaluated outcomes of salpingo-oophorectomy in 822 Dutch women with *BRCA1/2* mutations.[178] In the initial analysis, the analytic methods of previous studies were replicated in the HEBON cohort and breast cancer risk reduction was estimated at approximately 50 percent after surgery, similar to previous studies. A revised analysis was designed to minimize bias by excluding patients with cancer history at the time of *BRCA1/2* mutation testing, and allocating person-time before surgery to the non-surgical comparison group. The revised analysis indicated no associations between salpingo-oophorectomy and breast cancer for all patients (hazard ratio [HR], 1.09; 95% CI, 0.67 to 1.77), *BRCA1* or *BRCA2* subgroups, and patients younger than 51 years at the time of surgery (HR, 1.11; 95% CI, 0.65 to 1.90).

A new prospective cohort study of 3,722 *BRCA1/2* carriers from 12 countries including the United States also excluded patients with cancer history and allocated time before surgery to the non-surgical group (oophorectomy status was a time-dependent variable).[179] Like the HEBON study, this analysis found no association between oophorectomy and breast cancer incidence for all women (HR, 0.89; 95% CI, 0.69 to 1.14) or those with either *BRCA1* or *BRCA2* mutations. However, women with *BRCA2* mutations who were younger than age 50 had lower rates of breast cancer with surgery compared with women without surgery (HR, 0.17; 95% CI, 0.05 to 0.61).

The Epidemiological Study of *BRCA1* and *BRCA2* mutation carriers (EMBRACE) that enrolled 988 women in the United Kingdom found that oophorectomy was associated with reduced breast cancer incidence for women younger than age 45 years (HR, 0.39; 95% CI, 0.17 to 0.87), but not older women (HR, 1.14; 95% CI, 0.50 to 2.61),[180] similar to the previous study.[179] An additional new study of 93 U.S. women showed no reductions in breast cancer with oophorectomy.[182]

An older prospective cohort study of 551 *BRCA1/2* carriers from 11 North American and European registries met revised inclusion criteria for this update.[181] In this study, oophorectomy was associated with reduced breast (HR, 0.47; 95% CI, 0.29 to 0.77) and ovarian or peritoneal cancer (HR, 0.04; 95% CI, 0.01 to 0.16).

Included in the 2013 review, a fair-quality prospective cohort study evaluated the outcomes of 2,482 *BRCA1/2* mutation carriers at 22 North American and European centers; 1,458 with no history of breast cancer.[98] In this study, salpingo-oophorectomy was associated with reduced ovarian or primary peritoneal cancer (1.3 vs. 5.8%; HR, 0.28; 95% CI, 0.12 to 0.69), reduced breast cancer incidence (11.6 vs. 21.6%; HR, 0.54; 95% CI, 0.37 to 0.79) and all-cause mortality (1.8 vs. 5.9%; HR, 0.45; 95% CI, 0.21 to 0.95). Reductions in breast cancer-specific and ovarian cancer-specific mortality were not statistically significant.

Another fair-quality prospective cohort study included 673 U.S. women from families with known *BRCA1* mutation carriers.[99] Among 98 *BRCA1* carriers, oophorectomy was associated with reduced breast cancer incidence (18 vs. 42%; HR, 0.38; 95% CI, 0.15 to 0.97) with more reduction for women who had the procedure at younger ages. A retrospective U.S. study compared observed with expected breast cancer incidence rates among 634 women undergoing oophorectomy at the Mayo Clinic, 419 of whom were at high or moderate breast cancer risk.[100] In this study, oophorectomy was associated with reduced risks that were more pronounced in high-risk women who were under 50 years of age and premenopausal at time of surgery (observed to expected ratio [O/E] = 1/3.9; RR, 0.26; 95% CI, 0.001 to 0.99), compared with older postmenopausal women (O/E = 3/5.4; RR, 0.56; 95% CI, 0.11 to 1.33).

Key Question 5. What Are Adverse Effects of Interventions to Reduce Risk for *BRCA1/2*-Related Cancer?

Summary

For breast cancer screening, false-positive rates, additional imaging, and benign biopsies were higher for women undergoing intensive screening using MRI versus mammography, though studies were small. A Dutch study reported a diagnostic surgery rate of 55 percent with benign results for *BRCA1/2* mutation carriers after combined TVUS and CA-125 screening. Most women experienced no anxiety or depression after 5 to 8 years of screening with MRI, mammography, or clinical breast examination, and breast cancer worry decreased over time. One new before and after study that included survivors of breast or ovarian cancer reported no increase in breast cancer worry for women receiving a false-positive result with screening that included serum CA-125, TVUS, mammography, and breast MRI.

Although there are no trials of risk-reducing medications specifically in *BRCA1/2* mutation carriers, adverse effects would be expected to be similar to noncarriers. A systematic review and meta-analysis of four tamoxifen, two raloxifene, and two aromatase inhibitor placebo-controlled RCTs and one head-to-head trial of raloxifene and tamoxifen provided adverse event outcomes for women at various levels of risk. Trials were limited by heterogeneity, and data on long-term effects were incomplete, particularly for aromatase inhibitors. Tamoxifen and raloxifene

increased thromboembolic events compared with placebo; tamoxifen had a greater effect than raloxifene. Tamoxifen increased endometrial cancer and cataracts. All medications caused undesirable side effects for some women, such as vasomotor and musculoskeletal symptoms.

Case-series and before and after studies described surgical complications, physical symptoms, and psychological measures related to risk-reducing surgery. Studies lacked important outcomes, enrolled small numbers of participants, and had no comparison groups. Some women experienced physical complications of surgery, had postsurgical symptoms, or changes in body image, while some women had improved anxiety.

Evidence

Intensive Screening

Breast Cancer

No new studies of false-positive and negative results, recall rates, and additional procedures were identified. Two new studies of breast cancer worry, anxiety, and depression,[193,208] including updated long-term results of a previously included study,[209] met inclusion criteria (**Table 9** and **Appendix B Table 11**). The 2013 review included three studies (in four publications) of false-positive and negative results, recall rates, and additional procedures[201-204] (**Appendix B Table 12**), and two studies of discomfort, pain, and anxiety.[209,210]

False-positive and negative results, recall rates, and additional procedures. In the 2013 review, studies of false-positive and negative results, recall rates, and additional procedures included women with increased familial risk of breast cancer recruited from the Netherlands, the United Kingdom, and the United States. Two studies used prospective designs,[201-203] and one retrospectively analyzed data from a completed prospective study.[204] Sample sizes ranged from 73 to 1,909, and included from 18 to 100 percent *BRCA1/2* mutation carriers. Mean or median age at entry was 40 to 44 years, and mean or median followup was approximately 2 years or at least two annual scans by the time of analysis.[201,202]

Two studies reported false-positive rates of mammography compared with MRI.[202,204] The Dutch MRISC study reported results by screening round, and defined the false-positive rate as the number of positive test results for women who did not have cancer. The false-negative rate was defined as the number of negative test results for women who had cancer. This study reported higher false-positive rates for MRI compared with mammography on the first and subsequent imaging rounds (first round with prior mammography: 14 vs. 5.5%; subsequent rounds: 8.2 vs. 4.6%; $p<0.001$ for both rounds).[202] False-negative results for MRI were lower than mammography, although numbers were small.

In a U.S. study of 6-monthly breast cancer screening using MRI alternating with mammography, a result was considered a false-positive if initial findings on screening appeared suspicious, but followup clinical examination, imaging, or biopsy resulted in a final benign assessment. This study reported similar false-positive results for both modalities (11% MRI, 15% mammography), and did not report false-negative findings.[204]

Recall rates for annual MRI were higher than annual mammography in a study conducted in the United Kingdom that included *BRCA1/2* mutation carriers (11% per woman-year MRI, 3.9% mammography, 13% combined).[203] In this study, 245 of 279 recalls were for benign findings, amounting to 8.5 recalls per cancer detected.

The Dutch MRISC and U.S. studies also reported the number of benign additional imaging procedures or biopsies resulting from screening.[201,204] The Dutch MRISC study determined the need for additional procedures using the Breast Imaging Reporting and Data System (BI-RADS) score from the screening examination. Women with BI-RADS scores of 3 (probably benign) or 0 (need additional imaging evaluation) underwent further evaluations using ultrasound with or without fine-needle aspiration, or repeat mammography, or repeat MRI. Women with BI-RADS scores of 4 (suspicious abnormality) or 5 (highly suggestive of malignancy) underwent biopsy. Results indicated that 43 percent of biopsies after MRI were benign (24 of 56 showed no cancer), compared with 28 percent of biopsies after mammography that were benign (7 of 25).[201]

In the U.S. study, alternating MRI with mammography screening every 6 months yielded a greater proportion of additional imaging (targeted ultrasound) for women screened with mammography (8/11) than MRI (4/8).[204] However, rates of benign biopsies were similar (3/11 for mammography, 2/8 for MRI).

Screening discomfort, breast cancer worry, anxiety, and depression. A new before and after study evaluating the effects of false-positive screening results on cancer worry, as measured by the BSI, compared baseline scores with followup at 3 months and 1 year.[208] This study included 22 (13%) survivors of breast cancer and one survivor of ovarian cancer. Women receiving a false-positive result had increased cancer worry at the 3 month followup, but scores dropped below baseline levels by the 1 year followup (1.70 vs. 1.80 vs. 1.45, respectively).

In the 2013 review, a fair-quality prospective cohort study found no differences in discomfort, pain, and anxiety between women undergoing intensive screening with annual mammography, MRI, and biannual clinical breast exams and women receiving only biannual clinical breast exams.[209] In a new study, after 5 to 8 years of followup, levels of intrusion and avoidance decreased, as measured by the IES, in the 197 women receiving intensive screening.[193]

In a before and after study of MRI plus mammography, ultrasound, and clinical breast exams, women who were recalled reported higher anxiety scores compared with women who were not recalled at 4 to 6 weeks after screening (8.8 vs. 5.9, respectively, p=0.03).[210] These represent mid-range scores measured by the HADS. Between group differences were not statistically significant by 6 months (7.1 vs. 5.9, respectively).

Ovarian Cancer

Two studies met inclusion criteria, both from the 2013 review.[188,198] In a prospective study, 1,601 self-referred asymptomatic women with at least one relative diagnosed with ovarian cancer were screened with TVUS.[188] Forty-three percent of women were screened with only one ultrasound. In this study, 3.8 percent (61/1601) of screened women had suspicious findings on TVUS and were referred to surgery. Cancer was detected in 6 of 61 referred cases, yielding a false-positive

rate of 3.4 percent (95% CI, 2.6 to 4.5%). Addition of color flow imaging to ultrasound reduced the number of false-positive cases to 6 from 55.

The second study reported the number of benign diagnostic surgeries associated with ovarian cancer screening using annual serum CA-125 measurements and annual TVUS in 459 *BRCA1/2* mutation carriers in the Netherlands.[198] Abnormalities were detected in 9 percent (40/459) of women with complete data, which included 3 percent (38/1116) of screening visits, as well as visits for symptomatic complaints. Of 26 diagnostic procedures, cancer was not detected in 67 percent (4/6) following abnormal CA-125 measurement compared with 100 percent (9/9) following abnormal TVUS findings. Combined modalities resulted in a benign diagnostic surgery rate of 55 percent (6/11).

Risk-Reducing Medications

No studies evaluated the adverse effects of risk-reducing medications specifically in *BRCA1/2* mutation carriers, although adverse effects were reported in several RCTs of women at various levels of risk and have been summarized in meta-analyses for the USPSTF.[78,79] Studies include four placebo-controlled trials of tamoxifen,[221-224] two placebo-controlled trials of raloxifene,[84,225] a head-to-head RCT of tamoxifen versus raloxifene,[226] and two placebo-controlled trials of aromatase inhibitors, anastrozole[87,228,229] and exemestane.[86,230]

In these trials, thromboembolic events were increased for tamoxifen (RR, 1.93; 95% CI, 1.33 to 2.68; 4 trials; 4 cases/1,000 women over 5 years) and raloxifene (RR, 1.56; 95% CI, 1.11 to 2.60; 2 trials; 7/1,000) compared with placebo (**Table 10**).[78,79] Raloxifene caused fewer events than tamoxifen in the STAR trial (RR, 0.75; 95% CI, 0.60 to 0.93; 4/1,000).[226] Coronary heart disease events or stroke were not increased in placebo-controlled trials, and did not differ in STAR, although women randomized to raloxifene had higher stroke mortality than placebo in the RUTH trial (RR, 1.49; 95% CI, 1.00 to 2.24).[231] The aromatase inhibitors caused no cardiovascular adverse effects in these trials.

Tamoxifen caused more cases of endometrial cancer (RR, 2.25; 95% CI, 1.17 to 4.41; 3 trials; 4/1,000), and was related to more benign gynecologic conditions, surgical procedures including hysterectomy, and uterine bleeding than placebo.[78,79] Raloxifene and aromatase inhibitors did not increase risk for endometrial cancer or uterine bleeding. In the STAR trial, raloxifene caused fewer cases of endometrial cancer (RR, 0.55; 95% CI, 0.36 to 0.83; 5/1,000), hyperplasia, and procedures than tamoxifen.[226] Women using tamoxifen had more cataract surgeries than placebo in the NSABP P-1 trial.[221] Raloxifene did not increase risk for cataracts or cataract surgery compared with placebo, and caused fewer cataracts than tamoxifen in STAR (RR, 0.80; 95% CI, 0.72 to 0.95; 15/1,000).[226]

Most common side effects were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen and vasomotor symptoms and leg cramps for raloxifene. In STAR, raloxifene users reported more musculoskeletal problems, dyspareunia, and weight gain, while tamoxifen users had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms.[226]

Risk-Reducing Surgery

Mastectomy

Four observational studies (in five publications) of surgical complications, physical symptoms, or psychological outcomes related to risk-reducing mastectomy were included in the 2013 review[189,190,195,205,212] and nine new studies met inclusion for this update[185,186,192,196,197,199,207,211] (**Table 11** and **Appendix B Tables 13** and **14**). One new poor-quality study is not discussed.[185]

Surgical complications and physical symptoms. Three new fair-quality, single-arm retrospective cohort studies described surgical complications of risk-reducing mastectomy experienced by *BRCA1/2* mutation carriers. A study of 104 *BRCA1/2* mutation carriers (59 *BRCA1* and 45 *BRCA2*) in the United States reported a complication rate of 69.3 percent, including 27 complications requiring surgery.[207] The most common complication was skin necrosis (11 cases), followed by infection, seroma, hematoma, and implant removal. Unplanned surgical revisions were required to complete reconstruction in 59 patients. In a study of 223 high-risk women (58% *BRCA1/2* mutation carriers) in Sweden, 52 percent had complications within 30 days.[186] Skin necrosis occurred in 30 percent, wound infection in 17 percent, late wound infections (more than 30 days after surgery) in 10 percent, and implant complications in 30 percent (62 of 208) with implant reconstruction. Complications were similar for 358 Dutch women including 145 *BRCA1/2* mutation carriers without breast cancer.[197] Complications occurred among 82 women (49%), with one third occurring within 6 weeks of reconstructive surgery (most commonly bleeding, necrosis, and infection), and two thirds more than 6 weeks after reconstruction (capsule formation and poor cosmetic result) often requiring corrective surgery.

Three additional studies reported similar types of surgical complications,[195,196,205] while another study found no differences between women's reports of pain before mastectomy versus 6 months or 1 year after.[190]

Psychological outcomes. Four studies of psychological outcomes related to risk-reducing mastectomy are new to this update.[192,196,199,211] A before and after study of 50 high-risk women (44 *BRCA1/2* mutation carriers) reported decreased body image 6 months after surgery that returned to baseline by 1 year, and no differences in satisfaction with sexual relationships.[196] While general mental health improved and physical health declined at 6 months, both returned to baseline by 1 year. Additional small studies indicated decreased body image at 6 months after surgery that returned to baseline by 6 to 9 years, and decreased general and breast cancer specific distress over time;[192] no reduction in general wellbeing;[199] and high satisfaction with risk-reducing mastectomy.[211]

In the 2013 review, a before and after study of 90 high-risk women (37 *BRCA1*, 13 *BRCA2)* indicated decreased anxiety scores, as measured by the HADS, 6 months and 1 year after surgery (mean 3.80 vs. 3.83 vs. 5.59, respectively, p=0.0004).[189,190] The study also reported decreased pleasure in sexual activity, as measured by the pleasure subscale of the Sexual Activity Questionnaire (SAQ), 1 year after surgery compared with 6 months after surgery and before surgery (mean 11.18 vs. 12.21 vs. 12.28, respectively, p=0.005). Depression scores, body image

concerns, or other portions of the SAQ were not significantly different. Additional small case-series studies reported no significant differences on psychological or sexual activity measures.[195,205]

Salpingo-Oophorectomy

One observational study of surgical complications, physical symptoms, or psychological outcomes related to risk-reducing salpingo-oophorectomy or oophorectomy was included in the 2013 review,[194] and four new studies[187,191,200,206] met inclusion for this update (**Table 11** and **Appendix B Tables 13** and **14**).

Surgical complications and physical symptoms. In a new good-quality, single-arm retrospective study of 159 Dutch women (81% *BRCA1/2* mutations), intraoperative complications occurred in 1.3 percent (2 patients) and postoperative complications within 6 weeks of surgery in 3.1 percent (pain, infection, and hematoma).[200] In the 2013 review, a before and after study of mutation carriers (67 women without previous breast cancer) indicated that most women reported worsening of vasomotor symptoms ($p<0.01$), measured by the Menopause-Specific Quality of Life-Intervention scale, and decreased sexual functioning ($p<0.05$), measured by the SAQ, after risk-reducing salpingo-oophorectomy.[194]

Psychological outcomes. Three new studies met inclusion criteria for the update.[187,191,206] A cross-sectional study of 205 women (56 *BRCA1/2* mutation carriers) had high levels of fatigue, with 13 percent (27/205) diagnosed with chronic fatigue syndrome.[206] A cohort study of 78 women (54 *BRCA1/2* mutation carriers) compared 52 women with risk-reducing mastectomy with 26 women with risk-reducing oophorectomy.[191] Groups did not differ in anxiety, depression, or cancer specific distress, though both groups showed significant decreases in anxiety scores between 6 months and 1 year after surgery. Another small cohort study of 27 women (20 *BRCA1* mutation carriers and 7 *BRCA2*) compared eight women with either risk-reducing mastectomy, risk-reducing oophorectomy, or both with 19 women who underwent surveillance.[187] Groups did not differ in anxiety, depression, quality of life, or body image concerns. However, the combined surgery group had statistically significant decreases in breast cancer worry from baseline to 15 months after surgery, while the surveillance group did not reach statistical significance (difference from baseline: -0.11, 95% CI, -0.70 to 0.49 vs. -2.75, 95% CI, -5.15 to -0.35).

Chapter 4. Discussion

Summary of Review Findings

Table 12 summarizes the evidence reviewed for this update. No studies directly addressed the overarching question regarding the effectiveness of risk assessment, genetic counseling, and genetic testing in reducing cancer incidence and mortality (Key Question 1).

Fourteen discriminatory accuracy studies, including four new studies of existing tools, met inclusion criteria for Key Question 2a. No studies evaluated optimal ages, intervals, or harms (Key Question 3a) of risk assessment. Included studies evaluated the accuracy of 10 familial risk tools to predict risk for *BRCA1/2* mutations and guide referrals to genetic counseling and potential testing. These include the FHAT, MSS, RST, PAT, FHS-7, brief versions of BRCAPRO, IBIS tool (also known as Tyrer-Cuzick), and variations. Results indicated moderate to high discriminatory accuracy (AUC 0.68 to 0.96), although some tools were only evaluated in single studies. Reference standards, enrollment criteria, and methodology varied across studies, limiting comparisons. Risk was most often based on self-reported information, thus the accuracy of risk estimates was limited by the accuracy of reported family history.

Two risk prediction tools were designed and evaluated specifically in unselected patients in primary care settings (FHAT and PAT; AUC >0.70), while others were evaluated in cohorts of patients referred to cancer networks or populations with known genetic risk. The applicability of methods designed for specific groups and settings may be limited when implemented more broadly in practice. For example, the MSS was designed for use in non-Ashkenazi Jewish populations, while the RST, PAT, and IBIS tools integrate Ashkenazi Jewish ancestry into risk assessment. As genetic testing becomes more available, particularly with direct to consumer marketing, improved selection of candidates at the primary screening level as a means to refer to genetic counseling and testing becomes increasingly important. While methods validated in specific settings or among selected populations may show high accuracy in studies, their use in broader populations may require additional evaluation.

Twenty-eight studies, including one new study, evaluated the benefits and harms of genetic counseling in women without previous histories of breast or ovarian cancer (Key Questions 2b and 3b). No studies included women who were previously treated for breast or ovarian cancer. Results indicated no increases in breast cancer-related worry after genetic counseling, with decreases in seven studies and no changes in two. No studies reported increases in anxiety or depression, with decreases in three studies and no changes in three. In most studies, anxiety and depression scores were below clinical thresholds. Eight studies indicated that a woman's understanding of her breast cancer risk improved after genetic counseling and two reported decreased intention to undergo genetic testing after genetic counseling. Face-to-face counseling was preferred in some studies. Studies were limited by differences in designs and measures, use of dissimilar comparison groups, and enrollment of small numbers of women from specialty clinics.

Only one study evaluated different testing approaches to determine the presence of *BRCA1/2*

mutations in women at increased risk for *BRCA1/2*-related cancer (Key Question 2c).[164] Results of this RCT indicated that population-based testing of individuals with Ashkenazi Jewish ancestry detects more *BRCA1/2* mutations than family-history based testing. Measures of anxiety, health anxiety, depression, distress, uncertainty, and quality of life were similar between family history and population testing groups. Whether detection of *BRCA1/2* mutation carriers in families without cancer history leads to reduced cancer incidence, mortality, and long-term harms was not evaluated in this study.

Eighteen studies of potential harms of genetic testing, including four new studies, (Key Question 3c) reported that breast cancer-related worry and anxiety increased for women with positive results and decreased for others, although results differed across studies. A new study showed that women receiving test results experienced decreased breast cancer-related anxiety over the subsequent 12 months regardless of carrier status.[150] In another study, participants withdrawing after initial pre-test genetic counseling sessions described fear about the psychological impact of test results.[157] Understanding of a woman's risk of cancer improved after receiving test results in several studies. Studies were limited by variations in methodology and enrollment criteria, small numbers of participants, high loss to followup, lack of comparison groups, and heterogeneous outcomes. Other relevant outcomes were not studied including false-positive or negative results, impact on decisions regarding risk-reducing interventions, and health and social outcomes, among others.

No studies specifically evaluated optimal post-test genetic counseling approaches, or harms of post-test genetic counseling (Key Questions 2d and 3d), although several studies included for Key Question 2b and 3b included discussion of management options as part of the pre-test genetic counseling process.

Studies of interventions to reduce the incidence of *BRCA1/2*-related cancer and mortality in *BRCA1/2* mutation carriers include intensive screening, risk-reducing medications, and risk-reducing surgery (Key Question 4). No trials evaluated the effectiveness of intensive screening. Although no trials of risk-reducing medications specifically in *BRCA1/2* mutation carriers are available, several RCTs that included women with various levels of risk are relevant. A systematic review and meta-analysis of placebo-controlled RCTs of tamoxifen, raloxifene, and aromatase inhibitors anastrozole and exemestane, and a head-to-head trial of tamoxifen versus raloxifene provide updated outcomes.[78,79] Tamoxifen, raloxifene, and aromatase inhibitors are associated with reduced invasive breast cancer after 3 to 5 years of use compared with placebo; tamoxifen had a greater effect than raloxifene in the STAR trial. Risks for invasive cancer were reduced in all subgroups evaluated based on family history of breast cancer. Medications reduced ER positive, but not ER negative breast cancer, noninvasive breast cancer, or breast-cancer specific or all-cause mortality. Trials were limited by heterogeneity and data were lacking on doses, duration, and timing of use.

Six observational studies reported outcomes of risk-reducing mastectomy, two of salpingo-oophorectomy, and seven of oophorectomy. Risk-reducing bilateral mastectomy was associated with 90 to 100 percent reduction in breast cancer incidence for high-risk women and *BRCA1/2* mutation carriers. Breast cancer-specific mortality was reduced by 81 to 100 percent after risk-reducing mastectomy in one study. Newer studies of oophorectomy or salpingo-oophorectomy

that control for biases did not show associations between surgery and breast cancer risk, though some studies showed reduced risk among younger women after surgery. Oophorectomy or salpingo-oophorectomy was associated with 69 to 100 percent reduction in ovarian cancer risk in two studies, but no differences in all-cause mortality.

Studies of the potential adverse effects of intensive screening for breast cancer (Key Question 5) indicated that false-positive rates, additional imaging, and benign biopsies were higher for women undergoing intensive screening using MRI compared with mammography. A study of ovarian cancer screening reported a benign diagnostic surgery rate of 55 percent after screening with TVUS and CA-125. Most women experienced no anxiety after screening with MRI, mammography, or clinical breast examination, although women recalled for additional testing had transient anxiety.

Trials of risk-reducing medications indicated that tamoxifen and raloxifene are associated with increased thromboembolic events compared with placebo, and tamoxifen had a greater effect than raloxifene. Tamoxifen was associated with increased endometrial cancer and cataracts. The aromatase inhibitors did not cause these adverse effects in primary prevention trials, although followup was brief. All medications caused undesirable side effects for some women, such as vasomotor symptoms.

Case-series and before and after studies described surgical complications, physical symptoms, and psychological measures related to risk-reducing surgery. Some women experienced physical complications of surgery, postsurgical symptoms, or changes in body image, while some had improved anxiety. Studies lacked important outcomes, and the few available studies had small numbers of participants and no comparison groups.

Limitations

Limitations of this review include using only English-language articles and studies applicable to the United States, although this focus improves its relevance to the USPSTF recommendation. Also, the number, quality, and applicability of studies evaluated in the evidence review varied widely. Limitations of studies specific to each key question are briefly described in **Table 12.** Most studies in this review were conducted on highly selected samples of women, some with preexisting breast or ovarian cancer or from high-risk groups that were defined in various ways, or from previously identified cancer kindred. It is not known how the results of studies based on highly selected women in research settings, particularly in non-U.S. settings, translate to a general screening populations in U.S. clinical practice.

Studies are currently not available for several key questions in this review. No studies determined the optimal age for *BRCA1/2* mutation testing and how the age at testing influences benefits and harms. No studies evaluated whether testing for *BRCA1/2* mutations reduces cancer incidence and cause-specific or all-cause mortality and improves quality of life. The harms associated with receiving a false-negative test result or a result indicating intermediate pathogenic categories are also not known.

This systematic review focused on five key questions that limited its scope. Several additional issues are important to consider. The prevalence of pathogenic *BRCA1* and *BRCA2* mutations in general screening populations in the United States is not known, and the clinical significance of a positive test in the absence of family history of cancer is unclear. The impact of modifier genes on penetrance and detection of cancer susceptibility genes other than *BRCA1/2*[232-235] require a broader view of benefits and harms of population screening.

Understanding these concepts is particularly important in the context of direct to consumer advertising of genetic testing and the availability of multipanel tests. Results of testing 194,104 women using a 25-gene hereditary cancer panel at a commercial U.S. laboratory identified 9,751 pathogenic variants in 9,641women (59% *BRCA1/2*; 39% *ATM*, *CHEK2*, or *PALB2*).[236] However, only 24.7 percent of women with pathogenic variants had greater than a 20 percent lifetime risk for breast cancer based on clinical risk models. The clinical significance of identifying pathogenic variants in multi-gene panels commonly available in practice requires further investigation. Current NCCN guidelines reflect this uncertainty by recommending that multi-gene testing be offered in the context of professional genetic expertise for pre- and post-test counseling.[56]

Although this update explicitly included women with previously treated breast and ovarian cancer, in addition to women without cancer, to address gaps in prevention recommendations and clinical practice, few studies were available. Only studies of women diagnosed with breast or ovarian cancer at least 5 years before enrollment and who completed cancer treatment were included to assure that genetic testing was intended for risk reduction. As a result, 102 studies of women with prior breast and/or ovarian cancer were excluded because the time since diagnosis was less than 5 years or not reported (**Appendixes A3** and **A4**). Consequently, questions regarding genetic testing or risk reduction in this population have not been adequately studied.

Evidence of harms often relied on observational studies with designs that lacked quality rating criteria. Existing studies show that most women do not experience adverse effects from *BRCA1/2* risk assessment, genetic counseling, and genetic testing. However, long-term impact is unknown because most studies followed patients for less than 1 year. Studies used several types of measures and scales that limited comparisons and prohibited meta-analysis. Measures of anxiety or depression often lacked clinical thresholds, and when available, few studies reported results based on the number of individuals who met thresholds. No studies were available that considered the repercussions of not participating in genetic counseling (e.g., wrong test, overdiagnosis, misinterpretation of results, failure to test for a specific familial mutation), or measured genetic discrimination or labeling as a harm of testing.

Long-term harms were also inadequately measured for other risk-reducing interventions. For example, aromatase inhibitors demonstrated increased fractures and stroke in treatment trials of noninvasive[237] and early stage breast cancer,[238,239] but not in trials of risk-reduction that lacked followup data.[86,87,228-230]

Treatment effects are influenced by several factors that were not evaluated in studies. Salpingo-oophorectomy is associated with reduced breast cancer in younger but not older women, however, it is not clear how and when the benefit/harm ratio shifts for women facing this

decision. Younger women are subjected to additional harms related to the impact of risk-reducing surgery on reproductive life decisions. Also, the type of risk-reducing intervention a mutation carrier selects may depend on her specific mutation. For example, women with *BRCA1* mutations have a higher risk of ovarian cancer than those with *BRCA2* mutations. Medications are most effective in reducing risk for ER positive breast tumors, although they have not been specifically evaluated in women with *BRCA1/2* mutations. The proportion of ER positive tumors varies from 28 percent of those among women with *BRCA1* mutations to 63 percent with *BRCA2* mutations. It is not known how these factors influence patient decision making and eventual clinical outcomes.

Relevance for Priority Populations, Particularly Racial/Ethnic Minorities

The prevalence of specific pathogenic *BRCA1/2* mutations varies across geographical, ancestry, and familial groups, yet it is currently unclear how to use this information in clinical practice to effectively counsel and test individuals. Women with family histories of cancer who are from groups with known founder mutations, such as Ashkenazi Jews, may more clearly benefit from testing. However, testing may not be beneficial for women who identify with a specific group in the absence of family cancer history. Founder mutations in different ancestry groups may require different ways of understanding and weighing benefits and harms, particularly when test results create social stigma or other types of unintended harms. Estimating and understanding risk requires a high level of numeric literacy that must be considered for patients with language and education barriers. These issues require further study to more effectively guide clinical practice.

Future Research

In order to determine the appropriateness of risk assessment and genetic testing for *BRCA1/2* mutations in primary care, more information is needed about mutation prevalence and impact in the general population. Research has focused on highly selected women in referral centers and generally reported short-term outcomes. Issues such as access to genetic testing, effectiveness of screening approaches including risk stratification, use of system supports, and patient acceptance and education require additional study. Who should perform risk assessment and genetic counseling services, how should it be done, effectiveness of different modalities, what skills are needed, and its impact on patient choices and outcomes are unresolved questions. Trials comparing types of providers and protocols could address these issues. What happens after patients are identified as high-risk in clinical settings is also not known. The consequences of genetic testing on individuals and their relatives need to be assessed. Well-designed investigations using standardized measures and enrolling subjects that reflect the general population, including minority women and transgender individuals,[240,241] are needed. [240,241]

An expanded database or registry of patients receiving genetic counseling and testing for *BRCA1/2* mutations would provide essential information about predictors of cancer, response to interventions, and other modifying factors. Before 2013, all patients clinically tested through direct DNA sequencing in the United States utilized a single private laboratory, and patient data

were inaccessible. Developing a centralized accessible database with key variables to address these issues as genetic testing practices change in the wake of the U.S. Supreme Court decision [74] would be a major advance in this field. Additional data from women of varying socioeconomic, racial, and ancestry groups are needed. Currently available risk prediction tools may not apply to these populations.

Additional research on interventions is also needed. Without effectiveness trials of intensive screening, practice standards have preceded supporting evidence. For example, while screening with annual TVUS and serum CA-125 is considered for high-risk women, trials have yet to demonstrate improved clinical outcomes.[32,242] Studies of factors related to acceptance of risk-reducing interventions based on genetic information would be useful, such as determining if cancer incidence in relatives is reduced because they adopt risk-reducing interventions. This information could improve patient decision making and lead to better health outcomes.

Conclusions

Risk assessment, genetic counseling, and genetic testing to reduce *BRCA1/2*-cancer incidence and mortality as a prevention service has not been directly evaluated by current research. Risk assessment with familial risk tools accurately identifies high-risk women for genetic counseling. Genetic counseling reduces breast cancer worry, anxiety, and depression; increases understanding of risk; and decreases intention for mutation testing, while testing improves accuracy of understanding of risk. The effectiveness of intensive screening is not known, but it increases false-positive results and procedures. Risk-reducing medications and surgery are associated with reduced breast and ovarian cancer, but also have adverse effects.

The process of familial risk assessment in primary care, referral and evaluation by genetic counselors, genetic testing, and use of intensive screening and risk-reducing medications and surgeries is complex. Each step of the pathway requires careful interpretation of information, consideration of future risks, and shared decision making before moving on to the next step. Services must be well integrated and highly individualized in order to optimize benefits and minimize harms for patients as well as their families. In the absence of effectiveness trials supporting steps in this pathway, additional studies are need to better inform practice, particularly in the context of widespread access to commercial testing.

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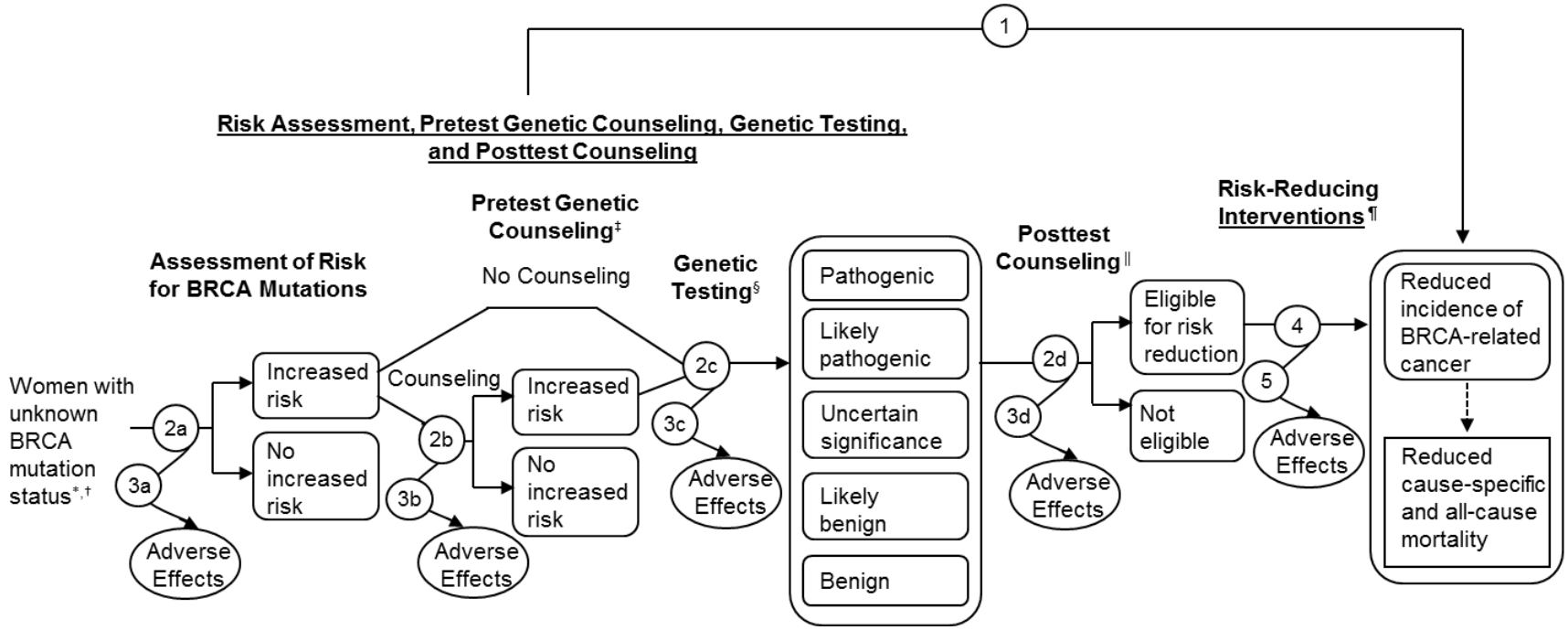
Figure 1. Analytic Framework



*Clinically significant pathogenic mutations in the *BRCA1* and *BRCA2* genes associated with increased risk for breast and/or ovarian cancer.
†Includes women who may have a previous diagnosis of breast or ovarian cancer, but have completed treatment.
‡Descriptions of genetic counseling, scope of services, and appropriate providers are described in the text.
§Testing may be done on the index patient, her relative with cancer, or her relative with highest risk, as appropriate.
‖ Includes interpretation of results, determination of eligibility for risk-reducing interventions, and patient decision making.
¶ Interventions include early detection through intensive screening (earlier and more frequent screening; use of additional screening methods), use of risk-reducing medications (aromatase inhibitors; tamoxifen; raloxifene), and risk-reducing surgery (mastectomy; salpingo-oophorectomy; other procedures) when performed for prevention purposes.

Table 1. Familial Risk Tools to Predict Individual Risk for *BRCA1/2* Mutations in Primary Care Settings*

Model	Data collection and calculation	Population (N)	Relatives with breast and ovarian cancer	Other factors	Comparison with other models	Reference standard	Performance characteristics for predicting risk for *BRCA1/2* mutations	Quality Rating
BRCAPRO-LYTE, BRCAPRO-LYTE-plus, BRCAPRO-LYTE-simple[115]	Evaluates brief versions of BRCAPRO† to guide referral to genetic counseling that uses full BRCAPRO	Patients with personal and/or family cancer history in three US hospital databases (4057)	1st, 2nd degree relatives	Number and types of relatives with breast and ovarian cancer; ages diagnosed	BRCAPRO	Mutation testing	Estimates based on different cut points: BRCAPRO-LYTE, sensitivity 57 to 93%; specificity 10 to 56%; BRCAPRO-LYTE-plus, sensitivity 39 to 76%, specificity 40 to 83%; BRCAPRO-LYTE-simple, sensitivity 43 to 83%; specificity 29 to 79%	Fair
Seven-question Family History Screening (FHS-7)[112]	One positive response to 7 items is referral threshold	Women visiting primary care clinics in Brazil (9218 completed FHS-7, 1246 referred, 902 completed evaluation)	1st degree	Any relatives with breast cancer age ≤50; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; ≥2 relatives with breast and/or ovarian cancer; ≥2 relatives with breast and/or colon cancer	None	Criteria for hereditary breast cancer syndrome‡	Sensitivity 88% (95% CI, 83 to 91%); specificity 56% (95% CI 54 to 59%); PPV 0.24 (95% CI, 21 to 27%); NPV 0.97 (95 to 98%); AUC 0.83 (95% CI 0.81 to 0.85)	Good
International Breast Cancer Intervention Study Model (IBIS)[111,117,122]	Compares performance with other established models	German Hereditary Breast and Ovarian Cancer Consortium (7352 families); families in cancer genetics clinics in the UK (1889) and Canada (300)	Female 1st, 2nd degree relatives, affected cousins and half-sisters	Environmental factors (i.e.,. parity) for female index patients only	BOADICEA; BRCAPRO; eClaus; Manchester; Penn II; Myriad II; FHAT	Mutation testing	German study: sensitivity 77%; specificity 56.5%; PPV 36%; NPV 88.5%; AUC 0.749 (95% CI 0.735 to 0.763); UK study: AUC 0.74 (95% CI 0.71 to 0.77); Canadian study: AUC 0.47 (95% CI 0.28 to 0.69)	Fair to good

Table 1. Familial Risk Tools to Predict Individual Risk for *BRCA1/2* Mutations in Primary Care Settings*

Model	Data collection and calculation	Population (N)	Relatives with breast and ovarian cancer	Other factors	Comparison with other models	Reference standard	Performance characteristics for predicting risk for *BRCA1/2* mutations	Quality Rating
Manchester scoring system[111,113,116,121,122]	Assigns points for responses to 12 items; referral threshold ≥10 points per mutation or ≥15 collectively (≥10% mutation probability)	Developed in families with cancer history in the UK (422); evaluated in 4 additional studies in UK and Canada (2880)	1st, 2nd, 3rd degree	Type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, and age at diagnosis	BOADICEA; BRCAPRO; FHAT; Myriad II	Mutation testing	Estimates based on different evaluation studies (≥10% mutation probability): sensitivity 58 to 93%; specificity 33 to 71%; AUC 0.75 to 0.80	Fair to good
Modified Manchester scoring system (MSS-2009)[120]	Assigns points for responses; referral threshold ≥10 points per mutation or ≥15 collectively (≥10% mutation probability)	German Hereditary Breast and Ovarian Cancer Consortium (9390 families)	1st, 2nd, 3rd degree	New version includes pathology (histology and hormone receptor status) of index patient in addition to original factors: type of cancer (breast, ovarian, pancreatic, or prostate), affected family members, age at diagnosis	Original MSS (MSS-2004) without pathology; recalibrated MSS (MSS-recal) with pathology for study sample	Mutation testing	≥10% mutation probability: MSS-2004, AUC 0.77 (95% CI 0.75 to 0.79); MSS-2009, AUC 0.80 (95% CI 0.78 to 0.82); MSS-recal, AUC 0.82 (95% CI 0.80 to 0.83)	Fair
Ontario Family History Assessment Tool (FHAT)[118, 121-123]	Assigns points for responses to 17 items; referral threshold ≥10 (≥22 lifetime risk for breast or ovarian cancer)	Developed in families with cancer history in Canada (184); evaluated in 3 additional studies in Canada and the US (3566)	1st, 2nd, 3rd degree	Age at diagnosis; bilateral breast cancer; breast and ovarian cancer in same person; male breast cancer; colon and prostate cancer	Claus; BRCAPRO	Mutation testing	Estimates based on different evaluation studies (≥22 lifetime risk): sensitivity 91 to 94%; specificity 15 to 51%; PPV 31%; AUC 0.68 to 0.83	Fair to good

Table 1. Familial Risk Tools to Predict Individual Risk for *BRCA1/2* Mutations in Primary Care Settings*

Model	Data collection and calculation	Population (N)	Relatives with breast and ovarian cancer	Other factors	Comparison with other models	Reference standard	Performance characteristics for predicting risk for *BRCA1/2* mutations	Quality Rating
Pedigree Assessment Tool (PAT)[119, 124]	Assigns points for responses to 5 items; referral threshold ≥8 points (≥10% mutation probability)	Developed in 3906 women without breast cancer presenting for screening mammography at a US community hospital; evaluated in families in US (520 families)	1st, 2nd, 3rd degree	Breast cancer age ≤50 or >50; ovarian cancer at any age; male breast cancer; Ashkenazi Jewish ancestry	Myriad II, Penn II,	Mutation testing; Myriad II	Mutation testing as reference standard (≥10% mutation probability): sensitivity 95.9%; specificity 20.1%; PPV 0.319; NPV 0.926; AUC 0.705; Myriad II as reference standard (≥10% mutation probability): sensitivity 100%; specificity 93%; PPV 0.63; NPV 1.00; AUC 0.96	Fair
Referral Screening Tool (RST)[114, 214]	≥2 positive responses to 13 items is referral threshold (≥10% mutation probability)	Unselected women undergoing screening mammogram (2464 completed RST, 296 randomly evaluated)	1st, 2nd degree	Breast cancer age ≤50 (self or relatives); ovarian cancer at any age (self or relatives); ≥2 breast cancer cases age >50 on same side of family; male breast cancer; Jewish ancestry	None	Pedigree analysis and estimates of mutation risk based on models (BOADICEA; BRCAPRO; FHAT; Myriad II)§	≥10% mutation probability: sensitivity 81%; specificity 92%; PPV 0.80; NPV 0.92; AUC 0.87; revised version : AUC 0.90 (95% CI 0.85 to 0.95)	Good

*Individual clinical scoring instruments are detailed in Appendix C1 and quality ratings in Appendix B Table 1.
†BRCAPRO-LYTE applies the BRCAPRO model using only information on the numbers and types of first- and second-degree relatives, which relatives are affected with breast and ovarian cancer, and their ages of diagnosis; BRCAPRO-LYTE-plus does not collect data on ages of affected relatives, but imputes ages based on a large external dataset; BRCAPRO-LYTE-simple imputes the number of relatives for each type of cancer and ages of unaffected relatives.
‡Based on evaluation including pedigree analysis, lifetime risk estimates from established models (Claus; Gail; Tyrer-Cuzick; Penn II), American Society of Clinical Oncology criteria, and review by two clinical geneticists.
§Detailed four-generation cancer pedigrees analyzed using four established hereditary risk models (BRCAPRO, Myriad II, BOADICEA, FHAT), with a ≥10% *BRCA1/2* mutation probability or a FHAT score of ≥10 as the definition of "high risk."

Abbreviations: AUC=area under the receiver operating characteristic curve; BOADICEA=breast and ovarian analysis of disease incidence and carrier estimation algorithm; FHS-7=seven-question Family History Screening; FHAT=family history assessment tool; IBIS= International Breast Cancer Intervention Study Model; NPV=negative predictive value; PAT=pedigree assessment tool; PPV=positive predictive value; RST=referral screening tool; UK=United Kingdom

Table 2. Studies of Genetic Counseling

Author, year	N	Provider of genetic counseling	Setting	Measures	Quality rating
Current Review					
Albada et al., 2016[125]	89	Geneticists (including residents) and genetic counselors (including in training)	Cancer Genetics Service Center	NSI	NA
2013 Review					
Bennett et al., 2008[127]	128	Genetic counselor	Cancer Genetics Service Center	DUKE-SSQ, HADS, IES, MCMQ, NSI	NA
Bennett et al., 2009[128]	128	Genetic counselor	Cancer Genetics Service Center	DUKE-SSQ, IES, MCMQ	NA
Bloom et al., 2006[129]	163	Master's level counselor	Telephone counseling	NSI	Poor
Bowen et al., 2002[66,*]	354	Genetic counselor or trained health counselor	NR	NSI	Fair
Bowen et al., 2004[71,*]	354	Genetic counselor or trained health counselor	NR	NSI	Fair
Bowen et al., 2006[130]	221	Psychologist, genetic counselor	University	BSI, NSI	Fair
Brain et al., 2002[131,†]	740‡	Clinical geneticist and genetic nurse specialist	NR	NSI, STAI	Good
Brain et al., 2011[132,†]	263	Clinician	NR	CWS-R	NA
Braithwaite et al., 2005[133]	72	Clinical nurse specialist	NR	HADS, NSI, STAI	Fair
Burke et al., 2000[67]	356	Genetic counselor	Medical office	NSI	Fair
Cull et al., 1998[68,§]	144‡	Geneticist and breast surgeon	Breast cancer family clinic	GHQ, NSI, STAI	Good
Fry et al., 2003[134]	263	Genetics consultant and specialist breast surgeon vs. Geneticist and genetics nurse specialist	Familial Breast Cancer Clinic	CWS	Fair
Gurmankin et al., 2005[135]	125	Health care provider	University breast and ovarian cancer risk evaluation program	NSI, STAI	NA
Helmes et al., 2006[136]	340‡	Board certified genetic counselor	NR	NSI	Fair
Hopwood et al., 1998[137]	174	Family History Clinics	Family history clinics	GHQ, NSI, PAS	Fair
Hopwood et al., 2004[138]	256	Genetic counselor	Cancer Genetics Service Center	CWS, GHQ, NSI	NA
Kelly et al., 2008[139]	78	Genetic counselor	NR	NSI	NA

Table 2. Studies of Genetic Counseling

Author, year	Breast cancer worry Increase	Breast cancer worry Decrease	Anxiety Increase	Anxiety Decrease	Depression Increase	Depression Decrease	Risk perception More accurate	Risk perception Less accurate	Intent to participate in testing Increase	Intent to participate in testing Decrease
Current Review										
Albada et al., 2016[125]	NR	NR	NR	NR	NR	NR	NR	0‖	NR	NR
2013 Review										
Bennett et al., 2008[127]	0	X	0	0	0	0	NR	NR	NR	NR
Bennett et al., 2009[128]	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bloom et al., 2006[129]	0	0	NR	NR	NR	NR	0	0	NR	NR
Bowen et al., 2002[66,*]	NR	NR	NR	NR	NR	NR	NR	NR	0	X
Bowen et al., 2004[71,*]	0	0	0	X	0	0	X	0	NR	NR
Bowen et al., 2006[130]	0	X¶	NR	NR	NR	NR	X**	0	0	X**
Brain et al., 2002[131,†]	0	X††	0	X	NR	NR	X	0	NR	NR
Brain et al., 2011[132,†]	0	X‡‡	NR	NR	NR	NR	NR	NR	NR	NR
Braithwaite et al., 2005[133]	0	X§§	0	X‖ ‖	NR	NR	X¶¶	0	NR	NR
Burke et al., 2000[67]	0	0	NR	NR	NR	NR	X	0	NR	X
Cull et al., 1998[68,§]	NR	NR	0	0	0	0	X***	X†††	NR	NR
Fry et al., 2003[134]	0	X	NR	NR	NR	NR	X	0	NR	NR
Gurmankin et al., 2005[135]	NR	NR	NR	NR	NR	NR	X§§	0	NR	NR
Helmes et al., 2006[136]	0	X‡‡‡	NR	NR	NR	NR	X‡‡‡	0	0	X‡‡‡
Hopwood et al., 1998[137]	0	0	0	0	NR	NR	X	0	NR	NR
Hopwood et al., 2004[138]	0	X	0	0	NR	NR	0	0	NR	NR
Kelly et al., 2008[139]	NR	NR	NR	NR	NR	NR	0	X§§	NR	NR

Table 2. Studies of Genetic Counseling

Author, year	N	Provider of genetic counseling	Setting	Measures	Quality rating
2013 Review					
Lerman et al., 1996[140]	227	Genetic counselor	Cancer centers	IES	Fair
Lerman et al., 1999[69]	364	Oncology nurses or genetic counselor	Hospital cancer center	IES	Fair
Lobb et al., 2004[141]	193	Clinical geneticists, an oncologist, and genetic counselors.	Not reported	HADS, IES, NSI	Good
Matloff et al., 2006[142]	64‡	Certified genetic counselor	Not reported	NSI	Fair
Mikkelsen et al., 2007[143,§§§]	1971	Physicians	Clinical department	IES	Fair
Mikkelsen et al., 2009[144,§§§]	1971	Physicians	Clinical department	HADS	Fair
Pieterse et al., 2011[145]	77‡	Clinical geneticists, residents in clinical genetics, genetic counselors	Department of medical genetics	IES, NSI, PPC, STAI, VAS	NA
Roshanai et al., 2009[146]	163	Specialist nurse	Cancer genetic clinic	HADS, SPIKES	Fair
Watson et al., 1998[148]	115	Clinical geneticist	Hospitals	CWS, GHQ-12, VAS	Good
Watson et al., 1999[149]	283	Clinical geneticists	In genetic counseling centers	GHQ, IES, NSI, STAI	Good

Table 2. Studies of Genetic Counseling

Author, year	Breast cancer worry Increase	Breast cancer worry Decrease	Anxiety Increase	Anxiety Decrease	Depression Increase	Depression Decrease	Risk perception More accurate	Risk perception Less accurate	Intent to participate in testing Increase	Intent to participate in testing Decrease
2013 Review										
Lerman et al., 1996[140]	0	0	NR	NR	NR	NR	X	0	NR	NR
Lerman et al., 1999[69]	0	0	NR	NR	NR	NR	NR	NR	X‖ ‖ ‖	0
Lobb et al., 2004[141]	NR	NR	0	0	0	0	0	0	NR	NR
Matloff et al., 2006[142]	NR	NR	NR	NR	NR	NR	X¶¶¶	0	NR	NR
Mikkelsen et al., 2007[143, §§§]	NR	NR	NR	NR	NR	NR	0****	0	NR	NR
Mikkelsen et al., 2009[144, §§§]	0	X	0	0	0	0	NR	NR	NR	NR
Pieterse et al., 2011[145]	NR	NR	0	X	NR	NR	X	0	NR	NR
Roshanai et al., 2009[146]	NR	NR	0	X	0	X	X††††	0	NR	NR
Watson et al., 1998[148]	0	0	0	0	0	0	X‡‡‡‡	0	NR	NR
Watson et al., 1999[149]	0	0	0	0	NR	NR	0	0	NR	NR

X=significant relationship; 0=studied, but not significant
*Studies use the same population (Bowen, 2002 and Bowen, 2004)
†Brain, 2011 uses the moderate risk group from Brain, 2002
‡Randomized
§Study done in a country other than the United States (e.g. The Netherlands, Scotland, Australia, or England)
‖1 year after counseling fewer women had accurate risk perception vs. immediately after counseling (34.6% vs. 48.6%)
¶Both intervention groups vs. control group
**Both treatment groups vs. control group
††Women at low- and moderate-risk decreased, while those at high-risk did not
‡‡Significant affect was observed immediately after, by 9 months affect was gone
§§Pre vs. post
‖‖Pre vs. post; and A vs. B
¶¶For counseling vs. GRACE
***Both treatment groups at treatment end
†††Video after counseling subjects at 1 month followup
‡‡‡Both intervention groups long-term
§§§Studies use the same population (Mikkelsen, 2007 and Mikkelsen, 2009)
‖ ‖ ‖African American subjects only
¶¶¶Time effect - change from pre- to post
****Interventions vs. control
††††At 2 week followup; NS by 8 months
‡‡‡‡Risk provided as odds ratio

Abbreviations: BSI=Brief Symptom Inventory; CWS=Cancer Worry Scale; CWS-R=Cancer Worry Scale- Revised; DUKE-SSQ=Duke Social Support Questionnaire; GHQ=General Health Questionnaire; GHQ-12=12-item General Health Questionnaire; HADS=Hospital Anxiety and Depression Scale; IES=Impact of Event Scale; MCMQ=Medical Coping Modes Questionnaire; NA=rating criteria not available; NR=not reported; NSI=Non Standard Instrument; PAS=Psychiatric Assessment Schedule;

Table 2. Studies of Genetic Counseling

PPC=Perceived Personal Control; SPIKES=Setting, Patient's perception, Invitation, Knowledge, Exploring/Empathy, Strategy/Summary; STAI=State-Trait Anxiety Inventory; VAS=Visual Analog Scale

Table 3. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Current Review			
Albada et al., 2016[125]	Cancer Genetics Service Center	Geneticists (including residents) and genetic counselors (including in training)	Dutch Breast Cancer guidelines, personal risk estimate (if enough data was available), no other information described
2013 Review			
Armstrong et al., 2005[126]	Not reported	Not reported	Genetic counseling not specified.
Bennett et al., 2008[127]	Cancer Genetics Service Center	Genetic counselor	Women with family history of breast/ovarian cancer referred by general practitioner or other medical specialists into the service. After assessment of information in family health questionnaire by genetic specialists, individual genetic risk of developing familial breast and ovarian cancer was calculated as a percentage of lifetime risk and stratified into high, moderate and "population" risk levels. Women considered high risk for breast/ovarian cancer were offered counseling, genetic testing, and annual mammography; women at moderate risk were offered annual mammography.
Bennett et al., 2009[128]	Cancer Genetics Service Center	Genetic counselor	See Bennett et al., 2008[126]
Bloom et al., 2006[129]	Telephone counseling	Master's level counselor	Telephone counseling session included: establishment of rapport and determination of special concerns, emotional readiness, risk notification by providing modified Gail model lifetime risk estimate and discussing in terms of her pre-test self-assessment of risk, de-escalation of tension regarding breast cancer check-up, evaluation of coping skills, reinforcement of problem solving and coping skills; information on health protective behaviors, early detection through American Cancer Society screening, and information on genetic testing when requested.
Bowen et al., 2002[66]	Not reported	Genetic counselor or trained health counselor	**Individual genetic counseling**: telephone contact with genetic counselor to review pedigree information and 1 2-hour session following protocol based on standard genetic practice, with a letter sent to participant within 2 weeks summarizing the session. **Group psychosocial counseling:** group of 4 to 6 participants met for 4, 2-hour sessions with trained health counselor, participants received risk assessment sheet, personalizing the group discussion to her own risk status, main topics: risk assessment, perception, screening, stress management and problem solving, and social support.
Bowen et al., 2004[71]	Not reported	Genetic counselor or trained health counselor	See Bowen et al, 2002[65]

Table 3. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Bowen et al., 2006[130]	University	Psychologist, genetic counselor	**Group psychological counseling:** psychologist led 4 2-hour, weekly sessions of 5-6 women per group, with each session including a 20-min group cohesion activity followed by 1 of 4 major intervention components: risk assessment and perception, education, stress management, and problem solving and social support. **Individual genetic counseling:** genetic counselor provided 1-hour counseling sessions and sessions covered several topics, including participant's family background, breast cancer risk assessment, *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population, non-genetic risk factors for breast cancer, and breast screening.
Brain et al., 2002[131]	Not reported	Clinical geneticist and genetic nurse specialist	Breast cancer surveillance, option to enter U.K. Tamoxifen Prevention Trial, annual surgical followup with surveillance and advice, genetic risk assessment and counseling.
Brain et al., 2011[132]	Not reported	Clinician	Women with a family history of breast cancer receive a specialist genetic assessment service. Control group received general risk level (low/population, moderate, or high) based on age, reproductive history and minimal family history; Intervention group received a specific percentage based on Claus model based on detailed family pedigree; genetic testing was available to women in Intervention group at high risk (≥ 25% risk).
Braithwaite et al., 2005[133]	Not reported	Clinical nurse specialist	**Risk counseling:** received pedigree with information from family history and assessed risk as low, moderate, or high based on GRACE guidelines, and participants were mailed letters summarizing content afterward. **GRACE:** completed pedigrees in GRACE and assessed their risk, learning their risk assessment and how to manage their risk, they received a numerical estimate of lifetime risk, a visual display of cumulative risk with general population as comparator, and a qualitative description, the clinical nurse specialists then offered to book mammography and arrange meetings with geneticists, where appropriate.
Burke et al., 2000[67]	Unclear	Genetic counselor	Adapted genetic counseling protocol for women with intermediate risk included pre-counseling telephone call gathering a complete family history, in-person genetic counseling session discussing breast cancer risk factors, focusing on issues relevant to the participant, reviewed pedigree information, communicated likelihood of mutation in participant's family, risk estimate sheet given to participant based on the Gail and Claus models and National Cancer Institute statistics for average risk, information about genetic testing, recommendations for breast cancer screening, and a followup letter summarizing the genetic counseling session.
Cull et al., 1998[68,*]	Breast cancer family clinic	Geneticist and breast surgeon	Individual meeting with geneticist to discuss individual risk and with breast surgeon to discuss risk management, participants either received a copy of the educational video about 10 days before the clinic consultation or took the video home after the post-clinic assessment.

Table 3. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Fry et al., 2003[134]	Familial Breast Cancer Clinic	Genetics consultant and specialist breast surgeon; Geneticist and genetics nurse specialist	**Standard (regional) service:** self-report family history and baseline questionnaire completed by all women; genetics consultant and genetics nurse specialist assigned categorical risk via Cancer Research Campaign. Women at low risk received a letter; women at moderate or high risk were offered an appointment at familiar breast cancer clinic where a genetics consultant discussed risk status and breast surgeon discussed risk management. Where appropriate, clinical exams and mammography were included in the appointment. Patients' general practitioners received summary data, and patients received followup questionnaires 4 weeks and 6 months later. **Novel (Community-based) service:** all women sent an appointment for a community-based clinic near their residence. Meetings run by genetics nurse specialist where family history was collected and compared to published criteria (Cancer Research Campaign) to determine risk. Women at low risk offered information, reassurance, and discharged. Women at increased risk (moderate or high) were offered an appointment at a regional center with a geneticist and genetics nurse specialist, and asked to complete followup questionnaires at 4 weeks and 6 months.
Gurmankin et al., 2005[135]	University breast and ovarian cancer risk evaluation program	Health care provider	**Pre-counseling interview:** assessed patient's breast cancer risk perception, BRCA mutation risk perception, worry about breast cancer, family history of cancer, breast cancer risk reduction behaviors, and demographic information. **Post counseling interview:** assessed patient's breast cancer risk, BRCA mutation risk, recall of actual risk information, and worry about breast cancer.
Helmes et al., 2006[136]	Not reported	Board certified genetic counselor	**In-person counseling:** review of family history, discussion of breast cancer risk, and education about breast cancer genes, discussed genetic testing considerations, including implications of results, testing strategies, potential risks and benefits of test, costs and psychological effects of test, gave information packet with personal risk information comparing woman's risk with average woman's risk, personal computer-drawn 3-generation pedigree, brochures on self-breast exams, pap test, and mammography; genetics visual aids, and list of community resources. **Telephone counseling:** information packet was sent in the mail with instructions to open at the beginning of the telephone counseling, which was identical in content and structure to in-person counseling.
Hopwood et al., 1998[137]	Family history clinics	Unclear	Family history consultation, not otherwise described.
Hopwood et al., 2004[138]	Cancer genetic service centers	Genetic counselor	Genetic counseling prior to testing varied by participating center, but offered or recommended some of the following: risk estimation (based on molecular genetic analysis or more often on family history), genetic risk counseling, clinical examination, screening/surveillance for early tumor detection (mammography, endoscopy, etc.), information on preventative strategies (surgery, diet, etc.), family planning advice, and referral for psychological assessment/support.
Kelly et al., 2008[139]	Not reported	Genetic counselor	Review of family cancer history, personal risk factors for breast and ovarian cancer, mechanisms of cancer inheritance, meaning of a positive and negative test result, and risks and benefits associated with testing.

Table 3. Types of Genetic Counseling Provided in Included Studies

Author, year	Setting	Provider of genetic counseling	Components of genetic counseling
Lerman et al., 1996[140]	Comprehensive cancer centers	Genetic counselor	Discussion of individual factors contributing to elevated risk, presentation of individualized risk data, recommendations for annual mammography and clinical breast exams, and instruction in breast self-exam.
Lerman et al., 1999[69]	Hospital and cancer center	Oncology nurses or genetic counselor	**Education only:** topics discussed included individual risk factors for breast and ovarian cancer and patterns of inheritance for breast and ovarian cancer susceptibility, subjects given qualitative estimates of risk of developing breast and ovarian cancer, and pedigrees reviewed, potential benefits, limitations, and risks of genetic testing for inherited breast and ovarian cancer susceptibility reviewed. **Education plus counseling:** provided the same education and materials described above and subjects were guided through questions exploring personal issues related to cancer and genetic testing, discussed the emotional impact of having a family history of cancer, psychosocial implications of genetic testing for inherited breast and ovarian cancer susceptibility, anticipated reactions to positive and negative test result, and intentions to communicate test results to family members and friends.
Lobb et al., 2004[141]	Not reported	Clinical geneticists, an oncologist, and genetic counselors	Counselors provided counseling at their discretion and study was to assess the different aspects of counseling, which included information giving concerning: breast cancer genetics, genetic testing, family history and risk, prophylactic surgery, breast cancer prevention, screening and management; communication style including: facilitating patient involvement, facilitating understanding, patient centeredness and partnership building, and supportive and counseling communications.
Matloff et al., 2006[142]	Not reported	Certified genetic counselor	Personalized letter summarizing patient data.
Mikkelsen et al., 2007[143]	University clinical departments	Physicians	Information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer.
Mikkelsen et al., 2009[144]	University clinical departments	Physicians	See Mikkelsen et al., 2007[137]
Pieterse et al., 2011[145]	Department of medical genetics	Clinical geneticists, residents in clinical genetics, genetic counselors	Session topics included family's occurrence of breast and other cancers, inheritance, and criteria on probability of inherited breast cancer, and the likelihood of hereditary breast cancer running in the family was estimated.
Roshanai et al., 2009[146]	University cancer genetic clinic	Specialist nurse	Included pedigree explanation, Buckman's Breaking Bad News model to inform at-risk relatives, pamphlet, videotape, copies of pedigree, and medical records.
Watson et al., 1998[148]	Hospitals	Clinical geneticist	Consultation provided information on pedigree based on risk calculation and information regarding management options based on risk level, with instructions offered on self-exam and clinical exam, with the intervention group also receiving an audiotape of the consultation to take home.
Watson et al., 1999[149]	Genetic counseling centers	Clinical geneticists	Not described.

Abbreviations: BRCA=breast cancer susceptibility gene; GRACE=Genetic Risk Assessment in the Clinical Environment; U.K.=United Kingdom

Table 4. Standardized Measures Used to Assess Distress

Measure	Abbreviation	Description
Beck Depression Inventory[247]	BDI	A 21-question multiple-choice self-report inventory for measuring the severity of depression. Scores of 0 to 9 indicate minimal depression, 10 to 18 mild depression, 19 to 29 moderate depression, 30 to 63 severe depression.
Beck Hopelessness Scale[269]	BHS	A 20-item scale to quantify hopelessness with scores ranging from 0 to 20 and a score above 9 indicating suicidal ideations.
Body Image after Breast Cancer[246]	BIBC	A 53-item questionnaire to assess the long term impact of breast cancer on body image in 6 key areas: vulnerability, body stigma, limitations, body concerns, transparency, arm concerns.
Body Image Scale[256]	BIS	A 10-item questionnaire for assessing body image changes in patients with cancer.
Brief Symptom Inventory[253]	BSI	A 53-item self-reported psychological symptom scale.
Center for Epidemiologic Studies-Depression[266]	CES-D	Measures symptoms of depression on a 20-item scale with scores ranging from 0 to 60; scores above 15 indicating high levels of depressive symptoms.
Coping Orientation to Problems Experienced Scale[253]	COPE	Covers 14 coping strategies as potential responses to stressors.
Decision Regret Scale[250]	DRS	A 5-item questionnaire to measure dissatisfaction or misgiving after making a medical decision.
DUKE Social Support Questionnaire[262]	DUKE-SSQ	Used to measure access to and satisfaction with social support on 8 items with scores ranging from 1 to 5. Affective subscale (DUKE-SSQ-A) includes items 1, 2, & 8; confident subscale (DUKE-SSQ-C) includes items 3 to 7.
Emotional Approach Coping Scale[268]	None	A 52-item questionnaire to measure both problem-solving (items 1-20) and emotion based (items 21 to 32) coping strategies. An additional 4 questions pertain to alcohol and drug use.
EuroQoL-5 Dimensions[260]	EQ-5D	A short, self reported questionnaire designed to evaluate an individual's state of overall health in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
General Health Questionnaire[258]	GHQ	A 60-item questionnaire to screen individuals for psychiatric disorders, scores are given as means and scores above 3 indicate disorders; a 30-item version of the same questionnaire uses a threshold of 6 to indicate general psychological distress.
Health Anxiety Inventory[264]	HAI score	The short version of the full Health Anxiety Inventory used to measure health anxiety.
Health-Related Quality of Life[243]	HR-QOL	A 14-item self-report questionnaire to assess an individual's quality of life based on: healthy days (items 1 to 4), activity limitations (items 5-9), and symptoms (items 10 to 14).
Hospital Anxiety and Depression Scale[249]	HADS	A 14-item self-report scale for the detection of depression and anxiety in hospitalized patients. Scores range from 1 to 21 interpreted as: normal (0 to 7), mild (8 to 10), moderate (11 to 14), severe (15 to 21). Subscales for anxiety (HADS-A) and depression (HADS-D).
Impact of Events Scale[275, 257]	IES	A 15-item or 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition. Scores range from 0 to 75, scores 9 to 25 indicate moderate difficulties and above 26 indicate clinical adaptation difficulties. Several variations are also used: Impact of Events Scale Revised (IES-R) 22-items (items A-V); Impact of Events Subscale- Intrusive Events (IES-I) items: A, B, C, F, I, N, P, T; Impact of Events Subscale-Avoidance (IES-A) items: E, G, H, K, L, M, Q, V; Impact of Events Subscale-Hyper arousal (IES-H) items: D, J, O, R, S, U.
Lerman Breast Cancer Worry Scale[259]	CWS or LCWS	A 3-item questionnaire to measure how frequently an individual worries about getting breast cancer, and the impact of worrying on mood and performance of daily activities. A 6-item version of the same questionnaire has scores ranging from 6 to 24; higher scores mean greater levels of worry

Table 4. Standardized Measures Used to Assess Distress

Measure	Abbreviation	Description
Medical Coping Modes Questionnaire[267]	MCMQ	A 19-item self-report questionnaire to quantify coping styles into 1 of 4 categories: confrontive, avoidant, resigned, nondominant
Medical Outcomes Study 36-Item Short Form[261] 12-Item Short Form[273] Swedish Short Term-36 Health Survey[271]	SF-36 or MOS SF-36	A 36 question health questionnaire for measuring health and well being in 8 core areas: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, mental health. The 12-item Short Form and Swedish Short Term-36 Health Survey are two of many variations.
Menopause-Specific Quality of Life Questionnaire[263]	MENQOL	A 29-item self-administered questionnaire to assess health-related quality of life post-menopause.
Multidimensional Impact of Cancer Risk Assessment[252]	MICRA	A measure of the impact of genetic test result disclosure in terms of distress, uncertainty , and positive –experience scales
Multidimensional Fatigue Symptom Inventory-Short Form[270]	MFSI-SF	A 30-item questionnaire to measures perceived sleep disturbance.
Perceived Personal Control scale[248]	PPC	A measure of genetic counseling outcomes, assesses counselees' perceptions of the degree of control they have over their genetic condition.
Pittsburgh Sleep Quality Index[254]	PSQI	A measure of subjective sleep disturbance in clinical populations.
Post-Traumatic Growth Inventory[245]	PTGI	An instrument for assessing positive outcomes reported by persons who have experienced traumatic events.
Satisfaction with Decision Scale[255]	SWD	A 6-item scale that measures satisfaction with health care decisions.
Sexual activity questionnaire[272]	SAQ	A 3 section self-reported questionnaire to assess sexual functioning, including: hormonal status, reasons for sexual inactivity, sexual functioning.
State-Trait Anxiety Inventory[244]	STAI	Measures an individual's current anxiety feelings. Scores range from 10 to 40. Scores above 22 indicate high anxiety.
Symptom Checklist-90[265]	SCL-90	A 90 question self-reported questionnaire to assess psychological status in the following categories: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.
Visual Analogue Scale[274]	VAS	Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale (no pain to worst pain ever experienced).

Table 5. Studies of Distress After Genetic Testing

Author, year Quality rating	N, study design	Mutation status	Genetic counseling	Comparison	Measures	Breast cancer worry	Anxiety	Depression
Current Review								
Andrews et al., 2004[150] Fair	60; pre-post	Positive or negative	Not described	A) Pretest (n=49) B) 7 to 10 days post results (n=31) C) 4 months post results (n=32) D) 12 months post results (n=27)	BDI, IES, STAI	0 A vs. B X decrease C & D vs. A	0	0
Lieberman et al., 2017[161] Good	1771; prospective cohort	Positive or negative	Low risk noncarriers received a letter including test results and routine surveillance recommendations; high risk noncarriers received in-person genetic counseling;	A) Carriers (n=19) B) Noncarriers (n=604) C) Self-referral (n=398) D) Recruited (n=417)	IES, PPC, STAI, SWD	X higher A vs. B & C vs. D	X higher A vs. B 0 C vs. D	NR
Lumish et al., 2017[163] Fair	103; prospective cohort	Positive or negative	Unknown	A) Carriers (n=14) B) Noncarriers (n=69) C) VUS (n=20)	IES, MICRA, SWD	X higher A vs. B & C	NR	NR
Manchanda et al., 2015[164] Good	1017; RCT	Positive or negative	Qualified genetic counselor with supervision from Regional Genetics Centre and a clinical fellow with experience in cancer genetics and management; structured to meet the goals of genetic counseling and cancer risk assessment.	A) FH-based strategy for testing B) Population-based strategy	HADS, HAI score, MICRA, SF-12	NR	0	0
Smith et al., 1999[170] Good	125,* prospective cohort	Positive or negative	Not described	A) Carrier (n=47) B) Noncarriers (n=78)	IES	X higher A vs. B	NR	NR
2013 Review								
Arver et al., 2004[151] NA	63; pre-post	Positive or negative	Genetically trained oncologist and oncology nurse	A) Pretest B) 2 months post results C) 1 year post results	HADS, SF-36	NR	X decrease C & B vs. A	0
Dagan and Shochat, 2009[152] Fair	73; case-control	Positive or negative	Unknown	A) Carriers (n=17) B) Noncarriers (n=20) C) Age-matched controls (n=36)	BSI, CRW, HR-QOL	X higher A & B vs. C	0	0

Table 5. Studies of Distress After Genetic Testing

Author, year Quality rating	N, study design	Mutation status	Genetic counseling	Comparison	Measures	Breast cancer worry	Anxiety	Depression
Ertmanski et al., 2009[153] NA	56; pre-post	Positive	Unknown	A) Pretest B) 1 month post results C) 1 year post results	IES, STAI	NR	0	NR
Foster et al., 2007[154] Fair	154; prospective cohort	Positive or negative	Unknown	A) Carriers (n=53) B) Noncarriers (n=101)	CWS-R, GHQ	X decrease over time for A & B	X increase over time for A & B	NR
Geirdal et al., 2005[156,†] Good	10,244; prospective cohort	Positive or unknown	Unknown	A) Positive (n=68) B) Not tested but FBOC (n=176) C) Not tested, age-matched controls (n=10,000)	BHS, GHQ, HADS, IES	NR	X higher B vs. A	X higher B vs. A
Geirdal and Dahl, 2008[155,†] Good	242; prospective cohort	Positive or unknown	Unknown	A) Positive (n=68) B) Not tested, but FBOC (n=174)	COPE, HADS	NR	X higher B vs. A	NR
Low et al., 2008[162] Fair	47; prospective cohort	Positive, true negative, or uncertain (grouped with true negative)	Genetic counselor	A) Positive (n=7) B) True negative + uncertain (n=40)	COPE, IES-R, PTGI	NR	X higher A vs. B	NR
Meiser et al., 2002[165] Good	143 prospective cohort	Positive or negative	Unknown	A) Carriers (n=30) B) Noncarriers (n=59) C) Not tested (n=51)	BDI, IES, MBSS, NSI, STAI	X higher A vs. C	X lower B vs. A & C	X lower B vs. A & C
Metcalfe et al., 2012[166] NA	17; pre-post	Positive	Unknown	A) Pretest B) 1 year post results C) 2 years post results	IES	X increase B vs. A & C	NR	NR
Reichelt et al., 2004[167,‡] Good	209; prospective cohort	Positive, negative, or unknown	Medical geneticist or experienced genetic counselor	A) Carriers (n=141) B) Noncarriers (68)	BHS, GHQ, HADS, IES	NR	0	0
Reichelt et al., 2008[168,‡] NA	181; pre-post	Positive or true negative	Genetic counselor	A) Pretest B) 6 weeks post results C) 18 months post results	HADS, IES	NR	0	0
van Dijk et al., 2006[171] Good	132; prospective cohort	Positive, true negative, or uninformative	Unknown	A) Positive (n=22) B) True negative (n=41) C) Uninformative (n=69)	IES, NSI	X higher A vs. B & C	X higher A vs. B & C	NR

Table 5. Studies of Distress After Genetic Testing

X = statistically significant; 0 = studied but not significant

*The study included 87 males which are described in the evidence table and text, but not on this table.
†Studies use the same population (Geirdal et al,, 2005 and Geirdal and Dahl, 2008)
‡Studies used the same population (Reichelt et al., 2004 and Reichelt et al., 2008)

Abbreviations: BDI=Beck Depression Inventory; BHS=Beck Hopelessness Scale; BSI=Brief Symptom Inventory; COPE=Emotional Approach Coping Scale; CRW=Cancer-Related Worry Scale; CWS-R=Cancer Worry Scale-Revised; FBOC=familial breast and/or ovarian cancer; GHQ=General Health Questionnaire; HADS=Hospital Anxiety and Depression Scale; HR-QOL=Health Related-Quality of Life; IES=Impact of Events Scale; IES-R=Impact of Events Scale-Revised; MICRA=Multi-dimensional Impact of Cancer Risk Assessment; MBSS=Miller Behavioral Style Scale; MICRA=Multidimentsional Impact of Cancer Risk Assessment; NA=not applicable; NR=not reported; NSI=not standardized instrument; PPC=Percieved Personal Control; PTGI=Post-Traumatic Growth Inventory; SF-36=Swedish SF-36 Health Survey; STAI=State-Trait Anxiety Inventory; SWD=Satisfaction with Decision Instrument; VUS=variant of uncertain significance

Table 6. Studies of Test Characteristics of Mammography Versus MRI for Breast Cancer Screening*

Author, year	Risk categories, *n*	Inclusion criteria	Mean age at entry, years (range)	Screening interval	Followup, months	Mutation status	Mammography vs. MRI Sensitivity, %	Mammography vs. MRI Specificity, %
Breast Cancer								
Current Review								
Vreeman et al., 2018[215]	*BRCA1*: 471 *BRCA2*: 299 All participants: 2773	BRCA carrier Positive FH of breast cancer Personal history of breast cancer Other (e.g. history of radiation, high-risk lesions)	*BRCA1*: 39 (23 to 75) *BRCA2*: 41 (23 to 73)	Annual	NR (retrospective)	*BRCA1* *BRCA2*	45 vs. 63; C=66 36 vs. 67; C=70	98 vs. 95; C=94 98 vs. 94; C=94
2013 Review								
Cortesi, et al., 2006[218]	Mutation carrier: 48 High: 674 Intermediate: 257 Slight increase: 346	BRCA carrier Positive FH Male breast cancer Suspected positive FH	42 (20 to 75) 42 (15 to 75) 43 (19 to 67) 40 (18 to 75)	Varied by risk category and age	Median 55	Mutation carrier†	50 vs. 100	NR
Leach, 2005[203] MARIBS study	*BRCA1*: 39 *BRCA2*: 86 High: 424	*BRCA1* carrier/relative *BRCA2* carrier/relative FH positive/other mutation/syndrome	Median 40 (31 to 55)	Annual	Variable, ≥2 scans per woman	*BRCA1* *BRCA2* All women	23 vs. 92‡; C=92 50 vs. 58; C=92 40 vs. 77‡; C=94	92 vs. 79‡; C=74 94 vs. 82‡; C=78 93 vs. 81‡; C=77
Le-Petross, et al., 2011[204]	*BRCA1*: 37 *BRCA2*: 36	*BRCA1* carrier/relative *BRCA2* carrier/relative	Median 44 (23 to 75)	Bi-annual, alternating	Median 24	*BRCA1/2*	Unable to report§ vs. 92	82 vs. 87
Rijnsburger, et al., 2010[219] Dutch MRISC study	*BRCA1*: 422 *BRCA2*: 172 High: 1069 Moderate: 489 Other: 5	*BRCA1* carrier *BRCA2* carrier 30 to 50% lifetime risk for BC‖ (high-risk) 15 to 30% lifetime risk for BC‖ (moderate-risk) Other mutation carrier	*BRCA1*: 39 *BRCA2*: 40 High-risk: 41 Moderate risk: 40	Annual	48	*BRCA1* *BRCA2* High Moderate	25 vs. 67‡ 62 vs. 69 46 vs. 77 47 vs. 67	95 vs. 91 94 vs. 92 95 vs. 89 95 vs. 90

*Includes women from families with known mutations or breast cancer
†MRI was not used to screen other risk categories
‡$p<0.05$
§All screen-detected cancers were detected by MRI only, mammography was not performed after detection with MRI to calculate sensitivity
‖Based on modified Claus tables

Abbreviations: BC=breast cancer; BRCA=breast cancer susceptibility gene; C=mammography plus MRI; FH=family history; MARIBS=Magnetic Resonance Imaging Breast Screening; MRI=magnetic resonance imaging; MRISC=Magnetic Resonance Imaging Screening Study; NA=not applicable; NR=not reporte

Table 7. Meta-Analysis of Results of Placebo-Controlled Trials of Risk-Reducing Medications—Benefits[77]

Outcome	RR for tamoxifen vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with tamoxifen (95% CI), *n*‡	RR for raloxifene vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with raloxifene (95% CI), *n*‡	RR for AIs vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with AIs (95% CI), *n*‡
Breast cancer												
Invasive	0.69 (0.59 to 0.84)	4	4.58 ± 0.96	7 (4 to 12) fewer	0.44 (0.24 to 0.80)	2	3.19 ± 0.59	9 (3 to 15) fewer	0.45 (0.26 to 0.70)	2	5.90 ± 0.64	16 (8 to 24) fewer
ER+	0.58 (0.42 to 0.81)	4	3.62 ± 0.76	8 (4 to 13) fewer	0.33 (0.15 to 0.70)	2	2.45 ± 0.42	8 (4 to 13) fewer	0.37 (0.19 to 0.63)	2	4.55 ± 0.53	15 (8 to 20) fewer
ER−	1.18 (0.93 to 1.53)	4	–	–	1.25 (0.60 to 2.58)	2	–	–	0.79 (0.35 to 1.79)	2	–	–
Noninvasive	0.72 (0.56 to 1.41)§	4	–	–	1.47 (0.61 to 3.85)	2	–	–	0.46 (0.16 to 1.42)	2	–	–
Mortality												
Breast cancer	1.20 (0.79 to 1.79)	4	–	–	NR‖	–	–	–	NR	–	–	–
All-cause	1.07 (0.91 to 1.23)	4	–	–	0.90 (0.63 to 1.05)	2	–	–	1.02 (0.58 to 1.82)	2	–	–
Fracture												
Vertebral	0.75 (0.48 to 1.15)¶	1	–	–	0.61 (0.53 to 0.73)	2	3.45 ± 0.35**	7 (5 to 9) fewer	1.28 (0.59 to 2.75)	2	–	–
Nonvertebral	0.66 (0.45 to 0.98)¶	1	1.55 ± 0.20	3 (0.2 to 5) fewer	0.97 (0.86 to 1.12)	2	–	–	1.05 (0.87 to 1.28)	2	–	–

*Number of trials included in meta-analysis.
†Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.
‡Numbers of events reduced for benefits or increased for harms compared with placebo per 1000 women assuming 5 years of use.
§The RR was significantly reduced in NSABP P-1, 2005 (60 vs. 93 events; RR, 0.63 [CI, 0.45–0.89]).[221]
‖2 breast cancer deaths in 7,601 women for raloxifene vs. 0 in 7,633 women for placebo.[84, 225]
¶NSABP P-1, 2005.[221]
**Estimated from the placebo group of the RUTH trial, 2006.[231]

Abbreviations: AIs=aromatase inhibitors; CI=confidence interval; ER−=estrogen receptor–negative; ER+=estrogen receptor–positive; NR=not reported; NSABP=National Surgical Adjuvant Breast and Bowel Project; RR=risk ratio; RUTH=Raloxifene Use for the Heart; SE=standard error

Table 8. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Mastectomy							
Current Review							
Surgery vs. no surgery							
Flippo-Morton et al., 2016[174] Fair	*BRCA 1/2* carrier Female No malignancy other than breast ± ovarian cancer	*BRCA1* positive† n=123 *BRCA2* positive n=122 Both *BRCA1* and *BRCA2* positive n=1	Age at testing: >35: 59% (51/87) ≤35: 41% (36/87)	RRM vs. RRSO alone vs. surveillance (among patients without cancer diagnosis): 0/38 vs. NR vs. 5/36 HR NA	NR	NR	2.5
Heemskerk-Gerritsen et al., 2013[177] Fair	*BRCA 1/2* carrier No history of cancer, mastectomy, or oophorectomy	*BRCA1* positive: n=405 *BRCA2* positive: n=165	35 (median)	BRRM vs. surveillance: 0/1379 PYO vs. 57/2017 PYO HR NA	NR	BRRM vs. surveillance All-cause mortality (PYO): 6/2253 vs. 1/1384 HR 0.20 (0.02 to 1.68) Breast cancer mortality (PYO): 4/2253 vs. 1/1384 HR 0.29 (0.03 to 2.61)	8.5 vs. 6.3 (median)
2013 Review							
Surgery vs. no surgery							
Domchek et al., 2010[98] Fair	*BRCA 1* carrier No history of salpingo-oophorectomy	*BRCA1* positive n=415‡	37	0/43 vs. 19/372 HR NA	NR	NR	2.7
Domchek et al., 2010[98] Fair	*BRCA 2* carrier No history of salpingo-oophorectomy	*BRCA2* positive n=245§	39	0/32 vs. 15/213 HR NA	NR	NR	2.5
Skytte et al., 2011[183] Good	*BRCA1/ 2* carrier No history of mastectomy or salpingo-oophorectomy	*BRCA1* positive n=201 *BRCA2* positive n=10	NR	3/96 vs. 16/211 HR 0.39 (0.12 to 1.36)	NR	NR	NR‖

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Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Mastectomy							
2013 Review							
Surgery group (observed vs. expected)[¶]							
Evans et al., 2009[173,**] NA	Lifetime risk of breast cancer >25%	High-risk *BRCA1/2* positive[††] n=202	NR	0/307 vs. 21.3 HR NA	NR	NR	7.5
Mastectomy							
2013 Review							
Surgery group (observed vs. expected)[¶]							
Hartmann et al., 1999[175] Hartmann et al., 2001[176] NA	Family history of breast cancer	High risk n=214	42	3/214 vs. 37 expected[‡‡]; Risk reduction 92% (77 to 98%)	n=2	Breast cancer: 2/214 vs.10 expected[‡‡]; Risk reduction 81% (31 to 98%)	14 (median)
Hartmann et al., 1999[175] and 2001[176] (continued)	(continued)	Moderate risk n=425	42	4/425 vs. 37 expected[§§]; Risk reduction 89.5% (p<0.001)	n=0	Breast cancer: 0/425 vs. 10 expected[§§]; Risk reduction 100% (70 to 100%)	14 (median)
Hartmann et al., 1999[175] and 2001[176] (continued)	(continued)	*BRCA1* or *BRCA2* positive[‖‖] n=18	41	0/18 vs. 6.1/18 expected[¶¶]; Risk reduction 100% (51 to 100) 0/18 vs. 4.5/18 expected***; Risk reduction 100% (33 to 100%)	NR	NR	13.4 (median)
Salpingo-oophorectomy or oophorectomy							
Current Review							
Surgery vs. no surgery							
Heemskerk-Gerritsen et al., 2015[178] HEBON study Fair	*BRCA 1/2* carrier Female No history of cancer, mastectomy, or oophorectomy	*BRCA1* positive: n=589 *BRCA2* positive: n=233	Median age at start of study: RRSO: 44 Non-RRSO: 33	12.1% (42/346) vs. 9.9% (47/476) HR 1.09 (0.67 to 1.77) *BRCA1*: HR 1.21 (0.72 to 2.06) *BRCA2*: HR 0.54 (0.17 to 1.66) Age < 51: HR 1.11 (0.65 to 1.90) Age ≥ 51: HR 1.78 (0.52 to 6.15)	NR	NR	3.2 (median)

Table 8. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Kotsopoulos et al., 2017[179] Fair	*BRCA1/2* carrier Female No history of any cancer or BRRM	*BRCA1* positive: n=2969 *BRCA2* positive: n=725	Mean age at baseline Surgery: 46.2 No surgery: 33.4	Annual incidence, all women: 1.87% vs. 1.59%, HR 0.89 (0.69 to 1.14) Any age at diagnosis: *BRCA1*: HR 0.97 (0.73 to 1.29) *BRCA2*: HR 0.68 (0.38 to 1.21) Age <50y at diagnosis: *BRCA1*: HR 0.84 (0.58 to 1.21) *BRCA2*: HR 0.17 (0.05 to 0.61)	NR	NR	5.6
Mavaddat et al., 2013[180] EMBRACE study Fair	*BRCA1/2* carriers Female No breast or ovarian cancer history (reported here), or history of unilateral breast cancer	*BRCA1* positive: n=501 *BRCA2* positive: n=485	Age at enrollment: 41.2	5.8% (18/309) vs. 6.8% (46/679), HR 0.62 (0.35 to 1.09) *BRCA1*: HR 0.52 (0.24 to 1.13) *BRCA2*: HR 0.79 0.35 to 1.80) Age < 45: HR 0.39 (0.17 to 0.87) Age ≥ 45: HR 1.14 (0.50 to 2.61)	NR	NR	3.3

Table 8. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Rebbeck et al., 2002[181] Fair	*BRCA1/2* carriers Female No history of ovarian cancer or unilateral oophorectomy; for study of breast cancer, no history of breast cancer or mastectomy	*BRCA1* positive: n=459 *BRCA2* positive: n=94	Surgery: 42.0 No surgery: 40.9	21.2% (21/99) vs. 42.3% (60/142), HR 0.47 (0.29 to 0.77) Age < 35: HR 0.39 (0.15 to 1.04) Age 35 to 50: HR 0.49 (0.26 to 0.90) Age ≥ 50: HR 0.52 (0.10 to 2.70)	0.8% (2/259) vs. 19.9% (58/292), HR 0.04 (0.01 to 0.16) No history of breast cancer: HR 0.06 (0.01 to 0.25) Age 35 to 50: HR 0.03 (<0.01 to 0.20) Age ≥ 50: HR 0.11 (0.02 to 0.76)	NR	8.2 vs. 8.8
Shah et al., 2009[182] Fair	*BRCA1/2* carriers or mutation probability > 75% Female	*BRCA1* positive: n=51 *BRCA2* positive: n=41	47 at enrollment (median)	Any oophorectomy: 11% (9/80) vs. 15% (2/13), p=NS Oophorectomy ≤ 40 years: 12% (3/25) vs. 12% (8/68), p=NS	NR	NR	3.2 (median)

Table 8. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Salpingo-oophorectomy or oophorectomy							
2013 Review							
Surgery vs. no surgery							
Domchek et al., 2010[98,**] Fair	*BRCA1*carrier No history of salpingo-oophorectomy	*BRCA1* positive n=1003‡	42	14% (32/236) vs. 20% (129/633) HR 0.63 (0.41 to 0.96)	2% (6/342) vs. 7% (49/661) HR 0.31 (0.12 to 0.82)	All cause: 2% (8/327) vs. 7% (43/608) HR 0.52 (0.24 to 1.14)	5.6
Domchek et al., 2010[98,**] Fair (continued)	*BRCA2* carrier No history of salpingo-oophorectomy	*BRCA2* positive n=554§	46	7% (7/100) vs. 23% (94/401) HR 0.36 (0.16 to 0.82)	0/123 vs. 14/431 HR NA	All cause: 0/120 vs. 17/403 HR NA	5.8
Kramer et al., 2005[98,†††] Fair	*BRCA1*-positive family[§§]; No history of bilateral mastectomy	*BRCA1* positive n=98	NR	18% (6/33) vs. 42% (27/65) HR 0.38 (0.15 to 0.97)	NR	NR	16.5
Kramer et al., 2005[99,†††] Fair (continued)	*BRCA1*-negative family[§§]; No history of bilateral mastectomy	*BRCA1* negative n=353	NR	3% (1/34) vs. 1% (4/319) HR NR	NR	NR	16.5
Kramer et al., 2005[99,†††] Fair (continued)	*BRCA1*-positive family[§§]; No history of bilateral mastectomy	Undetermined mutation status n=222	NR	0/18 vs. 2.5% (5/204) HR NA	NR	NR	16.5

Table 8. Studies of Risk-Reducing Surgery

Author, year, quality rating	Inclusion criteria	Risk factors Enrolled, *n*	Mean age at surgery, years	Breast cancer incidence Risk estimate (95% CI)	Ovarian cancer incidence Risk estimate (95% CI)	Mortality Risk estimate (95% CI)	Mean followup*, years
Struewing et al.,1995[184] Poor	Families with ≥3 cases of ovarian cancer or ≥2 cases ovarian cancer and ≥1 case breast cancer before age 50	First-degree relatives of breast or ovarian cancer cases n=390 n=12 families	NR	3/44 vs. 14/346 Risk estimate: NR	2/44 vs. 8/346‡‡‡ Risk estimate: NR	NR	NR§§§
Salpingo-oophorectomy or oophorectomy							
2013 Review							
Surgery group (observed vs. expected)‖¶¶							
Olson et al., 2004[100, †††] NA	Women with bilateral oophorectomy	High-risk¶¶¶ Surgery <60 years n=55	<60	3/55 vs. 5.4 RR 0.56 (0.11 to 1.33)	NR	NR	NA
Olson et al., 2004[100, †††] NA (Continued)	Women with bilateral oophorectomy	Surgery <50 years n=41	<50	1/41 vs. 3.9 RR 0.26 (0.001 to 0.99)	NR	NR	NA
Olson et al., 2004[100, †††] NA (continued)	Women with bilateral oophorectomy	Moderate risk**** Surgery <60 years n=193	<60	9/193 vs. 10.9 RR 0.83 (0.38 to 1.44)	NR	NR	NA
Olson et al., 2004[100, †††] NA (continued)	Women with bilateral oophorectomy	Surgery <50 years n=130	<50	5/130 vs. 7.7 RR 0.65 (0.21 to 1.32)	NR	NR	NA

*Based on followup to censoring date

†Mutation status reported for patients with and without a pre-existing breast cancer diagnosis when tested, and before exclusions for male sex and other cancer history (N=246); after exclusions, N=205, of whom n=87 had no cancer diagnosis.

‡*BRCA1* carriers evaluated in group including those with and without surgery

§*BRCA2* carriers evaluated in group including those with and without surgery

‖Total at-risk time in surgery group was 378.7 years versus 934.6 years in the no surgery group

¶Expected incidence based on life tables

**Study included women with prior breast cancer; only data on women with no prior breast cancer included in evidence review

††Total number of women with *BRCA1/2* mutation, regardless of breast cancer history; study did not provide the number of women with a mutation and without a prior history of breast cancer

‡‡Based on control group of sisters

§§Families testing positive for *BRCA1* mutation; families had multiple breast and ovarian cancer cases prior to testing

Table 8. Studies of Risk-Reducing Surgery

‖‖Subgroup of high-risk group
¶¶Based on high-penetrance model
***Based on low-penetrance model
†††Oophorectomy performed
‡‡‡Incidence includes post-oophorectomy ovarian carcinomatosis
§§§Followup for ovarian cancer incidence was 1665 p-y for no surgery group, 460 p-y for surgery group; Followup for breast cancer incidence was 1587 p-y for no surgery group, 484 p-y for surgery group
‖‖‖Expected incidence based on Gail model
¶¶¶One first-degree relative with breast cancer before age 50 years or one first-degree relative with ovarian cancer at any age and at least one other first or second-degree relative with either diagnosis at any age
****One first-degree relative with breast cancer at any age

Abbreviations: BRCA=breast cancer susceptibility gene; BRRM=bilateral risk-reducing mastectomy; CI=confidence interval; EMBRACE= Epidemiological Study of Familial Breast Cancer; HR=hazard ratio; NA=not applicable; NR=not reported; PYO=person-years of observation; p-y=person-years; RR=relative risk; RRSO=risk-reducing salpingo-oophorectomy

Table 9. Distress Due to Intensive Screening for Breast Cancer Among Mutation Carriers

Author, year, quality rating	N, study design	Mutation status	Comparison	Measures	Breast cancer worry	Anxiety	Depression	Sexual activity	Body image	General QOL
Current Review										
den Heijer et al., 2013[193,*] Fair	197; longitudinal cohort	25 *BRCA 1/2* mutation positive	A) Baseline (n=197) B) Long-term followup (5-8 years; n=197)	HADS, IES	X decreased A vs. B[†]	0	0	NR	NR	NR
Portnoy et al., 2015[208, ‡] NA	170; pre-post	100% *BRCA 1/2* mutation positive	A) False positive on screening (n=27) B) No false positive result (n=143)	BSI	0[§]	NR	NR	NR	NR	NR
2013 Review										
Rijnsburger, et al., 2004[209] Fair	288; prospective cohort and pre-post	35 *BRCA1/2* mutation positive	A) CBE (n=287) B) CBE + mammography (n=134) C) CBE + MRI (n=109)	EQ-5D, SCL-90, SF-36, VAS	NR	0	NR	NR	NR	0
Spiegel, et al., 2011[210] NA	55; pre-post	*BRCA1:* 54.5% (30/55) *BRCA2:* 45.5% (25/55)	A) Recall examinations (n=18) B) No recall examinations (n=37)	HADS, WIS	NR	X increase A vs. B[‖]	0	NR	NR	0

X=statistically significant difference; 0 = studied but not significant; NR=not reported.

*Long-term followup results of Rijnsburger et al., 2004[209]
†Intrusion and avoidance scales of IES decreased between baseline and long-term followup.
‡13% (22/170) of participants had a history of breast cancer, but had completed treatment; <1% (1/170) of participants had a history of ovarian cancer.
§Increased in group A at 3 months, but returned to baseline by 1 year followup, no significant difference with comparison.
‖At 4-6 weeks after screening only, returned to baseline levels by 6 months.

Abbreviations: BRCA=breast cancer susceptibility gene; BSI=Brief Symptom Inventory; CBE=clinical breast exam; EQ-5D=EuroQoL-5 Dimensions; HADS=Hospital Anxiety and Depression Scale; IES=Impact of Events Scale; MRI=magnetic resonance imaging; NA=not applicable; NR=not reported; QOL=quality of life; SCL-90=Symptom Checklist-90; SF-36=Short Form (36) Health Survey; VAS=Visual Analogue Scale; WIS=Breast Cancer Worry Interference Scale

Table 10. Meta-Analysis of Results of Placebo-Controlled Trials of Risk-Reducing Medications—Harms[77]

	RR for tamoxifen vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with tamoxifen (95% CI), *n*‡	RR for raloxifene vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with raloxifene (95% CI), *n*‡	RR for AIs vs. placebo (95% CI)	Trials, *n**	Placebo rate (±SE)†	Events reduced or increased with AIs (95% CI), *n*‡
Vascular												
VTE§	1.93 (1.33 to 2.68)	4	0.91 ± 0.19	5 (2 to 9) more	1.56 (1.11 to 2.60)	2	2.34 ± 0.25	7 (0.3 to 17) more	1.24 (0.65 to 2.16)	2	–	–
DVT	1.45 (0.73 to 2.59)	2	–	–	1.66 (0.79 to 5.14)	2	–	–	NR	–	–	–
PE	2.69 (0.54 to 8.13)	2	–	–	2.11 (0.82 to 6.12)	2	–	–	NR	–	–	–
CHD events	1.00 (0.75 to 1.30)	4	–	–	0.95 (0.80 to 1.10)	2	–	–	0.76 (0.41 to 1.49)	2	–	–
Stroke	1.36 (0.78 to 2.20)	4	–	–	1.04 (0.64 to 1.36)	2	–	–	0.98 (0.27 to 2.56)	2	–	–
Other												
Endometrial cancer	2.25 (1.17 to 4.41)	3	0.62 ± 0.10	4 (1 to 8) more	1.14 (0.54 to 2.17)	2	–	–	0.60 (0.09 to 3.07)	1	–	–
Cataracts	1.22 (1.08 to 1.48)	3	22.85 ± 0.75‖	26 (5 to 50) more	0.93 (0.82 to 1.06)	2	–	–	0.94 (0.70 to 1.27)	1	–	–

*Number of trials included in meta-analysis.
†Per 1000 women, estimated from a meta-analysis of rates from the placebo groups from the same trials included in the RRs.
‡Number of events reduced for benefits or increased for harms compared with placebo per 1,000 women assuming 5 years of use.
§Includes DVT and PE.
‖The placebo rate was from NSABP P-1, 2005.[221]

Abbreviations: AI=aromatase inhibitors; CHD=coronary heart disease; CI=confidence interval; DVT=deep vein thrombosis; n=number; NR=not reported; NSABP=National Surgical Adjuvant Breast and Bowel Project; PE=pulmonary embolism; RR=risk ratio; SE=standard error; VTE=venous thromboembolis

Table 11. Distress Due to Risk-Reducing Surgery

Author, year	N, study design	Mutation status	Comparison	Measures	Anxiety	Depression	Sexual activity	Body image	General QOL
Mastectomy									
Current Review									
Borreani et al., 2014[187]	27, cohort	74.1% (20/27) *BRCA1* 25.9% (7/27) *BRCA2*	A) Surveillance (n=19) B) Surgery (n=8)	CWS, HADS, MOS SF-12, NSI	0	0	NR	0	0
den Heijer et al., 2012[192,*]	36; pre-post	75% *BRCA 1/2*	A) Before surgery (n=36) B) 6 months after (n=36) C) 6-9 years after (n=36)	BIS, HADS, IES	NR	NR	NR	X Decrease B vs. A and increase C vs. B	X decrease B vs. A and C vs. B
Gopie et al., 2013[196]	50; pre-post	88% *BRCA 1/2*	A) Before surgery (n=50) B) 6 months after (n=32) C) 1 year after (n=32)	BIS, IES, NRV, SF-36	NR	NR	0	X decrease B vs. A 0 C vs. A	X decrease on PCS B vs. A increase on MCS B vs. A 0 A vs. C
Isern et al., 2008[199]	28; case-series	NR	A) Surgery (n=28) B) Reference group (n=968)	HADS, SF-36	0	0	NR	NR	X[†]
Stefanek, 1995[211]	14; case-series	NR	A) Surgery (n=14) B) Surveillance control (n=150)	CES-D, NSI	NR	0	NR	NR	X[‡]
2013 Review									
Brandberg, et al., 2008[190] Brandberg, et al., 2012[189]	90; pre-post	41.1% (37/90) *BRCA1* 14.4% (13/90) *BRCA2* 2.2% (2/90) unknown mutation	A) Before surgery (n=81) B) 6 months after (n=71) C) 1 year after (n=65)	BIS, HADS, NSI, SAQ, SF-36	X decrease B & C vs. A	0	X[§] decrease C vs. A & B	0	NR
Gahm, et al., 2010[195]	1784; case-series	NR	A) Surgery (n=59) B) Control (n=1725)	DRS, NSI, SF-36	NR	NR	NR	NR	0
Metcalfe, et al., 2004[205]	60; case-series	21.7% *BRCA1/2*	A) Age <50 years (n=46) B) Age ≥50 years (n=14)	BIBC, BSI, IES, SAQ	0	NR	0	NR	NR
Mastectomy vs. Oophorectomy									
Current Review									
Bresser et al., 2007[191,‖]	78; cohort	69% *BRCA 1/2*	A) Mastectomy (n=52) B) Oophorectomy (n=26)	HADS, IES	0	0	NR	NR	0

Table 11. Distress Due to Risk-Reducing Surgery

Author, year	N, study design	Mutation status	Comparison	Measures	Anxiety	Depression	Sexual activity	Body image	General QOL
Salpingo-oophorectomy									
2013 Review									
Finch et al., 2011[194]	67; pre-post	*BRCA1* or *BRCA2*	A) Before surgery B) After surgery	MENQOL, SAQ	NR	NR	X decrease B vs. A	NR	NR

X=statistically significant difference; 0=studied but not significant

*33% (12/36) of women had a history of breast cancer, but had completed treatment. 3% (1/36) of women had a history of ovarian cancer. This is also the same population that Bresser et al., 2007[191] is drawn from.
†This was only significant for the SF-36 subscales of physical functioning (p<0.0001), vitality (p=0.042), and social functioning (p=0.007).
‡86% (surgery) vs. 60% (surveillance), p<0.001 noted their breast cancer worry was at least a moderate problem.
§For pleasure subscale of SAQ only
‖35% (27/78) of women had a history of breast cancer but had completed treatment, and 1% (1/78) if women had history of ovarian cancer. This is also the same population that den Heijer, 2012[192] is drawn from.

Abbreviations: BIBC=Body Image after Breast Cancer; BIS=Body Image Scale; BRCA=breast cancer susceptibility gene; BSI=Brief Symptom Inventory; CES-D=Center for Epidemiologic Studies-Depression; DRS=Decision Regret Scale; HADS=Hospital Anxiety and Depression Scale; IES=Impact of Events Scale; MCS=Mental Component Summary of SF-36; MENQOL=Menopause-Specific Quality of Life-Intervention; NR=not reported; NRV=Nederlandse Relateie Vragenlijst (Dutch Relationship Questionnaire); NSI=not standard instrument; PCS=Physical Component Summary of SF-36; QOL=quality of life; SAQ=Sexual Activity Questionnaire; SF-36=Short Form (36) Health Survey

Table 12. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ 1. Benefits of risk assessment, genetic counseling, and genetic testing	Risk assessment; genetic counseling; genetic testing	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 2a. Accuracy of familial risk assessment methods by non-specialists	Risk assessment for familial *BRCA1/2*-related cancer risk	14 discriminatory accuracy studies of 10 risk assessment methods (n=43,813)	Methods have moderate to good discriminatory accuracy in predicting the probability of familial *BRCA1/2*-related cancer risk in individuals (AUC 0.68 to 0.96)	Consistent; precise	While some studies enrolled small numbers or inadequately described methods, most studies met criteria for fair and good quality	Moderate for benefit	Moderate to high
KQ 2a. Optimal ages and intervals for risk assessment	Risk assessment for *BRCA1/2*-related cancer risk	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 2b. Benefits of pre-test genetic counseling	Pre-test genetic counseling	28 studies (systematic reviews; RCTs; and cohort, case-control, and before and after studies) (n=6,446)	Genetic counseling decreases cancer worry, anxiety, and depression; increases the accuracy of risk understanding; and decreases intention for mutation testing. Face-to-face counseling was preferred in some studies.	Consistent; precise	Dissimilar comparison groups; small sizes; dissimilar interventions; heterogeneous outcome measures	High for benefit	High
KQ 2c. Optimal testing approaches	*BRCA1/2* mutation testing	1 RCT (n=1,034)	Universal testing of Ashkenazi Jews for founder mutations detected more carriers than testing only those meeting family history criteria	Not applicable	All participants had genetic counseling, so not a true population approach; not all were tested, so cannot determine the accuracy of this strategy	Low for benefit	Moderate
KQ 2d. Optimal post-test counseling approaches	Post-test genetic counseling	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable

Table 12. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ 3a. Harms of risk assessment	Risk assessment for *BRCA1/2*-related cancer risk	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 3b. Harms of pre-test genetic counseling	Pre-test genetic counseling	28 studies (systematic reviews; RCTs; and cohort, case-control, and before and after studies) (n=6,446)	Genetic counseling did not cause adverse effects in studies, but decreased cancer worry, anxiety, and depression; increased the accuracy of risk understanding; and decreased intention for mutation testing.	Consistent; precise	Dissimilar comparison groups; small sizes; dissimilar interventions; heterogeneous outcome measures	Moderate for harms	Moderate
KQ 3c. Harms of genetic testing	*BRCA1/2* mutation testing	18 studies (cohort, case-control, and before and after studies) (n=3,027)	Breast cancer worry and anxiety increased for women with positive results and decreased for others, while risk understanding improved	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures; high loss to followup	Moderate for benefits and harms (varies by test result)	Moderate
3d. Harms of post-test counseling	Post-test genetic counseling	No studies	Not applicable	Not applicable	Not applicable	Insufficient	Not applicable
KQ 4. Interventions to reduce BRCA-related cancer and mortality	Intensive screening	No effectiveness trials; 6 studies of test characteristics of screening (n=5,087)	Breast MRI has higher sensitivity than mammography for screening *BRCA1/2* carriers (71 vs. 41%); specificity is comparable (90 vs. 95%). Sensitivity of screening for ovarian cancer is 43% for TVUS; 71% for CA-125; specificity is 99 percent for either	Not applicable	Descriptive studies that do not provide data on effectiveness	Insufficient	Not applicable

Table 12. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ 4. Interventions to reduce BRCA-related cancer and mortality, continued	Risk-reducing medications: tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	No trials for *BRCA1/2* carriers; 9 RCTs for general populations (n=74,170)	Tamoxifen, raloxifene, anastrozole, and exemestane reduced invasive breast cancer and ER+ breast cancer compared with placebo. No differences for ER- or noninvasive breast cancer; all-cause or breast cancer-specific mortality	Consistent; precise	No results for *BRCA1/2* carriers specifically; clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	Insufficient for *BRCA1/2* carriers specifically; high for benefit for general populations	High for general populations
KQ 4. Interventions to reduce *BRCA1/2*-related cancer and mortality, continued	Risk-reducing surgery	6 descriptive studies of mastectomy; 7 descriptive studies of oophorectomy or salpingo-oophorectomy (n=9,938)	Bilateral mastectomy reduced breast cancer incidence 90 to 100% and breast cancer mortality 81 to 100% for high-risk women and mutation carriers. Oophorectomy or salpingo-oophorectomy reduced breast cancer 37 to 74%; salpingo-oophorectomy reduced ovarian cancer 69 to 100%	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Moderate for benefit	High
KQ 5. Harms of interventions to reduce incidence of *BRCA1/2*-related cancer and mortality, continued	Intensive screening	9 descriptive studies (n=5,628)	For breast cancer screening, false-positive rates, additional imaging, and benign surgeries were higher for intensive screening using MRI versus mammography; benign diagnostic surgery rate of 55% for mutation carriers screened with TVUS and CA-125	Consistent; precise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Low for harm	High

Table 12. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ 5. Harms of interventions to reduce incidence of *BRCA1/2*-related cancer and mortality, continued	Risk-reducing medications: tamoxifen, raloxifene, aromatase inhibitors (anastrozole; exemestane)	No trials for *BRCA1/2* carriers; 9 RCTs for general populations (n=74,170)	Tamoxifen and raloxifene increased thromboembolic events and tamoxifen increased endometrial cancer and cataracts compared with placebo; no differences for DVT; PE; CHD events; or stroke	Consistent; precise	No results for *BRCA1/2* carriers specifically; clinical heterogeneity across trials from varying eligibility criteria, adherence, and ascertainment of certain outcomes	Insufficient for *BRCA1/2* carriers specifically; high for harm for general populations	High for general populations
KQ 5. Harms of interventions to reduce incidence of *BRCA1/2*-related cancer and mortality, continued	Risk-reducing surgery	10 descriptive studies of mastectomy; 4 descriptive studies of oophorectomy (n=3,073)	Harms include physical complications of surgery, post-surgical symptoms, and changes in body image; psychological symptoms generally improve over time and some women have improved anxiety	Inconsistent, imprecise	Lack of studies with comparison groups; variations in methodology and enrollment criteria; heterogeneous outcome measures	Low for harm	Moderate

*Per 1000 women over 5 years of use.

Abbreviations: AUC=area under the receiver operating characteristic curve; *BRCA1/2*=breast cancer susceptibility gene; CA-125=cancer antigen-125; CHD=coronary heart disease; CI=confidence interval; DVT=deep vein thrombosis; ER+=estrogen receptor positive; ER-=estrogen receptor negative; KQ=key question; MRI=magnetic resonance imaging; PE=pulmonary embolism; RCT=randomized control trial; RR=risk ratio; TVUS=transvaginal ultrasound; vs=versus.

Appendix A1. Search Strategies

OVID MEDLINE® Database Searches

Risk Assessment – General Screening
Search Strategy:
---
1 exp Preventive Medicine/
2 exp Family Practice/
3 exp Primary Health Care/
4 exp General Practice/
5 exp general practitioners/
6 exp physicians, primary care/
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Breast Neoplasms/ or exp ovarian cancer/
9 exp disease susceptibility/
10 exp mass screening/
11 8 and (9 or 10)
12 exp Breast Neoplasms/ge or exp ovarian cancer/ge
13 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or brca1.mp.
14 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or brca2.mp.
15 11 or 12 or 13 or 14
16 7 and 15

Risk Assessment – Prediction Models
Search Strategy:
---
1 (gail adj model$).mp.
2 (claus adj model$).mp.
3 1 or 2
4 exp Models, Statistical/
5 exp risk/
6 exp Breast Neoplasms/ge
7 4 and 5 and 6
8 3 or 7

Genetic Counseling
Search Strategy:
---
1 exp Genetic Counseling/ or Genetic counseling.mp. or genetic counselling.mp.
2 decision making.mp. or exp Decision Making/
3 exp risk/
4 risk$.mp.
5 exp Breast Neoplasms/ or breast neoplasm$.mp. or Breast cancer$.mp. or exp ovarian neoplasms/ or ovarian cancer$.mp. or ovarian neoplasm$.mp.
6 1 and (2 or 3 or 4) and 5

Appendix A1. Search Strategies

Genetic Testing – General
Search Strategy:
---
1 exp Breast Neoplasms/mo, pc, ep, eh or exp ovarian neoplasms/mo, pc, ep, eh
2 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or brca1.mp.
3 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or brca2.mp.
4 2 or 3
5 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge
6 (sensitivity and specificity).mp.
7 exp "Sensitivity and Specificity"/
8 risk$.mp. or exp RISK/
9 5 and (6 or 7 or 8)
10 1 and 4 and 9
11 (201612* or 2017*).ed.
12 10 and 11

Genetic Testing – Harms
Search Strategy:
---
1 exp Breast Neoplasms/ or exp ovarian neoplasms/
2 exp genetic screening/ae or exp genetic services/ae or exp genetic counseling/ae or exp genetic screening/px or exp genetic services/px or genetic counseling/px
3 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge
4 exp stress, psychological/
5 ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or toll)).mp.
6 exp anxiety/ or anxious$.mp. or anxiet$.mp.
7 4 or 5 or 6
8 (1 and 2) or (3 and 7)

Risk-Reducing Interventions – General
Search Strategy:
---
1 exp Breast Neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr or exp ovarian Neoplasms/nu, pc, dh, rt, dt, rh, su, th, tr
2 exp Treatment Outcome/ or treatment outcome$.mp.
3 exp "Outcome Assessment (Health Care)"/ or outcome assessment$.mp.
4 1 or 2 or 3
5 exp Breast Neoplasms/mo, ep, eh or exp ovarian Neoplasms/mo, ep, eh
6 exp Breast Neoplasms/ or exp ovarian neoplasms/
7 exp MORTALITY/ or mortal$.mp. or mortality.fs.
8 exp INCIDENCE/ or incidence$.mp. or epidemiology.fs. or ethnology.fs.
9 7 or 8
10 6 and 9
11 5 or 10
12 exp RISK/
13 risk$.mp.
14 exp Genetic Predisposition to Disease/ or genetic predisposition to disease$.mp.
15 pedigree.mp. or exp PEDIGREE/
16 12 or 13 or 14 or 15
17 exp Breast Neoplasms/ge or exp ovarian neoplasms/ge
18 exp GENES, BRCA1/ or exp BRCA1 PROTEIN/ or brca1.mp.

19 exp GENES, BRCA2/ or exp BRCA2 PROTEIN/ or brca2.mp.
20 17 or 18 or 19
21 4 and 11 and 16 and 20

Risk-Reducing Interventions – Surgery Specific
Search Strategy:
---
1 exp Breast Neoplasms/pc
2 exp Ovarian Neoplasms/pc
3 (mastectom$ or oophoectom$ or ovariectom$).mp.
4 1 or 2
5 3 and 4
6 (family adj5 histor$).mp.
7 exp Genetic Predisposition to Disease/
8 brca.mp.
9 (brca1 or brca2).mp.
10 6 or 7 or 8 or 9
11 5 and 10

Risk-Reducing Interventions – Harms
Search Strategy:
---
1 exp Breast Neoplasms/dt, su or exp ovarian neoplasms/dt, su
2 exp Breast Neoplasms/pc or exp ovarian neoplasms/pc
3 chemoprevention.mp. or exp CHEMOPREVENTION/
4 primary prevention.mp. or exp Primary Prevention/
5 2 or 3 or 4
6 postoperative complications.mp. or exp Postoperative Complications/
7 intraoperative complications.mp. or exp Intraoperative Complications/
8 ae.xs. or ct.fs.
9 exp stress, psychological/
10 ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or toll)).mp.
11 ((psycholog$ or emotion$ or mental$) adj3 (stress$ or strain$ or burden$ or fear$ or toll)).mp.
12 exp anxiety/ or anxiet$.mp. or anxious$.mp.
13 9 or 10 or 11 or 12
14 6 or 7 or 8 or 13
15 1 and 5 and 14

BRCA – Case-Control Studies
Search Strategy:
---
1 exp case control studies/
2 brca$.mp.
3 1 and 2
4 exp breast neoplasms/
5 exp ovarian neoplasms/
6 4 or 5
7 3 and 6

Appendix A1. Search Strategies

Ethical, Legal, and Social Implications
Search Strategy:
---
1 ((breast$ or mammar$ or ovar$) adj3 (cancer$ or carcino$ or adenocarcin$ or tumor$ or tumour$ or malig$ or neoplas$)).mp. (261591)
2 screen*.mp. (443410)
3 (gene or genes or genetic$ or genotyp$ or genom$ or brca or dna).mp. (2509492)
4 2 or 3 (2814223)
5 1 and 4 (98623)
6 (law or laws or lawful$ or unlawful$ or legal$ or illegal$ or jurispru$ or legislat$ or litigat$ or liabil$ or malpract$).mp. (152351)
7 (prejudic$ or disqualif$ or deny or denying or denial or coerc$ or stigma$ or ((race* or racial* or ethnic* or minorit*) adj5 (discriminat* or segregat$))).mp. (47389)
8 (ethic$ or bioethic$ or moral$ or (human$ adj2 right$)).mp. (114469)
9 6 or 7 or 8 (286960)
10 5 and 9 (951)
11 bias$.mp. (118961)
12 5 and 11 (999)
13 10 or 12 (1921)

Additional Databases Searched for Overall Project
PsycINFO
Search Strategy:
---
1 ((Breast$ or mammar$ or ovar*) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2 ((Breast$ or mammar$) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3 1 not 2
4 exp Breast Neoplasms/
5 genetic counseling/
6 exp Genetic Testing/
7 5 or 6
8 4 and 7
9 exp GENETICS/
10 exp RISK ASSESSMENT/ or exp AT RISK POPULATIONS/ or exp RISK MANAGEMENT/ or exp RISK FACTORS/
11 4 and 9 and 10
12 8 or 11
13 1 or 12

Appendix A1. Search Strategies

EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
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1 ((Breast$ or mammar$ or ovar*) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, full text, keywords, caption text]
2 ((Breast$ or mammar$) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 not 2

EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
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1 ((Breast$ or mammar$ or ovar*) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, full text, keywords, caption text]
2 ((Breast$ or mammar$) adj5 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or adenocarcino$ or malig$ or metasta$) adj15 (((brca* or gene*) adj5 (screen* or test* or assay)) or ((brca* or gene* or heredit*) adj5 (risk* or predispos* or suscept* or counsel*)))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 not 2

Elsevier Embase®
Search Strategy:

(((brca:ab,ti) OR (('breast cancer'/exp OR 'ovary cancer'/exp) AND ('tumor suppressor gene'/exp))) AND ('risk assessment'/exp OR 'genetic screening'/exp OR 'genetic counseling'/exp)) AND [embase]/lim NOT [medline]/lim AND [english]/lim AND [humans]/lim

Appendix A2. Inclusion and Exclusion Criteria

Category	Included	Excluded
Setting	Primary care settings or clinical settings referable from primary care; settings comparable to U.S. practice	Other settings not applicable to the U.S.
Populations	**KQs 1–3:** Women with unknown BRCA mutation status. **KQs 4, 5:** Women with pathogenic *BRCA1* or *BRCA2* genes. **For women with prior breast cancer and/or ovarian cancer:** Studies that report the time since treatment completion (any time), or report the time since diagnosis with the minimum in the range ≥5 years.	**All KQs:** Women under treatment for breast or ovarian cancer, or for whom the intention of testing is to determine treatment rather than prevention interventions.* Assessment of mutations other than *BRCA1* and *BRCA2*. Intention of testing is to determine treatment for cancer. **KQs 1–3:** Women with known BRCA mutation carrier status unless the study is designed to address questions for women with unknown status (e.g., case-control, retrospective study) **All KQs, except KQ 2c:** Men
Interventions	**KQ 1:** Risk assessment initiated by a nonspecialist in genetics, pre-test genetic counseling, genetic testing, post-test counseling. **KQs 2a, 3a:** Risk assessment initiated by a nonspecialist in genetics. **KQs 2b, 3b:** Pre-test genetic counseling† delivered by a provider trained in genetics using methods meeting current standards of practice in the United States (described in text). **KQs 2c, 3c:** Genetic testing **KQs 2d, 3d:** Post-test counseling† **KQs 4, 5:** Intensive screening (earlier and more frequent screening; use of additional screening methods), use of risk-reducing medications (aromatase inhibitors; tamoxifen; raloxifene), and risk-reducing surgery (mastectomy; salpingo-oophorectomy; other procedures) when performed for prevention purposes.	**All KQs:** No intervention or intervention not described. **KQ 2a, 3a:** Assessments conducted solely by specialists (i.e., BRCAPRO, BOADICEA) or risk assessments for lifetime risk of breast and/or ovarian cancer. **KQ 2b, 2d, 3b, 3d:** Genetic counseling for risk management or decision aids. **KQs 4, 5:** Intervention not listed as included.
Comparisons	**KQ 1:** Risk assessment, pre-test genetic counseling, genetic testing, post-test counseling vs. usual care or alternative approaches. **KQs 2a, 3a:** Risk assessment by a nonspecialist in genetics vs. usual care or risk assessment by alternative approaches. **KQs 2b, 3b:** Pre-test genetic counseling vs. usual care or alternative approaches. **KQs 2c, 3c**: Genetic testing vs. usual care or alternative approaches. **KQ 2d, 3d:** Post-test counseling vs. usual care or alternative approaches. **KQs 4, 5:** Intensive screening, risk-reducing medications, or risk-reducing surgery vs. no intervention or alternative approaches.	**Benefits KQs:** No comparison or comparison not described.

Appendix A2. Inclusion and Exclusion Criteria

Category	Included	Excluded
Outcomes	**KQs 1, 4:** Incidence of BRCA-related cancer; disease-specific and all-cause mortality **KQ 2a:** Measures of test performance (sensitivity, specificity, positive and negative likelihood ratios, c statistic) **KQ 2b:** Patient outcomes of pre-test genetic counseling (improved accuracy of risk assessment and pretest probability for testing and improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes) **KQ 2c:** Patient health, implications of non-BRCA findings detected on multigene panels, psychological outcomes of testing **KQ 2d:** Patient outcomes of post-test counseling (improved patient knowledge, understanding of benefits and harms of interventions to reduce risk, risk perception, satisfaction, and health and psychological outcomes) **KQ 3a:** Inaccurate risk assessment, false-positive and false-negative results; adverse effects on the patient's family relationships; false reassurance; anxiety; cancer worry; and ethical, legal, and social implications **KQ 3b:** Inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse effects on the patient's family relationships; overdiagnosis and overtreatment; false reassurance, anxiety, decision regret; cancer worry; and ethical, legal, and social implications **KQ 3c:** Inappropriate testing; false-positive and false-negative results; adverse effects on the patient's family relationships; overdiagnosis and overtreatment; false reassurance; incomplete testing; misinterpretation of test results; anxiety, depression; cancer worry; and ethical, legal, and social implications **KQ 3d:** Inaccurate risk assessment; inappropriate testing; false-positive and false-negative results; adverse effects on the patient's family relationships; overdiagnosis and overtreatment; false reassurance, anxiety, decision regret; cancer worry; and ethical, legal, and social implications **KQ 5**: Immediate and long-term harms associated with screening (false-positive and false-negative results, overdiagnosis, and overtreatment; nonadherence); risk-reducing medications (thromboembolic and cardiovascular events, metabolic disorders, musculoskeletal symptoms, ophthalmologic disorders, and quality of life, others); risk-reducing surgery (surgical complications, sexual dysfunction, menopausal symptoms, mood changes, and quality of life); and ethical, legal, and social implications	Other outcomes not listed, including cost and cost-effectiveness, intermediate lab outcomes, individual risk factors not associated with a risk assessment tool, prevalence and penetrance data, risk estimates, predictors of outcomes, uptake of testing or interventions, and time to interventions.
Study Design	**All KQs:** Randomized, controlled trials; observational studies, with or without comparison groups **KQ 2:** Discriminatory accuracy studies **KQ 2c:** Modeling studies	**All KQs:** Case reports, case series **Benefits KQs:** Non-comparative studies **All KQs, except KQ 2c:** Modeling studies
Study Quality	Studies rated good- and fair-quality for meta-analyses using USPSTF quality criteria	Poor-quality studies

* We excluded studies if they did not report the time since treatment completion or time since diagnosis, or they did report the time since diagnosis, but the minimum was <5 years, or if the standard deviation would include <5 years.

†Genetic counseling component requirements:

Pre-test

1. Comprehensive evaluations of familial risk for inherited disorders using kindred analysis and models to estimate risk
2. Identification of candidates for testing
3. Patient education
4. Discussion of the benefits and harms of genetic testing

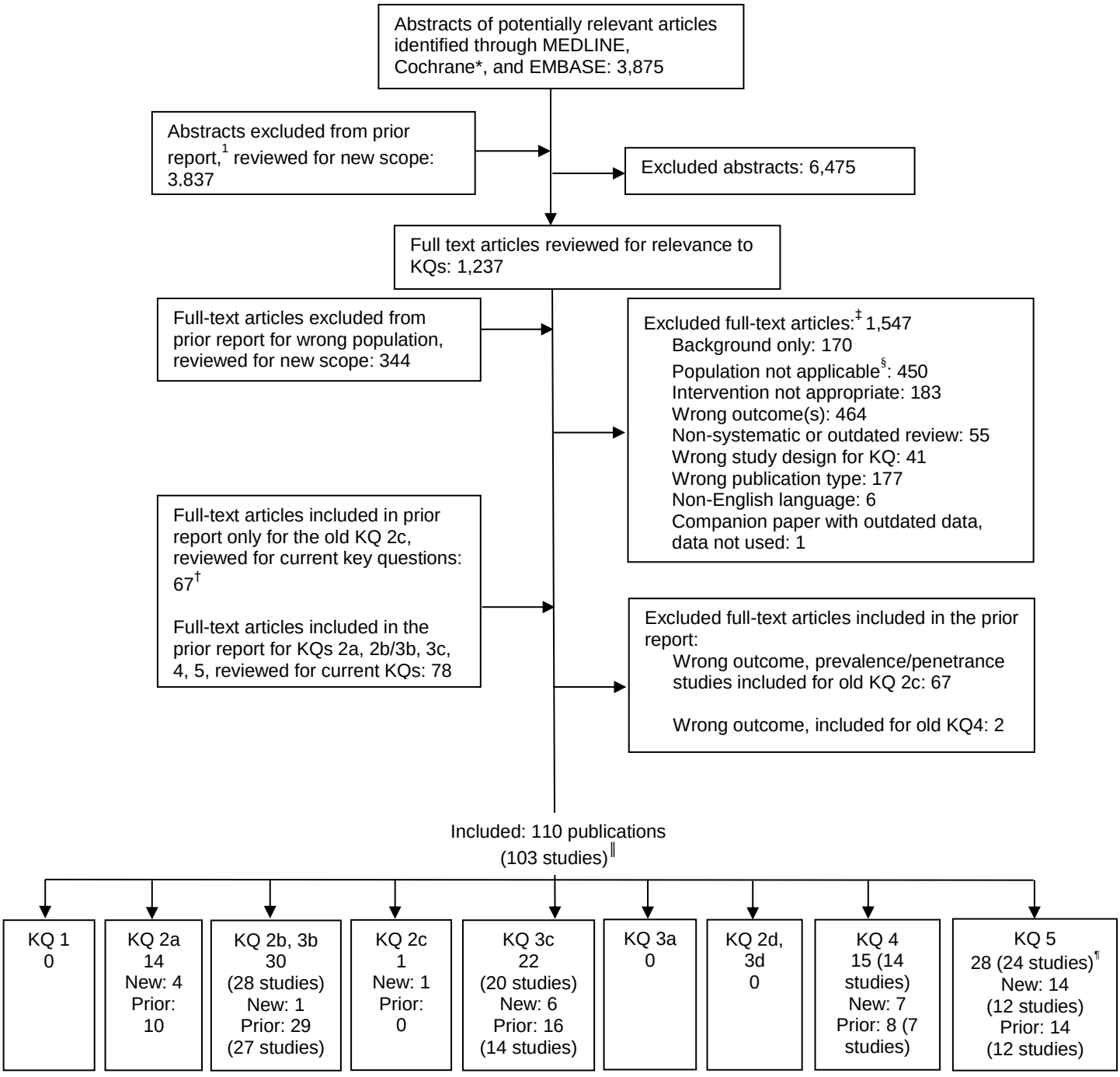
Post-test

1. Interpretation of results after testing
2. Discussion of management options

Appendix A2. Inclusion and Exclusion Criteria

Abbreviations: BRCA=breast cancer susceptibility gene; BRCAPRO=breast cancer susceptibility gene prediction model; BOADICEA=Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; KQ=key question; U.S.=United States; USPSTF=United States Preventive Services Task Force.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

†2 studies were included for KQ 2c and KQ 4 in the 2013 review, these studies were reviewed with the set of papers from the non KQ 2c pile.

‡See Appendix A4 for the list of excluded studies and Appendix A2 for the list of exclusion criteria.

§In this exclusion group are 82 studies that included women with prior breast and/or ovarian cancer, but did not report the time since cancer diagnosis and 21 studies that reported time since breast and/or ovarian cancer diagnosis, but the minimum was <5 years, or the standard deviation would include <5 years. The rest of the studies were excluded because they included women with current breast or ovarian cancer, women currently under treatment for breast or ovarian cancer, women undergoing testing to determine treatment planning, and men (except if applicable to testing approaches).

Appendix A3. Literature Flow Diagram

‖Studies that provided data and contributed to the body of evidence were considered 'included.'

¶1 new publication was a paper on the long-term results of a study included in the 2013 review.

1. Nelson HD, Fu R, Goddard K, Mitchell JP, Okinaka-Hu L, Pappas M, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality; 2013.

Appendix A4. Excluded Studies List

Studies included from prior report, excluded in current report

Exclusion Codes:
2 = Background information only
3 = Wrong population **3a** = Wrong population – did not report the time since treatment completion or time since diagnosis, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is >30% (or not reported at all) **3b** = Wrong population - reported the time since diagnosis, with the minimum in the range <5 years (or range not reported), or if SD would include <5 years, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is >30% (or not reported at all) **H1** = Wrong population - reported the time since diagnosis with the minimum in the range <5 years (or range not reported), or if SD would include <5 years, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is ≤30% **H2** = Wrong population – did not report the time since diagnosis, but did report the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is ≤30%
4 = Wrong intervention
5 = Wrong outcome
6 = Wrong publication type
7 = Wrong study design
8 = Not in English
9 = Non-systematic review or outdated review
10 = Companion paper with outdated data, data not used

Appendix A4. Excluded Studies List

Abeliovich D, Kaduri L, Lerer I, et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet. 1997 Mar;60(3):505-14. PMID: 9042909. Exclusion: E5

Al-Mulla F, Bland JM, Serratt D, et al. Age-dependent penetrance of different germline mutations in the BRCA1 gene. J Clin Pathol. 2009;62(4):350-6. doi: 10.1136/jcp.2008.062646. PMID: 19329713. Exclusion: E5

Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer. 2000;83(10):1301-8. PMID: 11044354. Exclusion: E5

Anton-Culver H, Cohen PF, Gildea ME, et al. Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer. Eur J Cancer. 2000;36(10):1200-8. PMID: 10882857. Exclusion: E5

Antoniou AC, Durocher F, Smith P, et al. BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families. Breast Cancer Res. 2006;8(1):R3. PMID: 16417652. Exclusion: E5

Antoniou AC, Pharoah PD, McMullan G, et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer. 2002 Jan 07;86(1):76-83. doi: 10.1038/sj.bjc.6600008. PMID: 11857015. Exclusion: E5

Beristain E, Martinez-Bouzas C, Guerra I, et al. Differences in the frequency and distribution of BRCA1 and BRCA2 mutations in breast/ovarian cancer cases from the Basque country with respect to the Spanish population: implications for genetic counselling. Breast Cancer Res Treat. 2007 Dec;106(2):255-62. PMID: 17262179. Exclusion: E5

Bernholtz S, Laitman Y, Kaufman B, et al. Phenocopy breast cancer rates in Israeli BRCA1 BRCA2 mutation carrier families: is the risk increased in non-carriers? Breast Cancer Res Treat. 2012 Apr;132(2):669-73. PMID: 22113258. Exclusion: E5

Boyd J, Sonoda Y, Federici MG, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA. 2000 May 03;283(17):2260-5. PMID: 10807385. Exclusion: E5

Brose MS, Rebbeck TR, Calzone KA, et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002;94(18):1365-72. PMID: 12237282. Exclusion: E5

Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst. 2006 Sep 06;98(17):1215-26. doi: 10.1093/jnci/djj332. PMID: 16954474. Exclusion: E5

Chen S, Iversen ES, Friebel T, et al. Characterization of BRCA1 and BRCA2 mutations in a large United States sample. J Clin Oncol. 2006 Feb 20;24(6):863-71. PMID: 16484695. Exclusion: E5

Cortesi L, Turchetti D, Marchi I, et al. Breast cancer screening in women at increased risk according to different family histories: an update of the Modena Study Group experience. BMC Cancer. 2006;6:210. PMID: 16916448. Exclusion: E5

Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med. 1997 May 15;336(20):1409-15. doi: 10.1056/NEJM199705153362002. PMID: 9145677. Exclusion: E5

Domchek SM, Gaudet MM, Stopfer JE, et al. Breast cancer risks in individuals testing negative for a known family mutation in BRCA1 or BRCA2. Breast Cancer Res Treat. 2010 Jan;119(2):409-14. PMID: 19885732. Exclusion: E5

Eccles DM, Englefield P, Soulby MA, et al. BRCA1 mutations in southern England. Br J Cancer. 1998;77(12):2199-203. PMID: 9649133. Exclusion: E5

Evans DG, Shenton A, Woodward E, et al. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. BMC Cancer. 2008;8:155. PMID: 18513387. Exclusion: E5

Appendix A4. Excluded Studies List

Finkelman BS, Rubinstein WS, Friedman S, et al. Breast and ovarian cancer risk and risk reduction in Jewish BRCA1/2 mutation carriers. J Clin Oncol. 2012 Apr 20;30(12):1321-8. PMID: 22430266. Exclusion: E5

FitzGerald MG, MacDonald DJ, Krainer M, et al. Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med. 1996 Testing Search 4.12.04;334(3):143-9. PMID: 8531968. Exclusion: E5

Fodor FH, Weston A, Bleiweiss IJ, et al. Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. Am J Hum Genet. 1998 Reference Search 3-17-04;63(1):45-51. PMID: 9634504. Exclusion: E5

Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet. 1998;62(3):676-89. PMID: 9497246. Exclusion: E5

Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: Analysis of 10,000 individuals. J Clin Oncol. 2002;20(6):1480-90. PMID: 11896095. Exclusion: E5

Gayther SA, Mangion J, Russell P, et al. Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nat Genet. 1997 4/7/05;15(1):103-5. PMID: 8988179. Exclusion: E5

Gayther SA, Russell P, Harrington P, et al. The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes. Am J Hum Genet. 1999;65(4):1021-9. PMID: 10486320. Exclusion: E5

Gershoni-Baruch R, Dagan E, Fried G, et al. Significantly lower rates of BRCA1/BRCA2 founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer. Eur J Cancer. 2000 May;36(8):983-6. PMID: 10885601. Exclusion: E5

Gronwald J, Cybulski C, Lubinski J, et al. Phenocopies in breast cancer 1 (BRCA1) families: implications for genetic counselling. J Med Genet. 2007 Apr;44(4):e76. PMID: 17400795. Exclusion: E5

Hartge P, Struewing JP, Wacholder S, et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. Am J Hum Genet. 1999 Original Search 6-20-03;64(4):963-70. PMID: 10090881. Exclusion: E5

Harvey SL, Milne RL, McLachlan SA, et al. Prospective study of breast cancer risk for mutation negative women from BRCA1 or BRCA2 mutation positive families. Breast Cancer Res Treat. 2011 Dec;130(3):1057-61. PMID: 21850394. Exclusion: E5

Hopper JL, Southey MC, Dite GS, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev. 1999;8(9):741-7. PMID: 10498392. Exclusion: E5

Janezic SA, Ziogas A, Krumroy LM, et al. Germline BRCA1 alterations in a population-based series of ovarian cancer cases. Hum Mol Genet. 1999;8(5):889-97. PMID: 0196379. Exclusion: E5

Kauff ND, Mitra N, Robson ME, et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. J Natl Cancer Inst. 2005 Sep 21;97(18):1382-4. PMID: 16174860. Exclusion: E5

King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. doi: 10.1126/science.1088759. PMID: 14576434. Exclusion: E5

Konecny M, Milly M, Zavodna K, et al. Comprehensive genetic characterization of hereditary breast/ovarian cancer families from Slovakia. Breast Cancer Res Treat. 2011 Feb;126(1):119-30. PMID: 21203900. Exclusion: E5

Korde LA, Mueller CM, Loud JT, et al. No evidence of excess breast cancer risk among mutation-negative women from BRCA mutation-positive families. Breast Cancer Res Treat. 2011 Jan;125(1):169-73. PMID: 20458532. Exclusion: E5

Kurian AW, Gong GD, John EM, et al. Breast cancer risk for noncarriers of family-specific BRCA1 and BRCA2 mutations: Findings from the Breast Cancer Family Registry. J Clin Oncol. 2011;29(34):4505-9. doi:

10.1200/jco.2010.34.4440. PMID: 22042950. Exclusion: E5

Langston AA, Malone KE, Thompson JD, et al. BRCA1 mutations in a population-based sample of young women with breast cancer. N Engl J Med. 1996;334:137-42. PMID: 8531967. Exclusion: E5

Liede A, Karlan BY, Baldwin RL, et al. Cancer incidence in a population of Jewish women at risk of ovarian cancer. J Clin Oncol. 2002;20(6):1570-7. PMID: 11896106 Exclusion: E5

Lubinski J, Huzarski T, Byrski T, et al. The risk of breast cancer in women with a BRCA1 mutation from North America and Poland. Int J Cancer. 2012 Jul 1;131(1):229-34. doi: 10.1002/ijc.26369. PMID: 21834074. Exclusion: E5

Malone KE, Daling JR, Neal C, et al. Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. Cancer. 2000;88(6):1393-402. PMID: 10717622. Exclusion: E5

Marroni F, Aretini P, D'Andrea E, et al. Penetrances of breast and ovarian cancer in a large series of families tested for BRCA1/2 mutations. Eur J Hum Genet. 2004 Nov;12(11):899-906. PMID: 15340362. Exclusion: E5

Metcalfe K, Lubinski J, Lynch HT, et al. Family history of cancer and cancer risks in women with BRCA1 or BRCA2 mutations. J Natl Cancer Inst. 2010 Dec 15;102(24):1874-8. PMID: 21098759. Exclusion: E5

Metcalfe KA, Finch A, Poll A, et al. Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. Br J Cancer. 2009 Jan 27;100(2):421-5. PMID: 19088722. Exclusion: E5

Metcalfe KA, Poll A, Royer R, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol. 2010;28(3):387-91. PMID: 20008623. Exclusion: E5

Milne RL, Osorio A, Cajal TRY, et al. The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. Clin Cancer Res. 2008 May 1;14(9):2861-9. PMID: 18451254. Exclusion: E5

Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(4):235-40. PMID: 11474660. Exclusion: E5

Moslehi R, Chu W, Karlan B, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. 2000 Apr;66(4):1259-72. doi: 10.1086/302853. PMID: 10739756. Exclusion: E5

Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. JAMA. 2005 Oct 19;294(15):1925-33. PMID: 16234499. Exclusion: E5

Neuhausen SL, Ozcelik H, Southey MC, et al. BRCA1 and BRCA2 mutation carriers in the Breast Cancer Family Registry: An open resource for collaborative research. Breast Cancer Res Treat. 2009;116(2):379-86. PMID: 18704680. Exclusion: E5

Newman B, Mu H, Butler LM, et al. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA. 1998 Testing Search 4-12-04;279(12):915-21. PMID: 9544765. Exclusion: E5

Oddoux C, Struewing JP, Clayton CM, et al. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet. 1996 June 20;14(2):188-90. PMID: 8841192. Exclusion: E5

Peto J, Collins N, Barfoot R, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999 Jun 02;91(11):943-9. PMID: 10359546. Exclusion: E5

Rijnsburger AJ, Obdeijn IM, Kaas R, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC screening study. J Clin Oncol. 2010;28(36):5265-73. PMID: 21079137. Exclusion: E5

Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of

Appendix A4. Excluded Studies List

649 women with ovarian cancer. Am J Hum Genet. 2001;68(3):700-10. PMID: 11179017. Exclusion: E5

Risch HA, McLaughlin JR, Cole DEC, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst. 2006 Dec 6;98(23):1694-706. PMID: 17148771. Exclusion: E5

Roa BB, Boyd AA, Volcik K, et al. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet. 1996 Oct;14(2):185-7. doi: 10.1038/ng1096-185. PMID: 8841191. Exclusion: E5

Robson M, Gilewski T, Haas B, et al. BRCA-associated breast cancer in young women. J Clin Oncol. 1998 May;16(5):1642-9. doi: 10.1200/jco.1998.16.5.1642. PMID: 9586873. Exclusion: E5

Rowan E, Poll A, Narod SA. A prospective study of breast cancer risk in relatives of BRCA1/BRCA2 mutation carriers. J Med Genet. 2007 Aug;44(8):e 89; author reply, e 8. PMID: 17673443. Exclusion: E5

Satagopan JM, Offit K, Foulkes W, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. 2001 May;10(5):467-73. PMID: 11352856. Exclusion: E5

Seymour IJ, Casadei S, Zampiga V, et al. Results of a population-based screening for hereditary breast cancer in a region of North-Central Italy: contribution of BRCA1/2 germ-line mutations. Breast Cancer Res Treat. 2008 Nov;112(2):343-9. PMID: 18092194. Exclusion: E5

Smith A, Moran A, Boyd MC, et al. Phenocopies in BRCA1 and BRCA2 families: evidence for modifier genes and implications for screening. J Med Genet. 2007;44:10-5. PMID: 17079251. Exclusion: E5

Stratton JF, Gayther SA, Russell P, et al. Contribution of BRCA1 mutations to ovarian cancer. N Engl J Med. 1997;336(16):1125-30. PMID: 9099656. Exclusion: E5

Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997 May 15;336(20):1401-8. doi: 10.1056/NEJM199705153362001. PMID: 9145676. Exclusion: E5

Sutcliffe S, Pharoah PD, Easton DF, et al. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. Int J Cancer. 2000;87:110-17. PMID: 10861460. Exclusion: E5

Tamboom K, Kaasik K, Aršavskaja J, et al. BRCA1 mutations in women with familial or early-onset breast cancer and BRCA2 mutations in familial cancer in Estonia. Hered Cancer Clin Pract. 2010;8(1) PMID: 20380699. Exclusion: E5

Tommasi S, Crapolicchio A, Lacalamita R, et al. BRCA1 mutations and polymorphisms in a hospital-based consecutive series of breast cancer patients from Apulia, Italy. Mutat Res. 2005 Oct 15;578(1-2):395-405. PMID: 16026807. Exclusion: E5

van der Kolk DM, de Bock GH, Leegte BK, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. Breast Cancer Res Treat. 2010 Dec;124(3):643-51. PMID: 20204502. Exclusion: E5

Vaziri SA, Krumroy LM, Rostai M, et al. Frequency of BRCA1 and BRCA2 mutations in a clinic-based series of breast and ovarian cancer families. Hum Mutat. 2001;17(1):74. PMID: 11139249. Exclusion: E5

Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst. 1999 Jul 21;91(14):1241-7. PMID: 10413426. Exclusion: E5

Weitzel JN, Lagos V, Blazer KR, et al. Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev. 2005 Jul;14(7):1666-71. doi: 10.1158/1055-9965.EPI-05-0072. PMID: 16030099. Exclusion: E5

Appendix A4. Excluded Studies List

Full-Text Papers Excluded From Searches

Exclusion Codes:
2 = Background information only
3 = Wrong population **3a** = Wrong population – did not report the time since treatment completion or time since diagnosis, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is >30% (or not reported at all) **3b** = Wrong population - reported the time since diagnosis, with the minimum in the range <5 years (or range not reported), or if SD would include <5 years, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is >30% (or not reported at all) **H1** = Wrong population - reported the time since diagnosis with the minimum in the range <5 years (or range not reported), or if SD would include <5 years, AND the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is ≤30% **H2** = Wrong population – did not report the time since diagnosis, but did report the percent of women affected by (or with a personal history of) breast and/or ovarian cancer combined is ≤30%
4 = Wrong intervention
5 = Wrong outcome
6 = Wrong publication type
7 = Wrong study design
8 = Not in English
9 = Non-systematic review or outdated review
10 = Companion paper with outdated data, data not used

Appendix A4. Excluded Studies List

Supreme Court of the United States, Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al. 133 S. Ct. 2107 (June 13, 2013). Exclusion: 2

StatBite: BRCA mutations increase risk of breast/ovarian cancer. J Natl Cancer Inst. 2010 Jun 2;102(11):755. PMID: 20498426. Exclusion: E6

BRCA1 and BRCA2: Cancer Risk and Genetic Testing. Bethesda, MD: National Cancer Institute; 2015. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed May 12 2019. Exclusion: E6

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/s0140-6736(15)61074-1. PMID: 26211827. Exclusion: 2

Aalfs CM, Mollema ED, Oort FJ, et al. Genetic counseling for familial conditions during pregnancy: An analysis of patient characteristics. Clin Genet. 2004;66(2):112-21. PMID: 15253761. Exclusion: E5

Abdollahian M, Das TK. A MDP model for breast and ovarian cancer intervention strategies for BRCA1/2 mutation carriers. IEEE J Biomed Health Inform. 2015 Mar;19(2):720-7. doi: 10.1109/JBHI.2014.2319246. PMID: 24771600. Exclusion: E7

Adams I, Christopher J, Williams KP, et al. What black women know and want to know about counseling and testing for BRCA1/2. J Cancer Educ. 2015 Jun;30(2):344-52. doi: 10.1007/s13187-014-0740-9. PMID: 25301325. Exclusion: E4

Adams S, Greeder L, Reich E, et al. Expression of cancer testis antigens in human BRCA-associated breast cancers: potential targets for immunoprevention? Cancer Immunol Immunother. 2011 Jul;60(7):999-1007. PMID: 21465317. Exclusion: E4

Adams-Campbell LL, Makambi KH, Palmer JR, et al. Diagnostic accuracy of the Gail model in the Black Women's Health Study. Breast J. 2007 Jul-Aug;13(4):332-6. PMID: 17593036. Exclusion: E4

Adank MA, van Mil SE, Gille JJP, et al. PALB2 analysis in BRCA2-like families. Breast Cancer Res Treat. 2011 Jun;127(2):357-62. PMID: 20582465. Exclusion: E3

Adejumo PO. Overview of genetic counselling in cancer care. JMBR. 2014;13(2):38-47. Exclusion: E6

Adonizio CS, Grana G, Sharan K, et al. Recurrent early-stage triple-negative breast cancer. Semin Oncol. 2010 Oct;37(5):419-28. PMID: 21074055. Exclusion: E7

Adrover E, Esteban I, Llort G, et al. Famosa: Evaluation of a multigene panel in patients with suspected HBOC. Ann Oncol. 2016;27doi: 10.1093/annonc/mdw364.32. Exclusion: E6

Agalliu I, Gern R, Leanza S, et al. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res. 2009 Feb 1;15(3):1112-20. PMID: 19188187. Exclusion: E3

Ager B, Butow P, Jansen J, et al. Contralateral prophylactic mastectomy (CPM): a systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. Breast. 2016 Aug;28:107-20. doi: 10.1016/j.breast.2016.04.005. PMID: 27290619. Exclusion: E3

Aguas F, Martins A, Gomes TP, et al. Prophylaxis approach to a-symptomatic post-menopausal women: Breast cancer. Maturitas. 2005 Nov;52(Suppl1):S23-S31. doi: 10.1016/j.maturitas.2005.06.015. PMID: 16126355. Exclusion: E9

Ahmad K. Cancer prophylaxis for women with Lynch syndrome. Lancet Oncol. 2006 Mar;7(3):200. PMID: 16538784. Exclusion: E3

Albada A, Ausems MG, van Dulmen S. Counselee participation in follow-up breast cancer genetic counselling visits and associations with achievement of the preferred role, cognitive outcomes, risk perception alignment and perceived personal control. Soc Sci Med. 2014 Sep;116:178-86. doi: 10.1016/j.socscimed.2014.07.012. PMID: 25016325. Exclusion: E3a

Albada A, van Dulmen S, Ausems MGEM, et al. A pre-visit website with question prompt sheet for counselees facilitates communication in the first consultation for breast cancer genetic counseling: findings from a randomized controlled trial. Genet Med. 2012 May;14(5):535-42. doi: 10.1038/gim.2011.42. PMID: 22241101. Exclusion: 2

Albada A, van Dulmen S, Bensing JM, et al. Effects of a pre-visit educational website on information recall and needs fulfilment in breast cancer genetic counselling, a randomized controlled trial. Breast Cancer Res. 2012;14(2):R37. PMID: 22394647. Exclusion: E3a

Albada A, van Dulmen S, Lindhout D, et al. A pre-visit tailored website enhances counselees' realistic

expectations and knowledge and fulfils information needs for breast cancer genetic counselling. Fam Cancer. 2012 Mar;11(1):85-95. PMID: 21901499. Exclusion: 2

Albada A, van Dulmen S, Spreeuwenberg P, et al. Follow-up effects of a tailored pre-counseling website with question prompt in breast cancer genetic counseling. Patient Educ Couns. 2015 Jan;98(1):69-76. doi: 10.1016/j.pec.2014.10.005. PMID: 25455796. Exclusion: E3a

Albada A, Vernooij M, van Osch L, et al. Does and should breast cancer genetic counselling include lifestyle advice? Fam Cancer. 2014 Mar;13(1):35-44. doi: 10.1007/s10689-013-9672-5. PMID: 23934600. Exclusion: E3a

Alexakos FM. Rhode Island primary care physicians' attitudes toward genetic testing for breast cancer. Med Health R I. 1999 May;82(5):171. PMID: 10343495. Exclusion: E5

Ali E, Athanasopoulos PG, Forouhi P, et al. Cowden syndrome and reconstructive breast surgery: case reports and review of the literature. J Plast Reconstr Aesthet Surg. 2011 Apr;64(4):545-9. PMID: 20627761. Exclusion: E3

Alkner S, Bendahl PO, Grabau D, et al. AIB1 is a predictive factor for tamoxifen response in premenopausal women. Ann Oncol. 2010 Feb;21(2):238-44. PMID: 19628566 Exclusion: E3

Aloraifi F, Alshehhi M, McDevitt T, et al. Phenotypic analysis of familial breast cancer: comparison of BRCAx tumors with BRCA1-, BRCA2-carriers and non-familial breast cancer. Eur J Surg Oncol. 2015 May;41(5):641-6. doi: 10.1016/j.ejso.2015.01.021. PMID: 25736863. Exclusion: E3

Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012 Jul 20;30(21):2654-63. doi: 10.1200/jco.2011.39.8545. PMID: 3413277. Exclusion: E3

Alsop K, Fereday S, Meldrum C, et al. Germ-line BRCA mutations in high-grade ovarian cancer: A case for routine BRCA mutation screening after a diagnosis of invasive ovarian cancer. J Clin Oncol. 2011;29(15). Exclusion: E3

Al-Tuama A, Bolger JC, Roche T, et al. Predicting risk in breast cancer: An assessment of screening tools. Ir J Med Sci. 2014;183(1):S54-S5. doi: 10.1007/s11845-013-1062-3. Exclusion: E6

Amara N, Blouin-Bougie J, Jbilou J, et al. The knowledge value-chain of genetic counseling for breast cancer: an empirical assessment of prediction and communication processes. Fam Cancer. 2016 Jan;15(1):1-17. doi: 10.1007/s10689-015-9835-7. PMID: 26334522. Exclusion: E5

American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society, Inc.; 2016. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2016/. Accessed May 16 2019. Exclusion: 2

American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society, Inc.; 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed May 16 2019. Exclusion: 2

American College of Surgeons. Cancer Program Standards 2016. Chicago, IL; 2016. http://www.facs.org/cancer/coc/programstandards2012.html. Accessed May 1 2019. Exclusion: 2

American Society of Clinical Oncology. Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. J Clin Oncol. 1996 May;14(5):1730-6; discussion 7-40. doi: 10.1200/JCO.1996.14.5.1730. PMID: 8622094. Exclusion: 2

American Society of Clinical Oncology. Li-Fraumeni Syndrome. 2016. http://www.cancer.net/cancer-types/li-fraumeni-syndrome. Accessed May 16 2019. Exclusion: 2

Andersen M, Drescher CW, Zheng Y, et al. Changes in cancer worry associated with participation in ovarian cancer screening. Psychooncology. 2007 Sep;16(9):814-20. doi: 10.1002/pon.1151. PMID: 17225260. Exclusion: E3

Andersen MR, Thorpe J, Buist DS, et al. Cancer risk awareness and concern among women with a family history of breast or ovarian cancer. Behav Med. 2016;42(1):18-28. doi: 10.1080/08964289.2014.947234. PMID: 25062114. Exclusion: E5

Anderson CK, Wallace S, Guiahi M, et al. Risk-reducing salpingectomy as preventative strategy for pelvic serous cancer. Int J Gynecol Cancer. 2013;23(3):417-21. PMID: 23385282. Exclusion: E6

Anderson E, Berg J, Black R, et al. Prospective surveillance of women with a family history of breast cancer: auditing the risk threshold. Br J Cancer.

2008;98(4):840-4. doi: 10.1038/sj.bjc.6604155. PMID: 30000894. Exclusion: E5

Anderson EE, Tejeda S, Childers K, et al. Breast cancer risk assessment among low-income women of color in primary care: a pilot study. J Oncol Pract. 2015 Jul;11(4):e460-7. doi: 10.1200/JOP.2014.003558. PMID: 26036266. Exclusion: E4

Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation.[Summary for patients in Ann Intern Med. 2006 Mar 21;144(6):I40; PMID: 16549849]. Ann Intern Med. 2006 Mar 21;144(6):397-406. PMID: 16549852. Exclusion: E5

Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmo Mammographic Screening Program. J Natl Cancer Inst Monogr. 1997;22:63-7. PMID: 9709278. Exclusion: E3

Andrieu N, Easton DF, Chang-Claude J, et al. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol. 2006 Jul 20;24(21):3361-6. PMID: 16801631. Exclusion: E5

Andrykowski MA, Boerner LM, Salsman JM, et al. Psychological response to test results in an ovarian cancer screening program: a prospective, longitudinal study. Health Psychol. 2004 Nov;23(6):622-30. doi: 10.1037/0278-6133.23.6.622. PMID: 15546230. Exclusion: E3

Andrykowski MA, Carpenter JS, Studts JL, et al. Psychological impact of benign breast biopsy: a longitudinal, comparative study. Health Psychol. 2002 Sep;21(5):485-94. PMID: 12211516. Exclusion: E3

Ang P, Lim IHK, Lee TC, et al. BRCA1 and BRCA2 mutations in an Asian clinic-based population detected using a comprehensive strategy. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2276-84. PMID: 18006916. Exclusion: E5

Angelos P, Bedrosian I, Euhus DM, et al. Contralateral prophylactic mastectomy: Challenging considerations for the surgeon. Ann Surg Oncol. 2015 Oct;22(10):3208-12. doi: 10.1245/s10434-015-4758-y. PMID: 26259752. Exclusion: E6

Annunziata MA, Muzzatti B, Narciso D, et al. Mood state profile and coping strategies after BRCA-1/2 genetic test disclosure: a retrospective study in Italy. Support Care Cancer. 2011 Jun;19(6):733-5. PMID: 21267604. Exclusion: E3

Antill Y, Reynolds J, Young M-A, et al. Risk-reducing surgery in women with familial susceptibility for breast and/or ovarian cancer. Eur J Cancer. 2006 Mar;42(5):621-8. PMID: 16434187. Exclusion: E3

Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003 May;72(5):1117-30. doi: 10.1086/375033. PMID: 12677558. Exclusion: 2

Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer. 2008 Apr 22;98(8):1457-66. doi: 10.1038/sj.bjc.6604305. PMID: 18349832. Exclusion: 2

Antoniou AC, Gayther SA, Stratton JF, et al. Risk models for familial ovarian and breast cancer. Genet Epidemiol. 2000 Feb;18(2):173-90. doi: 10.1002/(SICI)1098-2272(200002)18:2<173::AID-GEPI6>3.0.CO;2-R. PMID: 10642429. Exclusion: 2

Antoniou AC, Pharoah PDP, Easton DF, et al. BRCA1 and BRCA2 cancer risks. J Clin Oncol. 2006 Jul 10;24(20):3312-3; author reply 3-4. PMID: 16829658. Exclusion: E6

Antoniou AC, Pharoah PDP, Narod S, et al. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. J Med Genet. 2005 Jul;42(7):602-3. PMID: 15994883. Exclusion: E6

Antoniou AC, Shenton A, Maher ER, et al. Parity and breast cancer risk among BRCA1 and BRCA2 mutation carriers. Breast Cancer Res. 2006;8(6):R72. PMID: 17187672. Exclusion: E5

Antoniou AC, Wang X, Fredericksen ZS, et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nat Genet. 2010 Oct;42(10):885-92. PMID: 20852631. Exclusion: E5

Antonucci I, Provenzano M, Sorino L, et al. Comparison between CaGene 5.1 and 6.0 for BRCA1/2 mutation prediction: A retrospective study of 150 BRCA1/2 genetic tests in 517 families with breast/ovarian cancer. J Hum Genet. 2017;62(3):379-

87. doi: 10.1038/jhg.2016.138. PMID: 27928164. Exclusion: E5

Apicella C, Peacock SJ, Andrews L, et al. Determinants of preferences for genetic counselling in Jewish women. Fam Cancer. 2006;5(2):159-67. PMID: 16736286. Exclusion: E5

Arai M, Miki Y, Yamaguchi T, et al. [Clinical genetics for hereditary cancers: from the viewpoint of physicians working at a hospital specialized in cancer]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]. 2005 Jul;32(7):948-53. PMID: 16044953. Exclusion: 2

Arason A, Jonasdottir A, Barkardottir RB, et al. A population study of mutations and LOH at breast cancer gene loci in tumours from sister pairs: two recurrent mutations seem to account for all BRCA1/BRCA2 linked breast cancer in Iceland. J Med Genet. 1998 Jun;35(6):446-9. PMID: 9643283. Exclusion: 2

Ardern-Jones A, Kenen R, Eeles R. Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40. Eur J Cancer Care (Engl). 2005 Jul;14(3):272-81. PMID: 15952973. Exclusion: E3

Armakolas A, Ladopoulou A, Konstantopoulou I, et al. BRCA2 gene mutations in Greek patients with familial breast cancer. Hum Mutat. 2002;19(1):81-2. PMID: 11754111. Exclusion: E3

Armel SR, McCuaig J, Finch A, et al. The effectiveness of family history questionnaires in cancer genetic counseling. J Genet Couns. 2009 Aug;18(4):366-78. doi: 10.1007/s10897-009-9228-x. PMID: 19459037. Exclusion: E5

Armel SR, McCuaig J, Gojska N, et al. All in the family: Barriers and motivators to the use of cancer family history questionnaires and the impact on attendance rates. J Genet Couns. 2015 Oct;24(5):822-32. doi: 10.1007/s10897-014-9813-5. PMID: 25558824. Exclusion: E5

Armstrong AC, Evans GD. Management of women at high risk of breast cancer. BMJ. 2014;348:g2756. doi: 10.1136/bmj.g2756. PMID: 24778341. Exclusion: E6

Armstrong J, Toscano M, Kotchko N, et al. Utilization and outcomes of BRCA genetic testing and counseling in a national commercially insured population: the about study. Obstet Gynecol Surv. 2016;71(5):287-8. doi: 10.1097/01.ogx.0000482583.01182.ea. PMID: 26426480. Exclusion: E4

Armstrong J, Toscano M, Kotchko N, et al. American BRCA Outcomes and Utilization of Testing (ABOUT) study: a pragmatic research model that incorporates personalized medicine/patient-centered outcomes in a real world setting. J Genet Couns. 2015 Feb;24(1):18-28. doi: 10.1007/s10897-014-9750-3. PMID: 25209347. Exclusion: E6

Armstrong K, Quistberg DA, Micco E, et al. Prescription of tamoxifen for breast cancer prevention by primary care physicians. Arch Intern Med. 2006 Nov 13;166(20):2260-5. PMID: 17101945. Exclusion: E5

Arnold AG, Otegbeye E, Fleischut MH, et al. Assessment of individuals with BRCA1 and BRCA2 large rearrangements in high-risk breast and ovarian cancer families. Breast Cancer Res Treat. 2014 Jun;145(3):625-34. doi: 10.1007/s10549-014-2987-6. PMID: 24825132. Exclusion: E5

Artioli G, Borgato L, Cappetta A, et al. Overall survival in BRCA-associated ovarian cancer: case-control study of an Italian series. Eur J Gynaecol Oncol. 2010;31(6):658-61. PMID: 21319511. Exclusion: E5

Arts-de Jong M, Manders CM, Hoogerbrugge N, et al. Added value of family history in counseling about risk of BRCA1/2 mutation in early-onset epithelial ovarian cancer. Int J Gynecol Cancer. 2013 Oct;23(8):1406-10. doi: 10.1097/IGC.0b013e3182a1cf71. PMID: 23975082. Exclusion: E3

Arun B, Mohsin S, Miller A, et al. Acquisition of breast tissue in a biomarker modulation study using bexarotene in women at high risk of breast cancer [abstract]. J Clin Oncol. 2005;23(106). Exclusion: E6

Atkin CK, Smith SW. Improving communication practices to reduce breast cancer environmental risks. J Health Commun. 2010 Sep;25(6-7):587-8. doi: 10.1080/10410236.2010.496836. PMID: 20845154. Exclusion: E6

Audrain J, Schwartz MD, Lerman C, et al. Psychological distress in women seeking genetic counseling for breast-ovarian cancer risk: the contributions of personality and appraisal. Ann Behav Med. 1997 Fall;19(4):370-7. doi: 10.1007/bf02895156. PMID: 9706364. Exclusion: E5

Auranen A, Song H, Waterfall C, et al. Polymorphisms in DNA repair genes and epithelial ovarian cancer risk. Int J Cancer. 2005 Nov 20;117(4):611-8. PMID: 15924337. Exclusion: E5

Awadelkarim KD, Aceto G, Veschi S, et al. BRCA1 and BRCA2 status in a Central Sudanese series of

breast cancer patients: interactions with genetic, ethnic and reproductive factors. Breast Cancer Res Treat. 2007 Apr;102(2):189-99. PMID: 17333343. Exclusion: E4

Aygin D, Cengiz H. Life quality of patients who underwent breast reconstruction after prophylactic mastectomy: systematic review. Breast Cancer. 2018 Sep;25(5):497-505. doi: 10.1007/s12282-018-0862-8. PMID: 29721811. Exclusion: E3

Ayme A, Viassolo V, Rapiti E, et al. Determinants of genetic counseling uptake and its impact on breast cancer outcome: a population-based study. Breast Cancer Res Treat. 2014 Apr;144(2):379-89. doi: 10.1007/s10549-014-2864-3. PMID: 24519389. Exclusion: E4

Aziz S, Kuperstein G, Rosen B, et al. A genetic epidemiological study of carcinoma of the fallopian tube. Gynecol Oncol. 2001;80:341-5. PMID: 11263928. Exclusion: E4

Azzollini J, Scuvera G, Bruno E, et al. Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study. Eur J Intern Med. 2016;32:65-71. doi: 10.1016/j.ejim.2016.03.010. PMID: 27062684. Exclusion: E5

Azzouzi A-R, Stoppa-Lyonnet D, Roupret M, et al. BRCA2 mutation screening is clinically relevant in breast and early prostate cancer families. Int J Urol. 2007 May;14(5):445-6. PMID: 17511731. Exclusion: E6

Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: Systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand. 2013;92(3):245-55. PMID: 23240575. Exclusion: E5

Baars JE, Ausems MG, van Riel E, et al. Communication between breast cancer patients who received inconclusive genetic test results and their daughters and sisters years after testing. J Genet Couns. 2016 Jun;25(3):461-71. doi: 10.1007/s10897-015-9889-6. PMID: 26446011. Exclusion: E3a

Babb SA, Swisher EM, Heller HN, et al. Qualitative evaluation of medical information processing needs of 60 women choosing ovarian cancer surveillance or prophylactic oophorectomy. J Genet Couns. 2002;11(2):81-96. doi: 10.1023/A:1014571420844. PMID: 26141655. Exclusion: E5

Bacha OM, Gregoire J, Grondin K, et al. Effectiveness of risk-reducing salpingo-oophorectomy in preventing ovarian cancer in a high-risk French Canadian population. Int J Gynecol Cancer. 2012 Jul;22(6):974-8. doi: 10.1097/IGC.0b013e318257b936. PMID: 22740003. Exclusion: E3a

Baer HJ, Brawarsky P, Murray MF, et al. Familial risk of cancer and knowledge and use of genetic testing. J Gen Intern Med. 2010;25(7):717-24. PMID: 20361271. Exclusion: E5

Baldwin LM, Trivers KF, Andrilla CH, et al. Accuracy of ovarian and colon cancer risk assessments by U.S. physicians. J Gen Intern Med. 2014 May;29(5):741-9. doi: 10.1007/s11606-014-2768-2. PMID: 24519100. Exclusion: E3

Balleine RL, Provan PJ, Pupo GM, et al. Familial concordance of breast cancer pathology as an indicator of genotype in multiple-case families. Genes Chromosomes Cancer. 2010 Dec;49(12):1082-94. PMID: 20815029. Exclusion: E5

Balmana J, Diez O, Campos B, et al. Sex ratio distortion in offspring of families with BRCA1 or BRCA2 mutant alleles: an ascertainment bias phenomenon? Breast Cancer Res Treat. 2005 Aug;92(3):273-7. PMID: 16155798. Exclusion: E5

Bancroft EK, Locke I, Ardern-Jones A, et al. The carrier clinic: an evaluation of a novel clinic dedicated to the follow-up of BRCA1 and BRCA2 carriers--implications for oncogenetics practice. J Med Genet. 2010 Jul;47(7):486-91. doi: 10.1136/jmg.2009.072728. PMID: 20472659. Exclusion: E5

Bandera CA, Muto MG, Schorge JO, et al. BRCA1 gene mutations in women with papillary serous carcinoma of the peritoneum Obstet Gynecol. 1998;92(4):596-600. PMID: 9764635. Exclusion: E3

Bane AL, Beck JC, Bleiweiss I, et al. BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. Am J Surg Pathol. 2007 Jan;31(1):121-8. PMID: 17197928. Exclusion: E3

Barke LD, Freivogel ME. Breast cancer risk assessment models and high-risk screening. Radiol Clin North Am. 2017;55(3):457-74. doi: 10.1016/j.rcl.2016.12.013. PMID: 28411673. Exclusion: 2

Barlin J, Pike M, Otegbeye E, et al. Does postmenopausal risk-reducing salpingo-oophorectomy reduce the risk of BRCA-associated breast cancer? Gynecol Oncol. 2013;130(1):e103-e4. doi: 10.1016/j.ygyno.2013.04.304. Exclusion: E6

Appendix A4. Excluded Studies List

Barlow-Stewart K, Taylor SD, Treloar SA, et al. Verification of consumers' experiences and perceptions of genetic discrimination and its impact on utilization of genetic testing. Genet Med. 2009 Mar;11(3):193-201. PMID: 19287242. Exclusion: E5

Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355(2):125-37. PMID: 16837676. Exclusion: 2

Barry A, Merrigan A, Tormey S. Choosing the most suitable risk assessment model when establishing a Family Risk Assessment Breast Cancer Clinic. Ir J Med Sci. 2013;182:S73. doi: 10.1007/s11845-013-0908-z. Exclusion: E6

Barton M, CN W, IL L, et al. Complications following bilateral prophylactic mastectomy. J Natl Cancer Inst Monogr. 2005;35:61-6. PMID: 16287887. Exclusion: E3

Barton MK. Rates of testing for BRCA mutations in young women are on the rise. CA Cancer J Clin. 2016;66(4):269-70. doi: 10.3322/caac.21306. PMID: 27149306. Exclusion: E6

Basham VM, Lipscombe JM, Ward JM, et al. BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res. 2002;4(1) PMID: 11879560. Exclusion: E3

Basu NN, Ingham S, Hodson J, et al. Risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a 30-year semi-prospective analysis. Fam Cancer. 2015 Dec;14(4):531-8. doi: 10.1007/s10689-015-9825-9. PMID: 26239694. Exclusion: E3b

Basu NN, Littlechild S, Barr L, et al. Attitudes to contralateral risk reducing mastectomy among breast and plastic surgeons in England. Ann R Coll Surg Engl. 2016 Feb;98(2):121-7. doi: 10.1308/rcsann.2016.0039. PMID: 26741657. Exclusion: E5

Basu NN, Littlechild S, Evans G, et al. Contralateral risk reducing mastectomy e A national survey of surgeons' practices and perceptions. Eur J Surg Oncol. 2013;39(11):S64. doi: 10.1016/j.ejso.2013.07.190. Exclusion: E3

Batista LI, Lu KH, Beahm EK, et al. Coordinated prophylactic surgical management for women with hereditary breast-ovarian cancer syndrome. BMC Cancer. 2008;8:101. PMID: 18410690. Exclusion: E3

Baty BJ, Dudley WN, Musters A, et al. Uncertainty in BRCA1 cancer susceptibility testing. Am J Med Genet C Semin Med Genet. 2006 Nov 15;142C(4):241-50. PMID: 17068806. Exclusion: E3

Baumann SL. Family Systems genetic Illness Model--breast cancer. Clin J Oncol Nurs. 2006 Jun;10(3):377-81. PMID: 16789582. Exclusion: E6

Bayraktar S, Arun B. BRCA mutation genetic testing implications in the United States. Breast. 2017 Feb;31:224-32. doi: 10.1016/j.breast.2016.11.021. PMID: 27931006. Exclusion: E9

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Byrski T, Gronwald J, Huzarski T, et al. Response to neo-adjuvant chemotherapy in women with BRCA1-positive breast cancers. Breast Cancer Res Treat. 2008 Mar;108(2):289-96. PMID: 17492376. Exclusion: E3

Cabrera E, Blanco I, Yague C, et al. The impact of genetic counseling on knowledge and emotional responses in Spanish population with family history of breast cancer. Patient Educ Couns. 2010 Mar;78(3):382-8. PMID: 19948386. Exclusion: E3

Caiata-Zufferey M. Genetically at-risk status and individual agency. A qualitative study on asymptomatic women living with genetic risk of breast/ovarian cancer. Soc Sci Med. 2015 May;132:141-8. doi: 10.1016/j.socscimed.2015.03.037. PMID: 25813728. Exclusion: E4

Caiata-Zufferey M, Pagani O, Cina V, et al. Challenges in managing genetic cancer risk: a long-term qualitative study of unaffected women carrying BRCA1/BRCA2 mutations. Genet Med. 2015 Sep;17(9):726-32. doi: 10.1038/gim.2014.183. PMID: 25503500. Exclusion: E5

Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 2007 Sep 1;25(25):3985-90. PMID: 17761984. Exclusion: E5

Calzone KA, Prindiville SA, Jourkiv O, et al. Randomized comparison of group versus individual genetic education and counseling for familial breast and/or ovarian cancer. J Clin Oncol. 2005;23(15):3455-64. doi: 10.1200/JCO.2005.04.050. PMID: 15908654. Exclusion: E3

Cameron LD, Reeve J. Risk perceptions, worry, and attitudes about genetic testing for breast cancer susceptibility. Psychol Health. 2006;21(2):211-30. doi: 10.1080/14768320500230318. PMID: 21985118. Exclusion: E4

Campfield Bonadies D, Moyer A, Matloff ET. What I wish I'd known before surgery: BRCA carriers' perspectives after bilateral salipingo-oophorectomy. Fam Cancer. 2011 Mar;10(1):79-85. PMID: 20852945. Exclusion: E5

Cao A, Huang L, Shao Z. The Preventive Intervention of Hereditary Breast Cancer. Adv Exp Med Biol. 2017;1026:41-57. doi: https://dx.doi.org/10.1007/978-981-10-6020-5_3. PMID: 29282679. Exclusion: E9

Cao MZ. Analysis of BRCA1 mutations among familial and/or breast cancer praecox patients in the east of Shandong in China. Prog Mod Biomed. 2009;9:1028-30. Exclusion: E8

Cao W, Wang X, Li J-C. Hereditary breast cancer in the Han Chinese population. J Epidemiol. 2013;23(2):75-84. PMID: 23318652. Exclusion: E6

Capanu M, Concannon P, Haile RW, et al. Assessment of rare BRCA1 and BRCA2 variants of unknown significance using hierarchical modeling. Genet Epidemiol. 2011 Jul;35(5):389-97. doi: 10.1002/gepi.20587. PMID: 21520273. Exclusion: E5

Cappelli M, Verma S, Korneluk Y, et al. Psychological and genetic counseling implications for adolescent daughters of mothers with breast cancer. Clin Genet. 2005 Jun;67(6):481-91. PMID: 15857415. Exclusion: E5

Carlsson AH, Bjorvatn C, Engebretsen LF, et al. Psychosocial factors associated with quality of life among individuals attending genetic counseling for hereditary cancer. J Genet Couns. 2004 Oct;13(5):425-45. PMID: 15604640. Exclusion: E5

Carmichael H, Matsen C, Freer P, et al. Breast cancer screening of pregnant and breastfeeding women with BRCA mutations. Breast Cancer Res Treat. 2017 04;162(2):225-30. doi: 10.1007/s10549-017-4122-y. PMID: 28138892. Exclusion: E7

Appendix A4. Excluded Studies List

Carney ME, Basiliere MS, Mates K, et al. Detection of BRCA1 and BRCA2 mutations in a selected Hawaii population. Hawaii Med J. 2010 Nov;69(11):268-71. PMID: 21218378. Exclusion: E5

Carroll JC, Wilson BJ, Allanson J, et al. GenetiKit: a randomized controlled trial to enhance delivery of genetics services by family physicians. Fam Pract. 2011 Dec;28(6):615-23. doi: 10.1093/fampra/cmr040. PMID: 21746696. Exclusion: E3

Carser JE, Quinn JE, Michie CO, et al. BRCA1 is both a prognostic and predictive biomarker of response to chemotherapy in sporadic epithelial ovarian cancer. Gynecol Oncol. 2011 Dec;123(3):492-8. PMID: 21920589. Exclusion: E3

Caruso A, Vigna C, Maggi G, et al. The withdrawal from oncogenetic counselling and testing for hereditary and familial breast and ovarian cancer. A descriptive study of an Italian sample. J Exp Clin Cancer Res. 2008;27:75. PMID: 19025627. Exclusion: E5

Caruso A, Vigna C, Marozzo B, et al. Subjective versus objective risk in genetic counseling for hereditary breast and/or ovarian cancers. J Exp Clin Cancer Res. 2009;28:157. PMID: 20025726. Exclusion: E3

Caruso A, Vigna C, Sega FM, et al. BRCA1/2 genes - Psychological side effects of unknown mutation result. Eur J Cancer. 2011;47:S185. doi: 10.1016/S0959-8049(11)70946-7. Exclusion: E6

Casey MJ, Synder C, Bewtra C, et al. Intra-abdominal carcinomatosis after prophylactic oophorectomy in women of hereditary breast ovarian cancer syndrome kindreds associated with BRCA1 and BRCA2 mutations. Gynecol Oncol. 2005 May;97(2):457-67. PMID: 15863145. Exclusion: E3a

Casey WJ, 3rd, Rebecca AM, Andres LA, et al. Safety and efficacy of perforator flap breast reconstruction with combined intraabdominal procedures. Ann Plast Surg. 2010 Feb;64(2):144-50. PMID: 20098096. Exclusion: E3

Catania C, Feroce I, Barile M, et al. Improved health perception after genetic counselling for women at high risk of breast and/or ovarian cancer: construction of new questionnaires--an Italian exploratory study. J Cancer Res Clin Oncol. 2016 Mar;142(3):633-48. doi: 10.1007/s00432-015-2062-7. PMID: 26577826. Exclusion: E5

Cavallone L, Arcand SL, Maugard CM, et al. Comprehensive BRCA1 and BRCA2 mutation analyses and review of French Canadian families with at least three cases of breast cancer. Fam Cancer. 2010 Dec;9(4):507-17. PMID: 20694749. Exclusion: E5

Ceber E, Soyer MT, Ciceklioglu M, et al. Breast cancer risk assessment and risk perception on nurses and midwives in Bornova Health District in Turkey. Cancer Nurs. 2006 May-Jun;29(3):244-9. PMID: 16783126. Exclusion: E4

Centre for Reviews and Dissemination. The psychological impact of mammographic screening on women with a family history of breast cancer: a systematic review (Provisional abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E5

Centre for Reviews and Dissemination. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23257 women with ovarian cancer and 87303 controls (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E5

Centre for Reviews and Dissemination. MRI and mammography surveillance of women at increased risk for breast cancer: recommendations using an evidence-based approach (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E6

Centre for Reviews and Dissemination. Does this patient have a family history of cancer: an evidence-based analysis of the accuracy of family cancer history (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E5

Centre for Reviews and Dissemination. Collection and use of cancer family history in primary care (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: 2

Centre for Reviews and Dissemination. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E5

Centre for Reviews and Dissemination. Expanding the criteria for BRCA mutation testing in breast cancer survivors (provisional abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E6

Appendix A4. Excluded Studies List

Centre for Reviews and Dissemination. Preventing future cancers by testing women with ovarian cancer for BRCA mutations (structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Cost-effectiveness of population-based BRCA1/2 testing and ovarian cancer prevention for Ashkenazi Jews: a call for dialogue (Provisional abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Cost-effectiveness of testing for breast cancer susceptibility genes (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. The cost-utility of magnetic resonance imaging for breast cancer in BRCA1 mutation carriers aged 30-49 (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer (structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Breast cancer screening, outside the population-screening program, of women from breast cancer families without proven BRCA1/BRCA2 mutations: a simulation study (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Gene expression profiling and breast cancer care: what are the potential benefits and policy implications? (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E3

Centre for Reviews and Dissemination. BRCA1 mutations in Southern England (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E6

Centre for Reviews and Dissemination. Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E5

Centre for Reviews and Dissemination. Chemoprevention of breast cancer: a joint guideline from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E9

Centre for Reviews and Dissemination. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: evidence synthethis (Structured abstract). Database of Abstracts of Reviews of Effects. 2012(1). Exclusion: E6

Centre for Reviews and Dissemination. Prophylactic laparoscopic ovarian ablation for premenopausal breast cancer: medical and economic efficacy (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E3

Centre for Reviews and Dissemination. Costs and benefits of diagnosing familial breast cancer (Structured abstract). NHS Economic Evaluation Database. 2012(1)doi: 10.1002/14651858. Exclusion: E5

Centre for Reviews and Dissemination. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers (Provisional abstract). Database of Abstracts of Reviews of Effects; 2012. Exclusion: 2

Centre for Reviews and Dissemination. Nonpharmacologic strategies for managing common chemotherapy adverse effects: a systematic review

(Structured abstract). Database of Abstracts of Reviews of Effects; 2012. Exclusion: 2

Centre Oscar Lambret. Radical Fimbriectomy for Young BRCA Mutation Carriers (Fimbriectomy). 2011. https://clinicaltrials.gov/ct2/show/NCT01608074. Accessed May 16 2019. Exclusion: E6

Chadwell SE, He H, Knapke S, et al. Factors influencing clinical follow-up for individuals with a personal history of breast and/or ovarian cancer and previous uninformative brca1 and brca2 testing. J Genet Couns. 2018 Mar:No Pagination Specified. doi: 10.1007/s10897-018-0241-9. PMID: 29550970. Exclusion: E3

Chai X, Domchek S, Kauff N, et al. RE: Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst. 2015 Sep;107(9)doi: 10.1093/jnci/djv217. PMID: 26264690. Exclusion: E6

Chai X, Friebel TM, Singer CF, et al. Use of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2014 Nov;148(2):397-406. doi: 10.1007/s10549-014-3134-0. PMID: 25311111. Exclusion: E5

Challberg J, Ashcroft L, Lalloo F, et al. Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT. Br J Cancer. 2011 Jun 28;105(1):22-7. doi: 10.1038/bjc.2011.202. PMID: 21654687. Exclusion: E5

Chambers K, Armstrong Iii EJ, Flippo-Morton T, et al. Treatment decisions in individuals with deleterious mutations of BRCA-1 and/or BRCA-2. Ann Surg Oncol. 2012;19(2):32-3. doi: 10.1245/s10434-012-2344-06p. Exclusion: E5

Chambers K, Carpenter K, Flippo-Morton T, et al. BRCA-positive patients without cancer at the time of diagnosis and the plan of care chosen. Ann Surg Oncol. 2013;20(2):29. doi: 10.1245/s10434-013-2964-z. Exclusion: E6

Chambers KM, Armstrong EJ, Flippo T, et al. The follow-up sought after diagnosis of a BRCA-1 or BRCA-2 mutation. J Clin Oncol. 2012;30(27). Exclusion: E5

Chan JL, Johnson LNC, Sammel MD, et al. Reproductive Decision-Making in Women with BRCA1/2 Mutations. J Genet Couns. 2017 Jun;26(3):594-603. doi: https://dx.doi.org/10.1007/s10897-016-0035-x. PMID: 27796678. Exclusion: E5

Chan K, Morris GJ. Chemoprevention of breast cancer for women at high risk. Semin Oncol. 2006 Dec;33(6):642-6. PMID: 17145342. Exclusion: E9

Chang M, Lee SC, Min JW, et al. Validation study of a breast cancer risk assessment programme for Korean women. Eur J Cancer. 2014;50:S83. doi: 10.1016/S0959-8049(14)70078-4. Exclusion: E5

Chang-Claude J, Andrieu N, Rookus M, et al. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev. 2007 Apr;16(4):740-6. PMID: 17416765. Exclusion: E5

Chapman JS, Jacoby V, Chen LM. Managing symptoms and maximizing quality of life after preventive interventions for cancer risk reduction. Curr Opin Obstet Gynecol. 2015 Feb;27(1):40-4. doi: 10.1097/GCO.0000000000000146. PMID: 25502430. Exclusion: E6

Chart PL, Franssen E. Management of women at increased risk for breast cancer: Preliminary results from a new program. Can Med Assoc J. 1997;157:1235-42. PMID: 9361645. Exclusion: E5

Chavarri-Guerra Y, Blazer KR, Weitzel JN. Genetic cancer risk assessment for breast cancer in Latin America. Rev Invest Clin. 2017 Mar-Apr;69(2):94-102. PMID: 28453507. Exclusion: E9

Chen F-M, Hou M-F, Chang M-Y, et al. High frequency of somatic missense mutation of BRCA2 in female breast cancer from Taiwan. Cancer Lett. 2005 Apr 8;220(2):177-84. PMID: 15766593. Exclusion: E3

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007 Apr 10;25(11):1329-33. doi: 10.1200/JCO.2006.09.1066. PMID: 17416853. Exclusion: 2

Chen Y, Toland AE, McLennan J, et al. Lack of germ-line promoter methylation in BRCA1-negative families with familial breast cancer. Genetic Testing. 2006;10(4):281-4. PMID: 17253935. Exclusion: E5

Chern JY, Lee SS, Frey MK, et al. The influence of BRCA variants of uncertain significance in cancer risk management decision-making. J Clin Oncol. 2015;33(15). Exclusion: E5

Cherry C, Ropka M, Lyle J, et al. Understanding the needs of women considering risk-reducing salpingo-oophorectomy. Cancer Nurs. 2013 May-Jun;36(3):E33-8. doi:

10.1097/NCC.0b013e3182642cb5. PMID: 22964868. Exclusion: E4

Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol. 2008 Jan 1;26(1):20-5. PMID: 18165636. Exclusion: E3

Chiaffarino F, Parazzini F, Decarli A, et al. Hysterectomy with or without unilateral oophorectomy and risk of ovarian cancer. Gynecol Oncol. 2005 May;97(2):318-22. PMID: 15863124. Exclusion: E3

Chin T-M, Tan S-H, Lim S-E, et al. Acceptance, motivators, and barriers in attending breast cancer genetic counseling in Asians. Cancer Detect Prev. 2005;29(5):412-8. PMID: 16185817. Exclusion: E5

Chlebowski RT, Prentice RL. Menopausal hormone therapy in BRCA1 mutation carriers: uncertainty and caution. J Natl Cancer Inst. 2008 Oct 1;100(19):1341-3. PMID: 18812547. Exclusion: E4

Chopra I, Kelly KM. Cancer Risk Information Sharing: The Experience of Individuals Receiving Genetic Counseling for BRCA1/2 Mutations. J Health Commun. 2017 Feb;22(2):143-52. doi: 10.1080/10810730.2016.1258743. PMID: 28112991. Exclusion: E3a

Chowdhury S, Dent T, Pashayan N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med. 2013 Jun;15(6):423-32. doi: 10.1038/gim.2012.167. PMID: 23412607. Exclusion: E6

Christie J, Quinn GP, Malo T, et al. Cognitive and psychological impact of BRCA genetic counseling in before and after definitive surgery breast cancer patients. Ann Surg Oncol. 2012 Dec;19(13):4003-11. doi: 10.1245/s10434-012-2460-x. PMID: 22766984. Exclusion: E3

Chun DS, Berse B, Venne VL, et al. BRCA testing within the Department of Veterans Affairs: concordance with clinical practice guidelines. Fam Cancer. 2017;16(1):41-9. doi: 10.1007/s10689-016-9921-5. PMID: 27589855. Exclusion: E5

Cibula D, Zikan M, Dusek L, et al. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert Rev Anticancer Ther. 2011 Aug;11(8):1197-207. PMID: 21916573. Exclusion: E4

Cicchetti A, Ruggeri M, Di Brino E. Cost-effectiveness of a preventive testing strategy in relatives of patients with BRCA mutated ovarian cancer versus a no test strategy. Value Health. 2016;19(7):A696. Exclusion: E6

Cicero G, De Luca R, Dorangricchia P, et al. Risk perception and psychological distress in genetic counselling for hereditary breast and/or ovarian cancer. J Genet Couns. 2017 Oct;26(5):999-1007. doi: 10.1007/s10897-017-0072-0. PMID: 28283917. Exclusion: E3a

Ciernikova S, Tomka M, Kovac M, et al. Ashkenazi founder BRCA1/BRCA2 mutations in Slovak hereditary breast and/or ovarian cancer families. Neoplasma. 2006;53(2):97-102. PMID: 16575464. Exclusion: E5

Cini G, Mezzavilla M, Della Puppa L, et al. Tracking of the origin of recurrent mutations of the BRCA1 and BRCA2 genes in the North-East of Italy and improved mutation analysis strategy. BMC Med Genet. 2016;17:11. doi: 10.1186/s12881-016-0274-6. PMID: 26852130. Exclusion: E5

Claes E, Evers-Kiebooms G, Boogaerts A, et al. Diagnostic genetic testing for hereditary breast and ovarian cancer in cancer patients: women's looking back on the pre-test period and a psychological evaluation. Genetic Testing. 2004;8(1):13-21. PMID: 15140370. Exclusion: E3

Clague J, Villarreal-Garza C, Navarro AD, et al. Evaluation of the BOADICEA model for predicting BRCA1 and BRCA2 mutation carrier probabilities in high-risk US Hispanic and Mexican families: A report from the clinical cancer genetics community research network. Cancer Res. 2015;75(15)doi: 10.1158/1538-7445.AM2015-2761. Exclusion: E4

Clementino LS, Suzuki EH, de Oliveira KB. Risk assessment for breast cancer and BRCA mutations in women with personal and familial history. Acta Scientiarum - Health Sciences. 2013;35(2):263-71. doi: 10.4025/actascihealthsci.v35i2.12134. Exclusion: E5

Clements A, Henderson BJ, Tyndel S, et al. Diagnosed with breast cancer while on a family history screening programme: an exploratory qualitative study. Eur J Cancer Care (Engl). 2008 May;17(3):245-52. PMID: 18419627. Exclusion: E5

Cock-Rada AM, Ossa CA, Garcia HI, et al. A multi-gene panel study in hereditary breast and ovarian cancer in Colombia. Fam Cancer. 2018 01;17(1):23-30. doi: https://dx.doi.org/10.1007/s10689-017-0004-z. PMID: 28528518. Exclusion: E5

Cody N, Green A, McDevitt T, et al. Cascade screening in BRCA1/2 mutation carriers. Ir Med J.

2008 May;101(5):140-2. PMID: 18624259. Exclusion: E5

Coelho JJ, Arnold A, Nayler J, et al. An assessment of the efficacy of cancer genetic counselling using real-time videoconferencing technology (telemedicine) compared to face-to-face consultations. Eur J Cancer. 2005 Oct;41(15):2257-61. doi: 10.1016/j.ejca.2005.06.020. PMID: 16176873. Exclusion: E4

Cohen SA, Nixon DM. A collaborative approach to cancer risk assessment services using genetic counselor extenders in a multi-system community hospital. Breast Cancer Res Treat. 2016;159(3):527-34. doi: 10.1007/s10549-016-3964-z. PMID: 27581128. Exclusion: E5

Colditz GA, Willett WC, Hunter DJ, et al. Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA. 1993 Jul 21;270(3):338-43. PMID: 8123079. Exclusion: 2

Collins IM, Milne RL, Weideman PC, et al. Preventing breast and ovarian cancers in high-risk BRCA1 and BRCA2 mutation carriers. Med J Aust. 2013 Nov 18;199(10):680-3. PMID: 24237098. Exclusion: E5

Collins LC, Baer HJ, Tamimi RM, et al. The influence of family history on breast cancer risk in women with biopsy-confirmed benign breast disease: results from the Nurses' Health Study. Cancer. 2006 Sep 15;107(6):1240-7. PMID: 16902983. Exclusion: E5

Conner JR, Meserve E, Pizer E, et al. Outcome of unexpected adnexal neoplasia discovered during risk reduction salpingo-oophorectomy in women with germ-line BRCA1 or BRCA2 mutations. Gynecol Oncol. 2014 Feb;132(2):280-6. doi: 10.1016/j.ygyno.2013.12.009. PMID: 24333842. Exclusion: E7

Contant C, van Wersch A, Menke-Pluymers M, et al. Satisfaction and prosthesis related complaints in women with immediate breast reconstruction following prophylactic and oncological mastectomy. Psychol Health Med. 2004 Feb;9(1):71-84. doi: 10.1080/13548500310001637760. Exclusion: E3

Contant CM, Menke-Pluijmers MB, Seynaeve C, et al. Clinical experience of prophylactic mastectomy followed by immediate breast reconstruction in women at hereditary risk of breast cancer (HB(O)C) or a proven BRCA1 and BRCA2 germ-line mutation. Eur J Surg Oncol. 2002 Original Search 6-20-03

Reference Search 3-17-04;28(6):627-32. PMID: 12359199 Exclusion: E3

Contegiacomo A, Pensabene M, Capuano I, et al. An oncologist-based model of cancer genetic counselling for hereditary breast and ovarian cancer. Ann Oncol. 2004 May;15(5):726-32. PMID: 15111339. Exclusion: E3

Cook LS, Neilson HK, Lorenzetti DL, et al. A systematic literature review of vitamin D and ovarian cancer. Am J Obstet Gynecol. 2010;203(1):70. e1-. e8. PMID: 20227054. Exclusion: E5

Coopey SB, Acar A, Griffin M, et al. The impact of patient age on breast cancer risk prediction models. Breast J. 2018;24(4):592-8. doi: 10.1111/tbj.12976. Exclusion: E4

Copur MS, Percich S, Jordan A, et al. Cancer genetic counseling services (GCS) in a community-based cancer center (CBCC) in rural Nebraska: Effect of National Community Cancer Centers Program (NCCCP). J Clin Oncol. 2011;29(15). Exclusion: E4

Cortesi L, Masini C, Cirilli C, et al. Favourable ten-year overall survival in a Caucasian population with high probability of hereditary breast cancer. BMC Cancer. 2010;10:90. PMID: 20219108. Exclusion: E3

Costa S, Sacchetti M, Batista R, et al. Evaluation of the program BRCAPRO in a breast cancer centre. Eur J Cancer. 2012;48:S52. Exclusion: E6

Cott Chubiz JE, Lee JM, Gilmore ME, et al. Cost-effectiveness of alternating magnetic resonance imaging and digital mammography screening in BRCA1 and BRCA2 gene mutation carriers. Cancer. 2013 Mar 15;119(6):1266-76. doi: 10.1002/cncr.27864. PMID: 23184400. Exclusion: E7

Couch FJ, Sinilnikova O, Vierkant RA, et al. AURKA F31I polymorphism and breast cancer risk in BRCA1 and BRCA2 mutation carriers: a consortium of investigators of modifiers of BRCA1/2 study. Cancer Epidemiol Biomarkers Prev. 2007 Jul;16(7):1416-21. PMID: 17627006. Exclusion: E5

Couzin J. Breast cancer. Dissecting a hidden breast cancer risk. Science. 2005 Sep 9;309(5741):1664-6. PMID: 16150987. Exclusion: E6

Cox DG, Hankinson SE, Hunter DJ. No association between BRCA2 N372H and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2005 May;14(5):1353-4. PMID: 15894703. Exclusion: E5

Cox DG, Kraft P, Hankinson SE, et al. Haplotype analysis of common variants in the BRCA1 gene and risk of sporadic breast cancer. Breast Cancer Res. 2005;7(2):R171-5. PMID: 15743496. Exclusion: E5

Appendix A4. Excluded Studies List

Cragun D, Weidner A, Lewis C, et al. Racial disparities in BRCA testing and cancer risk management across a population-based sample of young breast cancer survivors. Cancer. 2017doi: 10.1002/cncr.30621. PMID: 28182268. Exclusion: E5

Crepeau AZ, Willoughby L, Pinsky B, et al. Accuracy of personal breast cancer risk estimation in cancer-free women during primary care visits. Women Health. 2008;47(2):113-30. PMID: 18681103. Exclusion: E5

Crispo A, D'Aiuto G, De Marco M, et al. Gail model risk factors: impact of adding an extended family history for breast cancer. Breast J. 2008 May-Jun;14(3):221-7. PMID: 18373641. Exclusion: E3

Crotser CB, Dickerson SS. Women receiving news of a family BRCA1/2 mutation: messages of fear and empowerment. J Nurs Scholarsh. 2010;42(4):367-78. doi: 10.1111/j.1547-5069.2010.01366.x. PMID: 21091619. Exclusion: 2

Crum CP, Drapkin R, Kindelberger D, et al. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res. 2007 Mar;5(1):35-44. doi: 10.3121/cmr.2007.702. PMID: 17456833. Exclusion: 2

Cruzado JA. Decision making of participants in cancer genetic counseling. Psicooncologia. 2010;7(2-3):341-62. Exclusion: E4

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Cullinane CA, Lubinski J, Neuhausen SL, et al. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer. 2005 Dec 20;117(6):988-91. PMID: 15986445. Exclusion: E5

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Ellisen LW, Kurian AW, Desmond AJ, et al. Clinical impact of multi-gene panel testing for hereditary breast and ovarian cancer risk assessment. J Clin Oncol. 2015;33(15). Exclusion: E5

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Elrick A, Ashida S, Ivanovich J, et al. Psychosocial and clinical factors associated with family communication of cancer genetic test results among women diagnosed with breast cancer at a young age. J Genet Couns. 2017 Feb;26(1):173-81. doi: 10.1007/s10897-016-9995-0. PMID: 27422778. Exclusion: E3

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BRCA2 sequence alterations in breast and/or ovarian cancer families of Eastern Spain. Breast Cancer Res Treat. 2008 Nov;112(1):69-73. PMID: 18060494. Exclusion: E5

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Evans D, Gareth R, Lennard F, et al. Eligibility for magnetic resonance imaging screening in the United Kingdom: effect of strict selection criteria and anonymous DNA testing on breast cancer incidence in the MARIBS Study. Cancer Epidemiol Biomarkers Prev. 2009 Jul;18(7):2123-31. PMID: 19567506. Exclusion: 2

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Evans DG, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet. 2009;46(9):593-7. PMID: 18413372. Exclusion: E5

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Evans DG, Howell A. Can the breast screening appointment be used to provide risk assessment and prevention advice? Breast Cancer Res. 2015;17:84. doi: 10.1186/s13058-015-0595-y. PMID: 26155950. Exclusion: E4

Evans DG, Howell A, Ingham SL, et al. Contralateral breast cancer risk in BRCA1/2-positive families needs to be adjusted for phenocopy rates particularly in second-degree untested relatives. Breast Cancer Res. 2013;15(1):401. doi: 10.1186/bcr3382. PMID: 23448362. Exclusion: E6

Evans DG, Ingham S, Dawe S, et al. Breast cancer risk assessment in 8,824 women attending a family history evaluation and screening programme. Fam Cancer. 2014 Jun;13(2):189-96. doi: 10.1007/s10689-013-9694-z. PMID: 24276527. Exclusion: E4

Evans DG, Ingham SL, Baildam A, et al. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2013 Jul;140(1):135-42. doi: 10.1007/s10549-013-2583-1. PMID: 23784379. Exclusion: E3b

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Evans DG, Woodward ER, Howell SJ, et al. Risk algorithms that include pathology adjustment for HER2 amplification need to make further downward adjustments in likelihood scores. Fam Cancer. 2017 04;16(2):173-9. doi: https://dx.doi.org/10.1007/s10689-016-9942-0. PMID: 27796713. Exclusion: E3

Evans DG, Young K, Bulman M, et al. Probability of BRCA1/2 mutation varies with ovarian histology: results from screening 442 ovarian cancer families. Clin Genet. 2008 Apr;73(4):338-45. doi: 10.1111/j.1399-0004.2008.00974.x. PMID: 18312450. Exclusion: 2

Evans DGR, Binchy A, Shenton A, et al. Comparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. Clin Genet. 2009 Feb;75(2):124-32. PMID: 19215246. Exclusion: E5

Evans DGR, Lalloo F, Ashcroft L, et al. Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. Cancer Epidemiol Biomarkers Prev. 2009 Aug;18(8):2318-24. PMID: 19661091. Exclusion: E5

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Appendix A4. Excluded Studies List

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Fakkert IE, Jansen L, Meijer K, et al. Breast cancer screening in BRCA1 and BRCA2 mutation carriers after risk reducing salpingo-oophorectomy. Breast Cancer Res Treat. 2011 Aug;129(1):157-64. PMID: 21373873. Exclusion: E5

Fakkert IE, Mourits MJE, Jansen L, et al. Breast cancer incidence after risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers. Cancer Prev Res (Phila). 2012 Nov;5(11):1291-7. doi: 10.1158/1940-6207.CAPR-12-0190. PMID: 23009828. Exclusion: H2

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Fang CY, Cherry C, Devarajan K, et al. A prospective study of quality of life among women undergoing risk-reducing salpingo-oophorectomy versus gynecologic screening for ovarian cancer. Gynecol Oncol. 2009 Mar;112(3):594-600. PMID: 19141360. Exclusion: H2

Fang CY, Miller SM, Malick J, et al. Psychosocial correlates of intention to undergo prophylactic oophorectomy among women with a family history of ovarian cancer. Prev Med. 2003 Nov;37(5):424-31. PMID: 14572427. Exclusion: E5

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Farr DE. The impact of false positive mammography results on breast cancer screening intention among Black women. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2018;79(11-B(E)):No Pagination Specified. PMID: 2018-40527-027. Exclusion: E6

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Farrell C, Lyman M, Freitag K, et al. The role of hereditary nonpolyposis colorectal cancer in the management of familial ovarian cancer. Genet Med. 2006 Oct;8(10):653-7. PMID: 17079882. Exclusion: E5

Farrelly A, White V, Meiser B, et al. Unmet support needs and distress among women with a BRCA1/2 mutation. Fam Cancer. 2013 Sep;12(3):509-18. doi: 10.1007/s10689-012-9596-5. PMID: 23264090. Exclusion: E4

Farshid G, Balleine RL, Cummings M, et al. Morphology of breast cancer as a means of triage of patients for BRCA1 genetic testing. Am J Surg Pathol. 2006 Nov;30(11):1357-66. PMID: 17063074. Exclusion: E3

Fehniger J, Lin F, Beattie M. Family communication of genetic test results and uptake of genetic testing in a diverse population of BRCA1 and BRCA2 (BRCA1/2) carriers. Gynecol Oncol. 2012;127(1):S22-S3. doi: 10.1016/j.ygyno.2012.07.062. Exclusion: E5

Fehniger J, Lin F, Beattie MS, et al. Family communication of BRCA1/2 results and family uptake of BRCA1/2 testing in a diverse population of BRCA1/2 carriers. J Genet Couns. 2013 Oct;22(5):603-12. doi: 10.1007/s10897-013-9592-4. PMID: 23666114. Exclusion: E5

Fejerman L, John EM, Huntsman S, et al. Genetic ancestry and risk of breast cancer among U.S. Latinas. Cancer Res. 2008 Dec 1;68(23):9723-8. PMID: 19047150. Exclusion: E4

Feki A, Irminger-Finger I. Mutational spectrum of p53 mutations in primary breast and ovarian tumors. Crit Rev Oncol Hematol. 2004 Nov;52(2):103-16. PMID: 15501075. Exclusion: E9

Ferla R, Calo V, Cascio S, et al. Founder mutations in BRCA1 and BRCA2 genes. Ann Oncol. 2007 Jun;18 Suppl 6:vi93-8. PMID: 17591843. Exclusion: E6

Field KM, Jenkins MA, Friedlander ML, et al. Predictors of the use of complementary and alternative medicine (CAM) by women at high risk for breast cancer. Eur J Cancer. 2009 Mar;45(4):551-60. PMID: 18996690. Exclusion: E5

Figueiredo JC, Haile RW, Bernstein L, et al. Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and noncarriers: the

WECARE Study. Breast Cancer Res Treat. 2010 Feb;120(1):175-83. PMID: 19597986. Exclusion: E5

Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006 Jul 12;296(2):185-92. PMID: 16835424. Exclusion: E3a

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Finch A, Metcalfe KA, Chiang J, et al. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psychooncology. 2013 Jan;22(1):212-9. doi: 10.1002/pon.2041. PMID: 21913283. Exclusion: E3a

Finch A, Narod SA. Quality of life and health status after prophylactic salpingo-oophorectomy in women who carry a BRCA mutation: A review. Maturitas. 2011 Nov;70(3):261-5. PMID: 21893388. Exclusion: E9

Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol. 2006 Jan;100(1):58-64. PMID: 16137750. Exclusion: E5

Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014 May 20;32(15):1547-53. doi: 10.1200/JCO.2013.53.2820. PMID: 24567435. Exclusion: E3a

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652-62. PMID: 16288118. Exclusion: E3

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998 Sep 16;90(18):1371-88. PMID: 9747868. Exclusion: 2

Fisher C, Bylund C, Rising C, et al. Managing women's uncertainty during genetic counseling sessions for BRCA testing. Psychooncology. 2015;24:51-2. doi: 10.1002/pon.3873. Exclusion: E5

Fisher CL, Maloney E, Glogowski E, et al. Talking about familial breast cancer risk: topics and strategies to enhance mother-daughter interactions. Qual Health Res. 2014 Apr;24(4):517-35. doi: 10.1177/1049732314524638. PMID: 24633365. Exclusion: E5

Fisher CL, Roccotagliata T, Rising CJ, et al. "I don't want to be an ostrich": Managing mothers' uncertainty during BRCA1/2 genetic counseling. J Genet Couns. 2017 Jun;26(3):455-68. doi: 10.1007/s10897-016-9998-x. PMID: 27473644. Exclusion: E5

Fishman A. The effects of parity, breastfeeding, and infertility treatment on the risk of hereditary breast and ovarian cancer: a review. Int J Gynecol Cancer. 2010 Oct;20(11 Suppl 2):S31-3. PMID: 20975359. Exclusion: E9

Fishman DA, Cohen L, Blank SV, et al. The role of ultrasound evaluation in the detection of early-stage epithelial ovarian cancer. Am J Obstet Gynecol. 2005;192(4):1214-22. PMID: 15846205. Exclusion: E5

Fleeman N, Martin Saborido C, Payne K, et al. The clinical effectiveness and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen: a systematic review (Structured abstract). Health Technol Assess; 2011. Exclusion: E3

Fleming PJ, Vadaparampil ST, Bonner D, et al. BRCA mutations and surgical decision making in a sample of young black women with invasive breast cancer. Cancer Epidemiology Biomarkers and Prevention. 2011;20(10)doi: 10.1158/1055-9965.DISP-11-A71. Exclusion: E3

Fletcher O, Johnson N, Dos Santos Silva I, et al. Family history, genetic testing, and clinical risk prediction: pooled analysis of CHEK2 1100delC in 1,828 bilateral breast cancers and 7,030 controls. Cancer Epidemiol Biomarkers Prev. 2009 Jan;18(1):230-4. PMID: 19124502. Exclusion: E5

Flores KG, Steffen LE, McLouth CJ, et al. Factors associated with interest in gene-panel testing and risk communication preferences in women from BRCA1/2 negative families. J Genet Couns. 2017 Jun;26(3):480-90. doi: 10.1007/s10897-016-0001-7. PMID: 27496122. Exclusion: E3

Appendix A4. Excluded Studies List

Forbes Shepherd R, Browne TK, Warwick L. A Relational Approach to Genetic Counseling for Hereditary Breast and Ovarian Cancer. J Genet Couns. 2017 Apr;26(2):283-99. doi: https://dx.doi.org/10.1007/s10897-016-0022-2. PMID: 27761849. Exclusion: E5

Fortuny D, Balmana J, Grana B, et al. Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort.[Erratum appears in Hum Reprod. 2009 Jul;24(7):1772]. Hum Reprod. 2009 Apr;24(4):1000-6. PMID: 19112076. Exclusion: E4

Foulkes WD. BRCA1 and BRCA2 - update and implications on the genetics of breast cancer: a clinical perspective. Clin Genet. 2014 Jan;85(1):1-4. doi: 10.1111/cge.12291. PMID: 24116874. Exclusion: E6

Foulkes WD, Knoppers BM, Turnbull C. Population genetic testing for cancer susceptibility: founder mutations to genomes. Nature Reviews Clinical Oncology. 2016 Jan;13(1):41-54. doi: 10.1038/nrclinonc.2015.173. PMID: 26483301. Exclusion: 2

Fourquet A, Stoppa-Lyonnet D, Kirova YM, et al. Familial breast cancer: clinical response to induction chemotherapy or radiotherapy related to BRCA1/2 mutations status. Am J Clin Oncol. 2009 Apr;32(2):127-31. PMID: 19307946. Exclusion: E3

Francken AB, Schouten PC, Bleiker EM, et al. Breast cancer in women at high risk: the role of rapid genetic testing for BRCA1 and -2 mutations and the consequences for treatment strategies. Breast. 2013 Oct;22(5):561-8. doi: 10.1016/j.breast.2013.07.045. PMID: 23972475. Exclusion: E3

Frank B, Hemminki K, Meindl A, et al. BRIP1 (BACH1) variants and familial breast cancer risk: a case-control study. BMC Cancer. 2007;7:83. PMID: 17504528. Exclusion: E5

Freedman AN, Wideroff L, Olson L, et al. US physicians' attitudes toward genetic testing for cancer susceptibility. Am J Med Genet. 2003;120 A(1):63-71. PMID: 12794694. Exclusion: E5

Freedman ML, Penney KL, Stram DO, et al. Common variation in BRCA2 and breast cancer risk: a haplotype-based analysis in the Multiethnic Cohort. Hum Mol Genet. 2004 Oct 15;13(20):2431-41. PMID: 15317758. Exclusion: E5

Freedman ML, Penney KL, Stram DO, et al. A haplotype-based case-control study of BRCA1 and sporadic breast cancer risk. Cancer Res. 2005 Aug 15;65(16):7516-22. PMID: 16103107. Exclusion: E5

Freisinger F, Domchek SM. Clinical implications of low-penetrance breast cancer susceptibility alleles. Curr Oncol Rep. 2009 Jan;11(1):8-14. PMID: 19080736. Exclusion: E9

Frey MK, Kim SH, Bassett RY, et al. Rescreening for genetic mutations using multi-gene panel testing in patients who previously underwent non-informative genetic screening. Gynecol Oncol. 2015 Nov;139(2):211-5. doi: 10.1016/j.ygyno.2015.08.006. PMID: 26296696. Exclusion: E5

Freysteinson WM, Deutsch AS, Lewis C, et al. The experience of viewing oneself in the mirror after a mastectomy. Oncol Nurs Forum. 2012 Jul;39(4):361-9. doi: 10.1188/12.ONF.361-369. PMID: 22750894. Exclusion: E3

Frezzo TM, Rubinstein WS, Dunham D, et al. The genetic family history as a risk assessment tool in internal medicine. Genet Med. 2003;5(2):84-91. PMID: CN-00558460. Exclusion: E5

Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed. 2005;7(2):60. PMID: 16369438. Exclusion: E9

Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 2007;7:152. PMID: 17683622. Exclusion: E5

Friedman E, Kotsopoulos J, Lubinski J, et al. Spontaneous and therapeutic abortions and the risk of breast cancer among BRCA mutation carriers. Breast Cancer Res. 2006;8(2):R15. PMID: 16563180. Exclusion: E4

Friedman LC. Psychological impact of receiving negative BRCA1 mutation test results in Ashkenazim. Genet Med. 1999;1(3):74-9. PMID: 11336456. Exclusion: H2

Friedman LC, Kalidas M, Elledge R, et al. Optimism, social support and psychosocial functioning among women with breast cancer. Psycho Oncology. 2006 Jul;15(7):595-603. doi: 10.1002/pon.992. PMID: 16287209. Exclusion: E3

Friedrichsen DM, Malone KE, Doody DR, et al. Frequency of CHEK2 mutations in a population based, case-control study of breast cancer in young women. Breast Cancer Res. 2004;6(6):R629-35. PMID: 15535844. Exclusion: E4

Frost MH, Hoskin TL, Hartmann LC, et al. Contralateral prophylactic mastectomy: long-term consistency of satisfaction and adverse effects and the significance of informed decision-making, quality

of life, and personality traits. Ann Surg Oncol. 2011 Oct;18(11):3110-6. PMID: 21947589. Exclusion: E3

Frost MH, Slezak JM, Tran NV, et al. Satisfaction after contralateral prophylactic mastectomy: the significance of mastectomy type, reconstructive complications, and body appearance. J Clin Oncol. 2005 Nov 1;23(31):7849-56. PMID: 16204003. Exclusion: E3a

Fumagalli D, Sotiriou C. Treatment of pT1N0 breast cancer: multigene predictors to assess risk of relapse. Ann Oncol. 2010 Oct;21 Suppl 7:vii103-6. PMID: 20943601. Exclusion: E9

Gaba FM, Manchanda R, Gaba FM, et al. Genetic testing for gynaecological cancer. Obstetrics, Gynaecology and Reproductive Medicine. 2017;27(1):29-31. doi: 10.1016/j.ogrm.2016.11.001. Exclusion: E3

Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci U S A. 2014 Sep 30;111(39):14205-10. doi: 10.1073/pnas.1415979111. PMID: 25192939. Exclusion: E3

Gabaldó Barrios X, Sánchez Bermúdez A, Sarabia Meseguer A, et al. Prevalence of BRCA mutation carriers with breast cancer without family history of cancer. Are physician recommendations for brca1/2 testing appropriate? Clin Chem Lab Med. 2014;52:S836. doi: 10.1515/cclm-2014-4027. Exclusion: E4

Gabaldó Barrios X, Sánchez Bermúdez AI, Sánchez P, et al. Clinical characteristics of gynecological cancer in BRCA mutation carriers and noncarriers. Clin Chem Lab Med. 2014;52:S819. doi: 10.1515/cclm-2014-4027. Exclusion: E4

Gaber RS, Thekkekara RJ, Gil DN, et al. Uptake of genetic testing for BRCA mutations in a medically underserved population. Cancer Res. 2016;76(4)doi: 10.1158/1538-7445.SABCS15-P6-12-09. Exclusion: E5

Gabos Z, Thoms J, Ghosh S, et al. The association between biological subtype and locoregional recurrence in newly diagnosed breast cancer. Breast Cancer Res Treat. 2010 Nov;124(1):187-94. PMID: 20814819. Exclusion: E3

Gabriel CA, Tigges-Cardwell J, Stopfer J, et al. Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk-reducing salpingo-oophorectomy. Fam Cancer. 2009;8(1):23-8. PMID: 18758995. Exclusion: E5

Gabrovska PN, Smith RA, O'Leary G, et al. Investigation of the 1758G>C and 2880A>G variants within the NCOA3 gene in a breast cancer affected Australian population. Gene. 2011;482(1-2):68-72. PMID: 21601620. Exclusion: E3

Gadducci A, Biglia N, Cosio S, et al. Gynaecologic challenging issues in the management of BRCA mutation carriers: oral contraceptives, prophylactic salpingo-oophorectomy and hormone replacement therapy. Gynecol Endocrinol. 2010 Aug;26(8):568-77. PMID: 20632911. Exclusion: E5

Gadducci A, Sergiampietri C, Tana R. Alternatives to risk-reducing surgery for ovarian cancer. Ann Oncol. 2013;24(suppl_8):viii47-viii53. PMID: 24131970. Exclusion: E9

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Appendix A4. Excluded Studies List

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Improvement IfCS. Magnetic resonance imaging (MRI) for the detection of breast abnormalities (structured abstract). Health Technol Assess. 2012(1)doi: 10.1002/14651858. Exclusion: E6

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Ingham SL, Sperrin M, Baildam A, et al. Risk-reducing surgery increases survival in BRCA1/2 mutation carriers unaffected at time of family referral. Breast Cancer Res Treat. 2013 Dec;142(3):611-8. doi: 10.1007/s10549-013-2765-x. PMID: 24249359. Exclusion: H2

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Appendix A4. Excluded Studies List

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Jervis S, Song H, Lee A, et al. A risk prediction algorithm for ovarian cancer incorporating BRCA1, BRCA2, common alleles and other familial effects. J Med Genet. 2015 Jul;52(7):465-75. doi: 10.1136/jmedgenet-2015-103077. PMID: 26025000. Exclusion: E5

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Johansen N, Liavaag AH, Tanbo TG, et al. Sexual activity and functioning after risk-reducing salpingo-oophorectomy: impact of hormone replacement therapy. Gynecol Oncol. 2016 Jan;140(1):101-6. doi: 10.1016/j.ygyno.2015.11.016. PMID: 26597462. Exclusion: E3

Johnatty SE, Beesley J, Chen X, et al. The BARD1 Cys557Ser polymorphism and breast cancer risk: an Australian case-control and family analysis. Breast Cancer Res Treat. 2009 May;115(1):145-50. PMID: 18481171. Exclusion: E5

Johnson N, Lancaster T, Fuller A, et al. The prevalence of a family history of cancer in general practice. Fam Pract. 1995 Sep;12(3):287-9. PMID: 8536831. Exclusion: 2

Jones A. Feasibility of tamoxifen in chemoprevention of breast cancer (meeting abstract). Br J Cancer. 1990;62(Suppl 12):3. Exclusion: E6

Jones T, Lockhart JS, Mendelsohn-Victor KE, et al. Use of cancer genetics services in African-American young breast cancer survivors. Am J Prev Med. 2016 Oct;51(4):427-36. doi: 10.1016/j.amepre.2016.03.016. PMID: 27117712. Exclusion: E5

Joosse SA, van Beers EH, Tielen IHG, et al. Prediction of BRCA1-association in hereditary non-BRCA1/2 breast carcinomas with array-CGH. Breast Cancer Res Treat. 2009 Aug;116(3):479-89. PMID: 18704682. Exclusion: E3

Joseph G, Kaplan C, Luce J, et al. Efficient identification and referral of low-income women at high risk for hereditary breast cancer: a practice-based approach. Public Health Genomics. 2012;15(3-4):172-80. PMID: 22488460. Exclusion: E5

Joseph M, Rab F, Panabaker K, et al. Anger, frustration, and regret among women with a strong family history of breast/ovarian carcinoma who subsequent to their breast cancer diagnosis tested BRCA-positive. Curr Oncol. 2014;21(2):e374. doi: 10.3747/co.21.2077. Exclusion: E3

Joseph M, Rab F, Panabaker K, et al. Feelings of women with strong family histories who subsequent to their breast cancer diagnosis tested BRCA positive. Int J Gynecol Cancer. 2015 May;25(4):584-92. doi: 10.1097/IGC.0000000000000403. PMID: 25675043. Exclusion: E3

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Judkins T, Rosenthal E, Arnell C, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. Cancer. 2012 Nov 1;118(21):5210-6. doi: 10.1002/cncr.27556. PMID: 22544547. Exclusion: 2

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Kamara D, Weil J, Youngblom J, et al. Cancer counseling of low-income limited english proficient latina women using medical interpreters: Implications for shared decision-making. J Genet Couns. 2017

Aug:No Pagination Specified. doi: 10.1007/s10897-017-0132-5. PMID: 28791541. Exclusion: E5

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Appendix A4. Excluded Studies List

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2014 Oct 10;32(29):3275-83. doi: 10.1200/JCO.2013.54.1987. PMID: 25199754. Exclusion: 2

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Smith RP, Ni X, Muram D. Breast cancer risk assessment: positive predictive value of family history as a predictor of risk. Menopause. 2011 Jun;18(6):621-4. PMID: 21343830. Exclusion: E5

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Son BH, Ahn SH, Kim S-W, et al. Prevalence of BRCA1 and BRCA2 mutations in non-familial breast cancer patients with high risks in Korea: the Korean Hereditary Breast Cancer (KOHBRA) Study. Breast Cancer Res Treat. 2012 Jun;133(3):1143-52. doi: 10.1007/s10549-012-2001-0. PMID: 22382806. Exclusion: E5

Song CG, Hu Z, Wu J, et al. The prevalence of BRCA1 and BRCA2 mutations in eastern Chinese women with breast cancer. J Cancer Res Clin Oncol. 2006;132(10):617-26. PMID: 16835750. Exclusion: E5

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Stratton JF, Pharoah P, Smith SK, et al. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol. 1998 May;105(5):493-9. PMID: 9637117. Exclusion: 2

Streff H, Profato J, Ye Y, et al. Cancer Incidence in First- and Second-Degree Relatives of BRCA1 and BRCA2 Mutation Carriers. Oncologist. 2016 07;21(7):869-74. doi: https://dx.doi.org/10.1634/theoncologist.2015-0354. PMID: 27306910. Exclusion: E5

Stroup AM, Smith KR. Familial effects of BRCA1 genetic mutation testing: changes in perceived family functioning. Cancer Epidemiol Biomarkers Prev. 2007 Jan;16(1):135-41. PMID: 17220342. Exclusion: E3a

Stuckey AR, Onstad MA. Hereditary breast cancer: an update on risk assessment and genetic testing in 2015. Am J Obstet Gynecol. 2015 Aug;213(2):161-5. doi: 10.1016/j.ajog.2015.03.003. PMID: 25747548. Exclusion: 2

Sueta A, Ito H, Kawase T, et al. A genetic risk predictor for breast cancer using a combination of low-penetrance polymorphisms in a Japanese population. Breast Cancer Res Treat. 2012 Apr;132(2):711-21. PMID: 22160591. Exclusion: E5

Sussner KM, Edwards TA, Thompson HS, et al. Ethnic, racial and cultural identity and perceived benefits and barriers related to genetic testing for breast cancer among at-risk women of African descent in New York City. Public Health Genomics. 2011;14(6):356-70. PMID: 21540561. Exclusion: E4

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Sussner KM, Thompson HS, Jandorf L, et al. The influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing for breast cancer among women of African descent. Psychooncology. 2009 Sep;18(9):945-55. PMID: 19090507. Exclusion: E4

Swanson CL, Bakkum-Gamez JN. Options in prophylactic surgery to prevent ovarian cancer in

high-risk women: how new hypotheses of fallopian tube origin influence recommendations. Curr Treat Options Oncol. 2016;17(5):20. PMID: 27032642. Exclusion: E6

Syamala V, Syamala VS, Sreeja L, et al. Hereditary breast/ovarian cancer: clinicopathological characteristics and survival of BRCA2 positive and negative cases. J Exp Ther Oncol. 2008;7(3):227-36. PMID: 19066131. Exclusion: E5

Szender JB, Kaur J, Clayback K, et al. Breadth of Genetic Testing Selected by Patients at Risk of Hereditary Breast and Ovarian Cancer. Int J Gynecol Cancer. 2018 01;28(1):26-33. doi: https://dx.doi.org/10.1097/IGC.0000000000001122. PMID: 28930807. Exclusion: E5

Takano EA, Mitchell G, Fox SB, et al. Rapid detection of carriers with BRCA1 and BRCA2 mutations using high resolution melting analysis. BMC Cancer. 2008;8:59. PMID: 18298804. Exclusion: E4

Tassone F, Cheng S, Gardiner K. Analysis of chromosome 21 yeast artificial chromosome (YAC) clones. Am J Hum Genet. 1992 Dec;51(6):1251-64. PMID: 1463009. Exclusion: 2

Tea MM, Tan YY, Staudigl C, et al. Improving comprehension of genetic counseling for hereditary breast and ovarian cancer clients with a visual tool. PLoS ONE [Electronic Resource]. 2018;13(7):e0200559. doi: https://dx.doi.org/10.1371/journal.pone.0200559. PMID: 30001421. Exclusion: E4

Teraoka SN, Bernstein JL, Reiner AS, et al. Single nucleotide polymorphisms associated with risk for contralateral breast cancer in the Women's Environment, Cancer, and Radiation Epidemiology (WECARE) Study. Breast Cancer Res. 2011;13(6):R114. PMID: 22087758. Exclusion: E5

Tercyak KP, Demarco TA, Mars BD, et al. Women's satisfaction with genetic counseling for hereditary breast-ovarian cancer: psychological aspects. Am J Med Genet A. 2004 Nov 15;131(1):36-41. PMID: 15389697. Exclusion: E3a

Tercyak KP, Johnson SB, Roberts SF, et al. Psychological response to prenatal genetic counseling and amniocentesis. Patient Educ Couns. 2001;43(1):73-84. PMID: 11311841. Exclusion: E4

Tereschenko IV, Basham VM, Ponder BA, et al. BRCA1 and BRCA2 mutations in Russian familial breast cancer. Hum Mutat. 2002;19(2):184. PMID: 11793480. Exclusion: E5

Thombs BD, Arthurs E, El-Baalbaki G, et al. Risk of bias from inclusion of patients who already have diagnosis of or are undergoing treatment for depression in diagnostic accuracy studies of screening tools for depression: systematic review. Br Med J (Clin Res Ed). 2011;343 PMID: 21852353. Exclusion: E4

Thompson HS, Sussner K, Schwartz MD, et al. Receipt of genetic counseling recommendations among black women at high risk for BRCA mutations. Genet Test Mol Biomarkers. 2012 Nov;16(11):1257-62. doi: 10.1089/gtmb.2012.0114. PMID: 23057569. Exclusion: 2

Thorlacius S, Olafsdottir G, Tryggvadottir L, et al. A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet. 1996 May;13(1):117-9. doi: 10.1038/ng0596-117. PMID: 8673089. Exclusion: 2

Thorlacius S, Sigurdsson S, Bjarnadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet. 1997;60:1079-84. PMID: 9150155. Exclusion: 2

Tilanus-Linthorst MMA, Kriege M, Boetes C, et al. Hereditary breast cancer growth rates and its impact on screening policy. Eur J Cancer. 2005;41(11):1610-7. PMID: 15978801. Exclusion: E5

Tilanus-Linthorst MMA, Obdeijn IMM, Bartels KCM, et al. First experiences screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat. 2000;63(1):53-60. PMID: 11079159. Exclusion: 2

Tilburt JC, James KM, Sinicrope PS, et al. Factors influencing cancer risk perception in high risk populations: A systematic review. Hered Cancer Clin Pract. 2011;9(1) PMID: 21595959. Exclusion: E3

Tiller K, Meiser B, Gaff C, et al. A randomized controlled trial of a decision aid for women at increased risk of ovarian cancer. Med Decis Making. 2006 Jul-Aug;26(4):360-72. PMID: 16855125. Exclusion: E4

Tiller K, Meiser B, Gould L, et al. Knowledge of risk management strategies, and information and risk management preferences of women at increased risk for ovarian cancer. Psychooncology. 2005 Apr;14(4):249-61. PMID: 15386771. Exclusion: E4

Tobacman JK, Tucker MA, Kase RG, M. H., et al. Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer-prone families. Lancet. 1982;2(8302):795-7. PMID: 6126666. Exclusion: E7

Appendix A4. Excluded Studies List

Tong A, Kelly S, Nusbaum R, et al. Intentions for risk-reducing surgery among high-risk women referred for BRCA1/BRCA2 genetic counseling. Psychooncology. 2015 Jan;24(1):33-9. doi: 10.1002/pon.3560. PMID: 24839250. Exclusion: E5

Tonin PN, Maugard CM, Perret C, et al. A review of histopathological subtypes of ovarian cancer in BRCA-related French Canadian cancer families. Fam Cancer. 2007;6(4):491-7. doi: 10.1007/s10689-007-9152-x. PMID: 17636423. Exclusion: 2

Torrance N, Mollison J, Wordsworth S, et al. Genetic nurse counsellors can be an acceptable and cost-effective alternative to clinical geneticists for breast cancer risk genetic counselling. Evidence from two parallel randomised controlled equivalence trials. Br J Cancer. 2006 Aug 21;95(4):435-44. PMID: 16832415. Exclusion: E3a

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Williamson M. FDA delays lab test changes until Trump takes office. The Bureau of National Affairs; 2016. https://www.bna.com/fda-delays-lab-n73014447523/. Accessed May 16 2019. Exclusion: 2

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Wise J. Ovary removal is linked to lower breast cancer mortality in BRCA1 carriers. BMJ.

2015;350:h2182. doi: 10.1136/bmj.h2182. PMID: 25911348. Exclusion: E6

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Wolfe CR, Reyna VF, Widmer CL, et al. Efficacy of a web-based intelligent tutoring system for communicating genetic risk of breast cancer: a fuzzy-trace theory approach. Med Decis Making. 2015 Jan;35(1):46-59. doi: 10.1177/0272989X14535983. PMID: 24829276. Exclusion: E4

Wood ME, Stockdale A, Flynn BS. Interviews with primary care physicians regarding taking and interpreting the cancer family history. Fam Pract. 2008;25(5):334-40. PMID: 18765407. Exclusion: E3

Woods JE. Breast reconstruction: current state of the art. Mayo Clin Proc. 1986 Jul;61(7):579-85. PMID: 3713262. Exclusion: 2

Woodson AH, Muse KI, Jackson M, et al. Impact of breast cancer and BRCA mutations on thoughts and feelings of future pregnancies. J Clin Oncol. 2012;30(27). Exclusion: E5

Wooster R, Weber BL. Breast and ovarian cancer. N Engl J Med. 2003 Jun 05;348(23):2339-47. doi: 10.1056/NEJMra012284. PMID: 12788999. Exclusion: 2

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Wu H, Zhu K, Jatoi I, et al. Factors associated with the incompliance with mammogram screening among individuals with a family history of breast cancer or ovarian cancer. Breast Cancer Res Treat. 2007 Mar;101(3):317-24. PMID: 16821080. Exclusion: E3

Wuttke M, Phillips KA. Clinical management of women at high risk of breast cancer. Curr Opin Obstet Gynecol. 2015 Feb;27(1):6-13. doi: 10.1097/GCO.0000000000000140. PMID: 25502281. Exclusion: E6

Xu L, Zhao Y, Chen Z, et al. Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in BRCA1 and BRCA2: a meta-analysis. Breast Cancer. 2015 Jul;22(4):327-34. doi: 10.1007/s12282-015-0619-6. PMID: 26022977. Exclusion: E3

Yang Q, Flanders WD, Moonesinghe R, et al. Using lifetime risk estimates in personal genomic profiles: estimation of uncertainty. Am J Hum Genet. 2009 Dec;85(6):786-800. PMID: 19931039. Exclusion: E5

Yang Q, Khoury MJ, Rodriguez C, et al. Family history score as a predictor of breast cancer mortality: prospective data from the Cancer Prevention Study II, United States, 1982-1991. Am J Epidemiol. 1998 Apr 01;147(7):652-9. PMID: 9554604. Exclusion: 2

Yin L, Grandi N, Raum E, et al. Meta-analysis: Circulating vitamin D and ovarian cancer risk. Gynecol Oncol. 2011;121(2):369-75. PMID: 21324518. Exclusion: E5

Yip C-H, Taib NA, Choo WY, et al. Clinical and pathologic differences between BRCA1-, BRCA2-, and non-BRCA-associated breast cancers in a multiracial developing country. World J Surg. 2009 Oct;33(10):2077-81. PMID: 19649760. Exclusion: E5

Yoon SY, Thong MK, Lee J, et al. A study on the impact of pre-test genetic counselling and genetic testing towards the psychological distress and cancer worry in unaffected relatives. Fam Cancer. 2013;12:S20-S1. doi: 10.1007/s10689-013-9605-3. Exclusion: E6

Zakowski SG, Valdimarsdottir HB, Bovbjerg DH, et al. Predictors of intrusive thoughts and avoidance in women with family histories of breast cancer. Ann Behav Med. 1997 Fall;19(4):362-9. doi: 10.1007/bf02895155. PMID: 9706363. Exclusion: E4

Zayhowski K, Park J, Boehmer U, et al. Cancer genetic counselors' experiences with transgender patients: A qualitative study. J Genet Couns. 2019 Feb 5doi: 10.1002/jgc4.1092. PMID: 30720922. Exclusion: E5

Zhang D, Bai B, Xi Y, et al. Is aspirin use associated with a decreased risk of ovarian cancer? A systematic review and meta-analysis of observational studies with dose-response analysis. Gynecol Oncol. 2016 Aug;142(2):368-77. doi: 10.1016/j.ygyno.2016.04.543. PMID: 27151430. Exclusion: E5

Zhang LR, Chiarelli AM, Glendon G, et al. Influence of perceived breast cancer risk on screening behaviors of female relatives from the Ontario site of the Breast Cancer Family Registry. Eur J Cancer Prev. 2011 Jul;20(4):255-62. PMID: 21467941. Exclusion: E5

Appendix A4. Excluded Studies List

Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011 May 1;121(2):353-7. doi: 10.1016/j.ygyno.2011.01.020. PMID: 21324516. Exclusion: 2

Zhang Y, Simondsen K, Kolesar JM. Exemestane for primary prevention of breast cancer in postmenopausal women. Am J Health Syst Pharm. 2012 Aug 15;69(16):1384-8. doi: 10.2146/ajhp110585. PMID: 22855103. Exclusion: E9

Zikmund-Fisher BJ, Ubel PA, Smith DM, et al. Communicating side effect risks in a tamoxifen prophylaxis decision aid: The debiasing influence of pictographs. Patient Educ Couns. 2008 Nov;73(2):209-14. doi: 10.1016/j.pec.2008.05.010. PMID: 18602242. Exclusion: E4

Zilliacus EM, Meiser B, Lobb EA, et al. Are videoconferenced consultations as effective as face-to-face consultations for hereditary breast and ovarian cancer genetic counseling? Genet Med. 2011 Nov;13(11):933-41. PMID: 21799430. Exclusion: E3a

Zimovjanova M, Bielčikova Z, Miskovicova M, et al. Preventive programme for carriers of genetic alteration in BRCA1/2 and other high-risk genes. Czech single institution evaluation-fifteen years experience. Eur J Cancer. 2018;92:S144. Exclusion: E6

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables
Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than
80 percent or attention to some but not all important confounding variables
Poor: Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
- For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
- For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Single arm cohort studies were rated based on initial assembly of group, consideration of potential confounders, important outcomes considered, measurements: equal, reliable, and valid (includes masking of outcome assessment), and reporting of attrition if applicable.

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:
- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles

indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients
Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

*Reference: U.S. Preventive Services Task Force Procedure Manual. June 2018. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A6. Expert Reviewers of the Draft Report

- Mary Daly MD, PhD, MSPH, Director, Risk Assessment Program, Department of Clinical Genetics, Fox Chase Cancer Center, Temple University
- Lori Erby ScM, PhD, CGC, National Human Genome Research Institute, NIH and the Johns Hopkins University
- Brandy Heckman-Stoddard, PhD, MPH, Chief, Division of Cancer Prevention, NCI
- Kathy Helzlsouer, MD, MHS, Associate Director, Epidemiology and Genomics Research Program, Chief Medical Officer, Division of Cancer Control and Population Sciences, NCI
- Kelly Metcalfe, RN, PhD, University of Toronto, Adjunct Scientist, Familial Breast Cancer Research Institute at the Women's College Research Institute, Toronto, Canada
- Brandy Peaker, MD, MPH, Centers for Disease Control and Prevention
- Robert Pilarski MS, LGC, MSW, Clinical Cancer Genetics Program, Division of Human Genetics, The Ohio State University
- Goli Samimi PhD, MPH, Program Director, Division of Cancer Prevention, NCI

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings

Appendix B Table 1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?
Current Review						
Biswas et al., 2016[115]	Yes	Yes	Yes	Unclear	Yes	Yes
Fischer et al., 2013[117]	Yes	Yes	Yes	Unclear	Yes	Yes
Kast et al., 2014[120]	Yes	Yes	Unclear	Yes	Yes	Yes
Teller et al., 2010[124]	No	Yes	Yes	Unclear	Yes	Yes
2013 Review						
Antoniou et al., 2008[111]	Yes	Yes	Yes	Unclear	Yes	Yes
Ashton-Prolla et al., 2009[112]	Yes	Yes	Yes	Yes	Yes	Yes
Barcenas et al., 2006[113]	Yes	Yes	Yes	Unclear	Yes	Yes
Bellcross et al., 2009[114]	Yes	Yes	Yes	Yes	Yes	Yes
Evans et al., 2004[116]	Yes	Yes	Yes	Yes	Yes	Yes
Gilpin, 2000[118]	Yes	Yes	Yes	Yes	Yes	Yes
Hoskins, 2006[119]	Yes	Yes	Yes	Unclear	Yes	Yes
Oros et al., 2006[121]	Unclear	Yes	Unclear	Unclear	Yes	Yes
Panchal et al., 2008[122]	Yes	No	Unclear	Unclear	Yes	Yes
Parmigiani et al., 2007[123]	No	Yes	Unclear	Unclear	Yes	Yes

Appendix B Table 1. Quality Assessment of Diagnostic Accuracy Studies

Author, year	Were the reference standard results interpreted without knowledge of the results of the index text?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality rating
Current Review						
Biswas et al., 2016[115]	Unclear	NA	Yes	Yes	Yes	Fair
Fischer et al., 2013[117]	Unclear	NA	Yes	Yes	Yes	Fair
Kast et al., 2014[120]	Unclear	NA	Yes	Yes	Yes	Fair
Teller et al., 2010[124]	Unclear	NA	Yes	Yes	Yes	Fair
2013 Review						
Antoniou et al., 2008[111]	Unclear	NA	Yes	Yes	Yes	Good
Ashton-Prolla et al., 2009[112]	Unclear	NA	Yes	Yes	Yes	Good
Barcenas et al., 2006[113]	Unclear	Unclear	Yes	Yes	Yes	Fair
Bellcross et al., 2009[114]	Yes	NA	Yes	Yes	Yes	Good
Evans et al., 2004[116]	Yes	NA	Yes	Yes	Yes	Good
Gilpin, 2000[118]	Unclear	NA	Yes	Yes	Yes	Good
Hoskins, 2006[119]	Unclear	NA	Yes	Yes	Yes	Fair
Oros et al., 2006[121]	Yes	NA	Yes	Yes	Yes	Fair
Panchal et al., 2008[122]	Unclear	NA	Yes	Yes	Yes	Fair
Parmigiani et al., 2007[123]	Unclear	NA	Yes	Yes	Yes	Fair

Appendix B Table 2. Quality Assessment of Randomized, Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Current Review						
Manchanda et al., 2015[164]	Yes	Unclear	Yes	Yes	Unclear	Yes
2013 Review						
Bloom et al., 2006[129]	Unclear	NR	NR	No	NR	NR
Bowen et al., 2002[66]	Yes	NR	Yes	Yes	No	No
Bowen et al., 2004[71]	Yes	Yes	Yes	Yes	No	No
Bowen et al., 2006[130]	NR	NR	Yes	Yes	No	No
Brain et al., 2002[131]	Yes	Yes	Yes	Yes	Unclear	Unclear
Braithwaite et al., 2005[133]	NR	NR	Yes	Yes	NR	Yes
Burke et al., 2000[67]	Yes	NR	Yes	Yes	No	No
Cull et al., 1998[68]	Yes	Yes	Yes	Yes	No	No
Fry et al., 2003[134]	Yes	Yes	Yes	Yes	No	No
Helmes, 2006[136]	NR	NR	Yes	Yes	NR	No
Lerman et al., 1996[140]	Yes	NR	Yes	Yes	Yes	No
Lerman et al., 1999[69]	Yes	NR	Yes	Yes	Yes	No
Matloff et al., 2006[142]	No	No	Yes	Yes	NR	No
Roshanai et al., 2009[146]	Unclear	Yes	Yes	Yes	NR	Yes
Watson et al., 1998[148]	Yes	Yes	Yes	Yes	No	No

Appendix B Table 2. Quality Assessment of Randomized, Controlled Trials

Author, Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to followup: differential/ high	Analyze people in the groups in which they were randomized?	Quality rating
Current Review					
Manchanda et al., 2015[164]	No	Yes	No	Yes	Good
2013 Review					
Bloom et al., 2006[129]	No	Yes	No	Yes	Poor
Bowen et al., 2002[66]	No	Yes	No	No	Fair
Bowen et al., 2004[71]	No	Yes	NR	No	Fair
Bowen et al., 2006[130]	No	Yes	No	Yes	Fair
Brain et al., 2002[131]	Unclear	Yes	No	Yes	Good
Braithwaite et al., 2005[133]	No	Yes	No	No	Fair
Burke et al., 2000[67]	No	Yes	No	NR	Fair
Cull et al., 1998[68]	No	Yes	No/Yes	NR	Good
Fry et al., 2003[134]	No	Yes	No/Yes	No	Fair
Helmes, 2006[136]	No	Yes	No	Yes	Fair
Lerman et al., 1996[140]	No	Yes	No	NR	Fair
Lerman et al., 1999[69]	No	Yes	No/Yes	NR	Fair
Matloff et al., 2006[142]	No	Yes	No	No	Fair
Roshanai et al., 2009[146]	No	Yes	No	No	Fair
Watson et al., 1998[148]	No	Yes	No	Yes	Good

Appendix B Table 3. Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?
Current Review					
Borreani et al., 2014[187]	Unclear	Not reported for our groups of interest	Not reported	Yes	Not reported
Bresser et al., 2007[191]	Unclear	Yes	Yes	Yes	Unclear
Evans et al., 2009[173] Manchester site	Yes	Yes - matching	Not reported	Not reported	Not reported
Flippo-Morton et al., 2016[174]	Yes	Not reported	Not reported	Not reported	Not reported
Heemskerk- Gerritsen, 2013[177]	Yes	Unclear	Not reported	Yes	Not reported
Heemskerk- Gerritsen, 2015[178]	Yes: nationwide cohort	Unclear	Not reported	Yes	Not reported
Kotsopoulos et al., 2017[179]	Unclear	No	No	Unclear	NR
Kramer et al., 2005[99]	Unclear	Not reported	Not reported	Yes for exposure	Not reported
Lumish et al., 2017[163]	Yes	Unclear	Not applicable	Yes	Not reported
Mavaddat et al., 2013[180] EMBRACE	Yes	Not reported for oophorectomy groups	Not reported	Yes	Not reported
Rebbeck et al., 2002[181]	Unclear	Yes - matching	Not reported	Unclear, self-report for exposure	Not reported
Shah et al., 2009[182]	Yes	Not reported for oophorectomy groups	Not reported	Not reported	Not reported
Isern et al., 2008[199]	Unclear	Unclear	Unclear	Yes	Unclear
van Oostrom, 2003 et al.,[172]	Unclear	Yes	Unclear	Yes	Unclear
2013 Review					
Domchek et al., 2010[98]	Yes	Not reported	Not reported	Yes for exposure, unclear for confounders (Domchek 2006)	Not reported
Foster et al., 2007[154]	Unclear	Not reported	Not reported	Yes	No
Geirdal et al., 2005[156]	Yes	Yes	Yes	Yes	No
Geirdal and Dahl, 2008[155]	Yes	No	No	Yes	No

Appendix B Table 3. Quality Assessment of Cohort Studies

Author, Year	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Current Review					
Borreani et al., 2014[187]	Not applicable	Unclear	Not applicable	Yes	Fair
Bresser et al., 2007[191]	Not applicable	Yes	Unclear	Yes	Fair
Evans et al., 2009[173] Manchester site	Yes	No	Unclear	Unclear	Fair
Flippo-Morton et al., 2016[174]	Yes	No	No	Not reported	Fair
Heemskerk- Gerritsen, 2013[177]	No, but Cox model censored at last contact	Yes, though race not included	Not reported	Yes	Fair
Heemskerk- Gerritsen, 2015[178]	No, but Cox model censored at last contact	Yes, though race not included	Not reported	Yes	Fair
Kotsopoulos et al., 2017[179]	No, but Cox model censored at last contact	Yes	NR	Yes	Fair
Kramer et al., 2005[99]	No	Age only	Not reported	Yes	Fair
Lumish et al., 2017[163]	Not applicable	Yes	Not applicable	Yes	Fair
Mavaddat et al., 2013[180] EMBRACE	Yes	Yes	Yes	Yes	Fair
Rebbeck et al., 2002[181]	Not applicable, retrospective	Yes	Not applicable, retrospective	Yes	Fair
Shah et al., 2009[182]	Yes	Yes	No	Not reported	Fair
Isern et al., 2008[199]	Not applicable	Yes	Unclear	Yes	Fair
van Oostrom, 2003 et al.,[172]	Yes	Unclear	Unclear differential, but high overall (24% dropped)	Yes	Poor
2013 Review					
Domchek et al., 2010[98]	No	Yes, though race not included	Not reported	Yes	Fair
Foster et al., 2007[154]	Yes	Yes	No	Yes	Fair
Geirdal et al., 2005[156]	Yes	Unclear	No	Yes	Good
Geirdal and Dahl, 2008[155]	Yes	Yes	No	Yes	Good

Appendix B Table 3. Quality Assessment of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?
Hopwood et al., 1998[137]	Unclear	Yes	Yes	Yes	No
Julian-Reynier et al., 2011[159]	Unclear	Yes	Yes	Yes	No
Kinney et al., 2005[160]	No	Not reported	Not reported	Yes	No
Kramer et al., 2005[99]	Yes	Not reported	Not reported	Yes	No
Lobb et al., 2004[141]	Unclear	Yes	Yes	Yes	No
Low et al., 2008[162]	Unclear	No	Not reported	Yes	No
Meiser et al., 2002[165]	Unclear	Yes	Yes	Yes	No
Mikkelsen et al., 2007[143]	Yes	No	No	Yes	No
Mikkelsen et al., 2009[144]	Yes	No	No	Yes	No
Reichelt et al., 2004[167]	Yes	Not reported	Not reported	Yes	No
Rijnsburger et al., 2004[209]	No	No	Not reported	Yes	Unclear - Not reported
Skytte et al., 2011[183]	Yes	No - rates of RRSO differed	Not reported	Yes	Not reported
Struewing et al., 1995[184]	Unclear	Not reported	Not reported	Not reported	Not reported
van Dijk et al., 2006[171]	Yes	Not reported	Not reported	Yes	No
Watson et al, 1999[149]	Unclear	Yes	Yes	Yes	No

Appendix B Table 3. Quality Assessment of Cohort Studies

Author, Year	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Hopwood et al., 1998[137]	Yes	Yes	No	Yes	Fair
Julian-Reynier et al., 2011[159]	Yes	Yes	No	Yes	Good
Kinney et al., 2005[160]	No	Yes	Not reported	Yes	Poor
Kramer et al., 2005[99]	No	Yes	Not reported	Yes	Fair
Lobb et al., 2004[141]	Yes	Yes	No	Yes	Good
Low et al., 2008[162]	Yes	Yes	Yes	Yes	Fair
Meiser et al., 2002[165]	Yes	Yes	No	Yes	Good
Mikkelsen et al., 2007[143]	Yes	Yes	No	Yes	Fair
Mikkelsen et al., 2009[144]	Yes	Yes	No	Yes	Fair
Reichelt et al., 2004[167]	Yes	Yes	No	Yes	Good
Rijnsburger et al., 2004[209]	Yes	Yes	No	Yes	Fair
Skytte et al., 2011[183]	Yes	Age only	No	Yes	Fair
Struewing et al., 1995[184]	No (by individual)	No	Unclear - 4 of 16 families identified were lost to followup	Not reported	Poor
van Dijk et al., 2006[171]	Yes	Yes	No	Yes	Good
Watson et al, 1999[149]	Yes	Yes	No	Yes	Good

Appendix B Table 4. Quality Assessment of Single Arm Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Is there high attrition?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating
Current Review							
Alamouti et al., 2015[185]	Unclear	Not reported	Not reported	No	Not reported	Unclear	Poor
Andrews et al., 2004[150]	Yes	Yes	Not reported	Yes	Yes	Yes	Fair
Arver et al., 2011[186]	Yes: national inventory	Unclear	Not reported	Not applicable	Not applicable	Unclear	Fair
den Heijer et al., 2013[193]	Unclear	Yes	Unclear	Not applicable	Not applicable	Yes	Fair
Godard et al., 2007[157]	Yes	Yes	Not reported	Yes	Yes	Yes	Good
Heemskerk- Gerritsen et al., 2007[197]	Yes	Yes	Not reported	No	Not reported	Yes	Fair
Kenkhuis et al., 2010[200]	Yes	Yes	Not reported	Not applicable	Not applicable	Yes	Good
Lieberman et al., 2017[161]	Yes	Yes	Not reported	Yes	Yes	Yes	Good
Nurudeen, 2017[207]	Unclear	Yes	Not reported	No	Not reported	Yes	Fair
Smith et al., 1999[170]	Yes	Yes	Not reported	Yes	Yes	Yes	Good
Stefanek et al., 1995[211]	Unclear	Unclear	Unclear	Not applicable	Not applicable	Yes	Poor
2013 Review							
Evans et al., 2009[173] All sites	Yes	Not reported	Not reported	Yes	No (2%)	Unclear	Fair
Hartmann et al., 1999[175] Hartmann et al., 2001[176]	Yes	Yes	Not reported	Not applicable	Not applicable	Yes for cancer, unclear for death	Fair
Olson et al., 2004[100]	Yes	Yes	Not reported	Not applicable	Not applicable	Unclear	Fair

Appendix B Table 5. Quality Assessment of Case-Control Studies

Author, year	Did the study attempt to enroll all or random sample of cases using pre- defined criteria?	Were the controls derived from the same population as the cases?	Were the groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did the study use accurate methods for identifying outcomes?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Quality rating
2013 Review								
Armstrong et al., 2005[126]	Yes	No	No	No	Yes	Yes	Yes	Good
Dagan and Shochat, 2009[152] Shochat and Dagan, 2010[169]	Yes	Unclear	Matched	No	Yes	Yes	Yes	Fair

Appendix B Table 6. Quality Assessment of Systematic Review

Author, year	Research questions and inclusion include components of PICO	Explicit statement of a priori development of methods	Any deviations from protocol, if so are they so justified	Explanation of study design inclusion	Comprehensive literature search	Duplicate study selection and data abstraction
2013 Review						
Smerecnick et al., 2009[147]	Yes	Yes	Not reported	Yes	Yes	Selection: Yes Abstraction: Yes

Author, year	List of studies (included and excluded) provided	Characteristics of the included studies provided	Satisfactory technique used for assessing risk of bias in individual studies	Conflict of interest (including funding sources) a) Systematic Review b) Individual Studies	If meta-analysis performed, were appropriate methods used for combination of results
2013 Review					
Smerecnick et al., 2009[147]	Excluded: No Included: Yes	Yes	No	Review: Yes Studies: No	Not applicable

Author, year	If meta-analysis performed, were potential impacts of risk of bias on meta-analysis or other evidence synthesis assessed	Was risk of bias taken into account when interpreting/discussing results	Satisfactory explanation for, and discussion of, any heterogeneity observed in the results	If quantitative synthesis, was there adequate investigation of publication bias (small study bias) and discuss its likely impact on the results	Rating
2013 Review					
Smerecnick et al., 2009[147]	Not applicable	No, quality not assessed	Unclear	Yes	Moderate

Abbreviation: PICO=Patients, Intervention, Comparison, and Outcomes

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Current Review						
Albada et al., 2016[125] NA	Risk perception	To report on a study of the counselees' expressed understanding as a response to the risk estimate and surveillance recommendation and whether they express surveillance intentions in the final consultation for breast cancer genetic counseling.	Before and after	Eligible: NR Enrolled: Unclear, only reported for whole group, not unaffected women only Analyzed: 89	The Netherlands	Consecutive new counselees seen at the department of Medical Genetics of the University Medical Centre Utrecht (UMCU).
2013 Review						
Armstrong et al., 2005[126] Good	Cancer worry Attitudes	To assess the association between race and use of genetic counseling for *BRCA1/2* testing among women at risk of carrying a *BRCA1/2* mutation and to evaluate the potential contributions of socioeconomic characteristics about genetic testing, and interactions with primary care physicians to this association.	Case-control	Eligible: NR Enrolled: NR Randomized: NR Analyzed: 408 (217 cases, 191 controls)	U.S.	Visit to University of Pennsylvania Health System **Cases:** women from reference population who presented for genetic counseling, mean age 42.5 years, 29% Jewish **Controls:** random sample of women from reference population, mean age 53.1 years, 11% Jewish

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
Current Review			
Albada et al., 2016[125] NA	Only unaffected women Mean age (years): 37.9 (SD 10.6)	Inclusion: Female counselees aged ≥18 years who were the first of their first degree family members to seek breast cancer genetic counseling. Exclusion: Lack of internet or email access.	39.3% population risk (<20% lifetime risk) 47.2% moderate risk (20-30% lifetime risk) 13.5% high risk (≥30% lifetime risk)
2013 Review			
Armstrong et al., 2005[126] Good	**Cases vs. controls** Mean age (years): 42.5 (range: 19 to 66) vs.53.1 (range: 20 to 89) Race/ethnicity Black: 7.4% vs. 29% Asian American: 3.3% vs. 3.2% White: 85% vs. 66% Hispanic: 0% vs. 2.1% Other: 4.6% vs. 0% Religious heritage	Inclusion: Women aged 18-80 years, seen a primary care physician within the University of Pennsylvania Health System in the 3 years prior to the start of the study, and with FDR or SDR with a breast or ovarian cancer diagnosis Exclusion: Personal diagnosis of breast or ovarian cancer, identified as being unable to participate because of illness or mental incapacity by their primary care physician. Controls: previously participated in *BRCA1/2* genetic	FDR or SDR with a breast or ovarian cancer diagnosis

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
	Jewish: 29% vs. 11% Christian: 52% vs. 60% Other: 13% vs. 13% NR: 5.9% vs. 16%	counseling	

Author, year Quality	Interventions	Measures	Duration of followup
Current Review			
Albada et al., 2016[125] NA	Dutch Breast Cancer guidelines, personal risk estimate (if enough data was available), no other information described	Risk perception alignment with counselor	2008 to 2010 1 year
2013 Review			
Armstrong et al., 2005[126] Good	A) Genetic counseling prior to testing, otherwise not described B) Controls	None	1999 to 2003 Not applicable

Author, year Quality	Results	Conclusions	Funding source
Current Review			
Albada et al., 2016[125] NA	**Accurate vs. overestimation vs. underestimation** Immediately after counseling (n=70): 48.6% vs. 38.6% vs. 12.9% -Population-risk (n=28): 53.6% vs. 46.4% vs. 0 -Moderate-risk (n=32): 37.5% vs. 43.8% vs. 18.8% -High-risk (n=8): 62.5% vs. 0 vs. 37.5% 1 year after counseling (n=78): 34.6% vs. 55.1% vs. 10.3% -Population-risk (n=30): 26.7% vs. 73.3% vs. 0 -Moderate-risk (n=38): 36.8% vs. 55.3% vs. 7.9% -High-risk (n=8): 50% vs. 0 vs. 50%	A large percentage of counselees overestimated their risk post counseling. Expressed understanding of risk estimate during counseling appointments was not associated with postcounseling risk perception alignment. Significant decrease in accurate risk perception in the year post counseling might indicate that counselees' perception of their risk drifts further away from the risk estimate given by the counselor.	Grant from the Dutch Cancer Society (Nivel 2010-4875)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Armstrong et al., 2005[126] Good	**Logistic regression model of association between race and use of genetic counseling: OR (95% CI)** -Black (vs. White): 0.28 (0.09 to 0.89) -Increased age: 0.97 (0.93 to 0.99) -Increased probability of BRCA mutation: 1.25 (1.10 to 1.42) -Increased risk perception for breast cancer: 2.88 (1.98 to 4.21) -Increased risk perception for ovarian cancer: 1.56 (1.02 to 2.38) -Increase ovarian cancer worry: 1.56 (1.02 to 2.38) -Belief that testing leads to discrimination: 0.74 (0.57 to 0.96) -Increased belief that testing provides reassurance: 1.60 (1.15 to 2.23) -Gynecologist discussed BRCA testing: 1.79 (1.02 to 3.13) -PCP discussed BRCA testing: 1.93 (1.00 to 3.74) -NS associations: marital status, education, income, health insurance, increased breast cancer worry, belief that testing provides information, belief that testing creates anxiety, and number of visits to gynecologist or PCP	Blacks are less likely to undergo genetic counseling than Whites. Women who believe testing is likely to lead to discrimination were not likely to undergo genetic counseling. Older women were less likely to undergo genetic counseling than younger women. Women with an increased risk perception for either breast or ovarian cancer were likely to undergo genetic counseling.	The American Cancer Clinical Research Training Grant and the Robert Wood Johnson Generalist Physician Faculty Scholar Award

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Bennett et al., 2008[127] NA	Psychological	To examine the relationship between measures of anxiety and depression and a number of variables identified to be associated with distress	Before and after	Eligible: 367 Enrolled: 319 Analyzed: 128	U.K.	Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Bennett et al., 2008[127] NA	Mean age of 43.3 years	Inclusion: Women undergoing assessment for risk of breast/ovarian cancer at the CGSW and who completed followup questionnaires Exclusion: Did not complete risk assessment process before the end of the study	23% low-risk 45% moderate-risk 31% high-risk

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Bennett et al., 2008[127] NA	CGSW referral guidelines and BRCAPRO risk calculation model	DUKE Social Support Questionnaire (DUKE- SSQ, scale 1 to 5) Hospital Anxiety and Depression Scale (HADS, subscales 0 to 21) Perceived health Quality of Life Impact of Events Scale (IES, subscales 0 to 28) Medical Coping Modes Questionnaire (MCMQ, scale NR)	Years: NR 1 week following risk notification

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Bennett et al., 2008[127] NA	**Baseline vs. followup after risk assessment** Mean scores (SE) HADS-D: 4.44 (3.77) vs. 4.05 (3.85); NS HADS-A: 8.02 (4.56) vs. 7.03 (4.41); NS IES-I: 13.17 (10.57) vs. 7.76 (8.95); p<0.001 IES-A: 12.19 (10.78) vs. 8.45 (9.61); p<0.01 Perceived health, quality of life (scale 0 to 100): 76.74 (20.10) vs. 77.96 (17.68); p<0.05 DUKE-SSQ (scale not described): 27.15 (11.93) vs. 24.97 (11.02); p<0.01 **Correlations between key independent variables and HADS-A vs. HADS-D** Age, level or risk assigned, and MCMQ-confrontation were not significant IES-I: 0.703 (p<0.01) vs. 0.448 (p<0.01) IES-A: 0.636 (p<0.01) vs. 0.365 (p<0.01)	Following risk status disclosure women did not have changes in their level of anxiety or depressed, as measured by the HADS, their intrusive thoughts and avoidance of intrusive thoughts declined after notification, while their perceived quality life of health and satisfaction increased. This indicates the level or risk disclosed does not negatively impact women's psychological well being.	Not reported

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
	DUKE-SSQ-confidant: 0.364 (p<0.01) vs. 0.493 (p<0.01) DUKE-SSQ-affective: 0.375 (p<0.001) vs. 0.411 (p<0.01 Perceived health: -0.493 (p<0.01) vs. -0.664 (p<0.01) Hopeless about getting cancer: 0.389 (p<0.01) vs. 0.366 (p<0.01) Hopeless about health: 0.374 (p<0.01) vs. 0.197 (p<0.05) Control over getting cancer: -0.372 (p<0.01) vs. 0.175 (NS) MCMQ-avoidance: 0.429 (p<0.001) vs. 0.271 (p<0.01) MCMQ-acceptance-resignation: 0.383 (p<0.01) vs. 0.206 (p<0.05) Neuroticism: 0.265 (p<0.01) vs. 0.193 (p<0.05)		

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Bennett et al., 2009[128] NA	Cancer worry Psychological	To explore the relationship between a number of factors hypothesized to be associated with the frequency of intrusive worries close to the time women were informed of their genetic risk for developing breast and/or ovarian cancer	Before and after	Eligible: 221 Enrolled: 221 Analyzed: 128	U.K.	Women referred for genetic risk assessment to a large Cancer Genetics Service for Wales (CGSW) center

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Bennett et al., 2009[128] NA	Mean age of 44.3 years (SD 10.81; range: 18 to 76)	Inclusion: Women undergoing assessment for risk of breast/ovarian cancer at the CGSW and who completed followup questionnaires Exclusion: Did not complete risk assessment process before the end of the study	30/128 (23.4%) at population-risk 61/128 (47.7%) at moderate-risk 37/128 (28.9%) at high-risk

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Bennett et al., 2009[128] NA	CGSW referral guidelines and BRCAPRO risk calculation model	DUKE Social Support Questionnaire (DUKE- SSQ, scale 1 to 5) Impact of Events Scale (IES, subscales 0 to 28) Medical Coping Modes Questionnaire (MCMQ, scale NR)	Years: NR Approximately 5 to 7 weeks

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Bennett et al., 2009[128] NA	**Baseline vs. followup after risk assessment** IES-I (estimated from graph) High-risk: 12.5 vs. 7.8 (p<0.001) Moderate-risk: 12.5 vs. 7.9 (p<0.001) Low-risk: 11.8 vs. 8.2 (p<0.001) Between group differences were not significant (p=0.694) IES-A (estimated from graph) High-risk: 13.1 vs. 8.3 (p<0.05) Moderate-risk: 10.6 vs. 8.9 (p<0.05) Low-risk: 10 vs. 11.3 (p<0.05) Between group differences for low risk vs. moderate and high-risk was significant (p<0.05) **Key variables associated with IES intrusion scores** Cognitive response Control over risk for cancer: -0.279 (p<0.001) Hopelessness about developing cancer: 0.412 (p<0.001) Emotional response to risk information Hopeful: -0.331 (p<0.001) Relieved: -0.278 (p<0.001) Calm: -0.506 (p<0.001) Anxious: 0.438 (p<0.001) Social support Confidant support: 0.232 (p<0.01) Affective support: 0.208 (p<0.05) Coping Confrontation: 0.284 (p<0.001) Avoidance: 0.442 (p<0.001) Acceptance-resignation: 0.391 (p<0.001) Variables not associated with IES intrusion scores: age, risk status, and surprised emotional response to risk information Similar results were found for IES avoidance scores.	Levels of worry fell among all women following risk assessment, regardless of risk status assignment. Only women with low (population) risk had high frequencies of avoidance after risk assessment. Intrusive worries were associated with a lack of confidant support and a confrontive coping response.	Not reported

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Bloom et al., 2006[129] Poor	Risk perception Cancer worry Health behaviors	To compare women in a telephone counseling intervention to controls and determine whether perceived risk would be more consistent with objective risk; and whether there would be reduction in breast cancer worries, improvement in health protective behaviors, and an increase in breast cancer screening.	RCT	Eligible: NR Enrolled: 163 Randomized: 163 (80 in intervention, 83 in control) Analyzed: 149 (71 in intervention, 78 in control)	U.S.	Sisters of women diagnosed with breast cancer at age ≤50. Predominantly Euro-American, well-educated, and substantial majority receive regular breast cancer screening.
Bowen et al., 2002[66] Fair Same population as Bowen et al., 2004[71]	Interest in genetic testing	To test the effects of breast cancer risk on interest in genetic testing in women who have a family history of breast cancer.	RCT	Eligible: 561 Enrolled: 357 Randomized: 357 (120 to genetic counseling, 114 to psychosocial group, 123 to delayed counseling) Analyzed: 317 (105 to genetic counseling, 103 to psychosocial, 109 to delayed counseling)	U.S.	Women recruited from the Seattle area-- see Bowen et al, 1999. All volunteered after seeing a notice, hearing about the study from a network or through a relative with cancer.

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Bloom et al., 2006[129] Poor	Mean age of 47.4 years (SD 7.2) 77% Euro-American 6.1% Black 9.2% Latina 8.0% Asian/Other	Inclusion: Not reported Exclusion: Prior breast cancer	All had ≥1 FDR (sister) with breast cancer diagnosis ≤ age 50
Bowen et al., 2002[66] Fair Same population as Bowen et al., 2004[71]	Psychological counseling arm: Mean age of 41.9 years (SD 11.3) 90% White, non Hispanic 3.5 % White, Hispanic 0.9% Black 2.6% Asian or Pacific Islander 1.8% Native American 0.9% Multiracial Genetic counseling arm: Mean age of 42.8 years (SD 11.8) 94% White, non Hispanic 0.0% White, Hispanic 0.8% Black 1.7% Asian or Pacific Islander	Inclusion: Women aged 18 to 74, lived within 60 miles of research center, agreed to participate in counseling & complete questionnaires, and had ≥1 relative affected by breast cancer Exclusion: Lack of family history of breast cancer, age outside the 18 to 74 range, more than one close relative affected by breast cancer, living outside the catchment area and lack of interest in completing the study	**Family history:** Close relatives affected by breast cancer included grandmothers, mothers, sisters, and aunts **Risk level:** Gail and Claus scores, along with population data

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
	1.7% Native American 1.7% Multiracial Control arm: Mean age of 42.4 years (SD 11.5) 93% White, non Hispanic 0.0% White, Hispanic 2.5% Black 3.3% Asian or Pacific Islander 0.0% Native American 0.8% Multiracial		

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Bloom et al., 2006[129] Poor	A) Telephone counseling from a master's level counselor within 2 weeks; breast cancer worries measured by 4-point Likert scale; perceived risk measured on 5-point scale; rating chances of diagnosis (0 to 100%). Telephone counseling session included: establishment of rapport and determination of special concerns, emotional readiness; risk notification by providing modified Gail model lifetime risk estimate and discussing in terms of her pre-test self-assessment of risk; de-escalation of tension regarding breast cancer checkup; evaluation of coping skills, reinforcement of problem solving and coping skills; information on health protective behaviors; early detection through American Cancer Society screening; and information on genetic testing when requested. B) Delayed telephone counseling following the post-test	NSI: 3-item measure of breast cancer worry: perceived risk of breast cancer, health behaviors, and breast cancer screening	1999 to 2002 6 months
Bowen et al., 2002[66] Fair Same population as Bowen et al., 2004[71]	A) IGC: Phone call to review pedigree information followed by a single 2-hour counseling session. Subject given information on her own risk for breast cancer using Gail and Claus scores along with population data. Information given on genetic testing, current knowledge about nonhereditary risk factors, and current screening techniques. Summary letter provided. B) PGC: Four, 2-hour group meetings with 4 to 6 women led by a health counselor. Included: risk assessment and perception, education, stress management, problem-solving and social support. Personal risk for breast cancer, interpretation and appropriate screening provided privately to subjects. C) CG: Offered choice of counseling modality after the final followup.	NSI: 3-item questionnaire to assess awareness, candidacy, and interest in genetic testing Tolerance for ambiguity assessed using a questionnaire derived from previous research 5-point response scale to beliefs about genetic testing	Years: NR 6 months

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Bloom et al., 2006[129] Poor	Women overestimated their risk of breast cancer by an average of 25 percentage points; proportion of women underestimating risk was larger in women with perceived lower risk (40%) than those who perceived it as the same (16%) or higher (10%) or much higher (5%) than the risk of other women (p=0.009) Women reduced their overestimation more if the initial overestimate was higher (p<0.0001); and intervention effect was significant only in women aged 50 years and over (p=0.004)	Telephone counseling appears to reduce risk overestimates in women with higher than average risk and to promote healthy behaviors in sisters of women with breast cancer.	Grant 4EB-5800 from the California Breast Cancer Research Program
Bowen et al., 2002[66] Fair Same population as Bowen et al., 2004[71]	Counseling on risk slightly changed levels of interest in genetic testing in women with a family history. Those who participated in counseling were less interested in genetic testing and less likely to view themselves as good candidates. Stigma and access beliefs about genetic testing were related to the effect of counseling on whether women thought they should participate in testing. As women gained more information, they were slightly less likely to want to participate in testing.	Individual counseling was more predictive of women's increased awareness than psychosocial group counseling.	The National Cancer Institute and the National Human Genome Institute (HG01190)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Bowen et al., 2004[71] Fair Same population as Bowen et al., 2002[66]	Cancer worry Psychological factors Risk perception	To test the effects of two types of breast cancer risk counseling (group psychosocial or individual genetic) on perceived risk, negative affect, and worry about breast cancer	RCT	Eligible: 561 Enrolled: 354 Randomized: 354 (118 genetic counseling arm, 114 psychosocial counseling arm, 122 delayed intervention arm) Analyzed: 348 (117 genetic counseling arm, 110 psychosocial counseling arm, 121 delayed intervention arm)	U.S.	Recruitment from among family members with breast cancer and through notices in local electronic and print outlets. Recruitment completed in 8 months. Women with a range of actual breast cancer risk levels were included.
Bowen et al., 2006[130] Fair	Risk perception Cancer worry Interest in genetic testing	To test the efficacy of 2 counseling methods in Ashkenazi Jewish women with average or moderately increased risk of breast cancer.	RCT	Eligible: 347 Enrolled: 221 Randomized: 221 (68 to psychosocial counseling, 77 to genetic counseling, 75 to control) Analyzed: 96% followup rate	U.S.	Ashkenazi Jewish women from the greater Seattle, Washington area

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Bowen et al., 2004[71] Fair Same population as Bowen et al., 2002[66]	Mean age, years (SD) Genetic counseling: 42.6 (11.8) Psychosocial counseling: 42.1 (11.4) Delayed intervention: 42.5 (11.5)	Inclusion: Women aged 18 to 74 with≥1 relative with breast cancer, no personal history of breast or ovarian cancer, no family history consistent with a BRCA mutation for breast cancer risk, living within 60 mile radius of research center, willingness to complete research activities and completed and returned baseline questionnaire Exclusion: Not Reported	**Family history:** Self-report of any family history of breast cancer **Risk level:** Calculated by use of Gail and Claus models, along with population data
Bowen et al., 2006[130] Fair	Mean age of 47 years 100% Ashkenazi Jewish	Inclusion: Women aged 18 to 74 years with ≥1 Ashkenazi Jewish ancestor, who lived within 60 miles of Seattle Exclusion: Personal history of breast or ovarian cancer, family history consistent with an autosomal dominant inheritance of breast cancer predisposition	≥1 Ashkenazi Jewish ancestor

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Bowen et al., 2004[71] Fair Same population as Bowen et al., 2002[66]	Telephone screening survey to determine eligibility, followed by mailed baseline survey. Those who returned completed surveys were randomized to individual genetic counseling (IGC), group psychosocial counseling (PC), or a delayed intervention control group (CG). A) IGC: Telephone contact with genetic counselor to review pedigree information. One 2-hour session following protocol based on standard genetic practice. Letter sent to participant within 2 weeks summarizing the session. B) PC: Group of 4-6 participants met for four, 2-hour sessions with trained health counselor. Each participant received her own risk assessment sheet, personalizing the group discussion to her own risk status. Main topics: risk assessment and perception, screening, stress management and problem solving, and social support. C) CG: Offered counseling following study completion For ICG and PC, brief survey on reactions to counseling within 4 weeks of last counseling contact. Mailed 2nd assessment 6 months after randomization, with a reminder call and offer of phone completion to those who did not return survey after 2 weeks.	NSI: 4-item questionnaire to assess risk perception Survey to assess reactions to counseling	Years: NR 6 months
Bowen et al., 2006[130] Fair	A) Group psychosocial counseling: psychologist led 4 2-hour, weekly sessions of 5-6 women per group. Each session included 20-min group cohesion activities followed by 1 of 4 major intervention components: risk assessment and perception, education, stress management, and problem solving and social support. B) Individual genetic counseling: genetic counselor provided 1-hour counseling sessions, individually. Sessions covered several topics, including participant's family background, breast cancer risk assessment, *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population, nongenetic risk factors for breast cancer, and breast screening. C) Delayed counseling: no counseling, served as control.	BSI: 53-item self-reported psychological symptom scale NSI: Continuous scale of 0 to 100 to assess risk perception	Years: NR 6 months

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Bowen et al., 2004[71] Fair Same population as Bowen et al., 2002[66]	Women's perceived risk for breast cancer decreased by 50% for the two counseling groups relative to control (p<0.01). Cancer worry decreased in both counseling groups by one scale point (p<0.05). There were no differential effects of counseling type on perceived risk or cancer worry. Women in psychosocial counseling experienced more anxiety change than those in the other groups. Depression was not impacted by study group.	Some women reported high levels of attendance, and satisfaction with counselors and counseling; women in the genetic counseling arm reported more frequently talking about concerns than did women in psychosocial groups. Perceived risk and worry can be reduced with both types of short- term interventions.	The National Human Genome Institute, the National Cancer Institute, and the National Office for Research on Women's Health (HG/CA01190)
Bowen et al., 2006[130] Fair	**A vs. B vs. C (results at followup)** Perceived risk (scale 0 to 100%): 18 (SD 16) vs. 18 (SD 16) vs. 32 (SD 23); p<0.001 both counseling groups vs. control Cancer worry (scale 4 to 16): 5.2 (SD 1.5) vs. 4.9 (SD 1.1) vs. 6.1 (SD 1.9); p<0.001 both counseling groups vs. control Awareness of genetic testing (range from 1=almost nothing to 4=a lot): 2.6 (SD 0.7) vs. 2.6 (SD 0.7) vs. 2.2 (SD 0.7); p<0.001 both counseling groups vs. control Interest in having genetic testing (range from 1=definitely not to 4=definitely yes): 2.4 (SD 0.9) vs. 2.4 (SD 0.9) vs. 2.8 (SD 0.8); p<0.01 both counseling groups vs. control Candidacy judgment (range from 1=definitely not to 4=definitely yes): 2.0 (SD 0.8) vs. 2.0 (SD 0.8) vs. 2.6 (SD 0.8); p<0.05 both counseling groups vs. control Fear of stigma (scale range unclear, higher score indicates higher fear of stigma): 3.4 (SD 1.1) vs. 3.4 (SD 1.1) vs. 3.3 (SD 1.2); no significant difference between groups Access to genetic testing (scale range unclear, higher score indicates more unrestricted access): 3.8 (SD 1.4) vs. 3.9 (SD 1.4) vs. 4.3 (SD 1.4); p<0.05 both counseling groups vs. control Information flow (scale range unclear, higher score indicates more restrictions on information flow): 2.0 (SD 1.1) vs. 2.1 (SD 1.0) vs. 1.9 (SD 0.9); p<0.05 both counseling groups vs. control	Counseling, either group or individual, reduced cancer worry, lowered inflated risk perceptions, and decreased interest in genetic testing. Included in Smerecnik, 2009 review.	National Human Genome Research Institute grant HG01190

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Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Brain et al., 2002[131] Good	Psychological factors	To compare the psychological impact of a multidisciplinary specialist genetics service with surgical provision in women at high risk and lower risk of familial breast cancer	RCT	Eligible: 1,000 Enrolled: 740 Randomized: 735 (369 control, 366 trial) Analyzed: 653 (315 control, 338 trial)	Wales	Welsh women with family history of breast cancer referred to breast cancer clinic by doctor in 18 month trial period (1996 to 1997). Randomized to trial (n=366) or control group (n=369).
Brain et al., 2011[132] NA Moderate-risk group from Brain et al., 2002[137]	Cancer worry	To provide 6 year followup on women in TRACE study, and the predictors of long-term cancer worry, perceived risk, and health behaviors.	Before and after	Eligible: 545 Enrolled: 384 Analyzed: 263	U.K.	Women who took part in the TRACE study
Braithwaite et al., 2005[133] Fair	Risk perception	To examine the acceptability of the GRACE prototype to women with a family history of breast cancer and test the hypothesis that GRACE would perform as well as the nurse counselor at improving women's risk perceptions without causing adverse emotional reactions.	RCT	Eligible: 89 Enrolled: 72 Randomized: 72 (38 to GRACE, 34 to clinical nurse specialist) Analyzed: 58	U.K.	Women with a family history of breast cancer recruited through newspaper ads and posters

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Brain et al., 2002[131] Good	**Mean age, years (SD), low vs. moderate vs. high risk** Control group: 48.6 (10.25) vs. 40.5 (9.13) vs. 39.2 (7.33) Trial group: 52.9 (7.75) vs. 41.6 (8.52) vs. 33.7 (8.19)	Inclusion: Women with a first-degree female relative diagnosed with breast cancer before age 50 or with bilateral breast cancer diagnosed at any age, ≥2 FDRs with breast cancer, or a FDR and SDR with breast cancer Exclusion: Personal history of breast cancer, previously received genetic counseling, or were not a resident of Wales	**Family history risk definition:** First degree female relative diagnosed with breast cancer before age 50; first degree female relative with bilateral breast cancer at any age; ≥2 FDRs with breast cancer; or a FDR and SDR with breast cancer. **Risk definition:** In trial group, risk was assessed on detailed pedigree data collected and analyzed by geneticist using Claus model. In control group, surgical assessment of risk was based on info collected on age, reproductive history, and minimal family history.

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
Brain et al., 2011[132] NA Moderate-risk group from Brain et al., 2002[137]	Mean age of 42.3 years (SD 8.22)	Inclusion: Women who took part in TRACE study, identified as moderate-risk, and were approved by their physician to be contacted Exclusion: Not reported	Moderate risk not otherwise described
Braithwaite et al., 2005[133] Fair	**GRACE (n=37) vs. counseling (n=34)** 18-34 years: 62.2% vs. 67.6% 35-49 years: 27% vs. 20.6% ≥50 years: 10.8% vs. 11.8% White: 91.9% vs. 94.1% Other race: 8.1% vs. 5.8%	Inclusion: Having ≥1 FDR or SDR with breast cancer Exclusion: Personal history of breast cancer	All had ≥1 FDR or SDR with breast cancer

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Brain et al., 2002[131] Good	A) Control group: 1) Breast cancer surveillance; 2) surgical assessment of individual breast cancer risk; 3) option to enter U.K. Tamoxifen Prevention Trial; and 40 annual surgical followup with surveillance and advice. B) Trial group: components 1, 3, and 4 of control group with genetic risk assessment and counseling.	NSI: 3-item scale to assess interest in genetic testing STAI: Measures an individual's current anxiety feelings	Years: NR Immediately
Brain et al., 2011[132] NA Moderate-risk group from Brain et al., 2002[137]	A) Claus model B) Generalized risk level based on age, reproductive history, and minimal family history	Cancer Worry Scale-Revised (CWS-R, scale 6 to 24) Perceived risk (single item scale 1 to 5)	Years: NR 6 years
Braithwaite et al., 2005[133] Fair	Both interventions were 1 session Cognitive outcomes assessed at baseline, postclinic, and at 3 months A) Risk counseling arm: Clinical nurse specialist undertook counseling sessions and drew pedigree with information from family history and assessed risk as low, moderate, or high based on GRACE guidelines. Participants were mailed letters summarizing content afterward. B) GRACE: Participants completed their pedigrees in GRACE and assessed their risk, learning their risk assessment and how to manage their risk. They received a numerical estimate of lifetime risk; a visual display of cumulative risk with general population as comparator; and a qualitative description. Clinical nurse specialists then offered to book mammography and arrange meetings with geneticists, where appropriate.	HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients NSI: Measured attitude, perceived benefit, risk perception, and satisfaction and risk communication on a Likert scale STAI: Measures an individual's current anxiety feelings	Years: NR 3 months

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Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Brain et al., 2002[131] Good	State anxiety: Significant main effect of time, with decreased anxiety from baseline to followup (p=0.03). Breast cancer worry: Significant overall reduction from baseline to followup. Significant interaction between risk information and time. Decline in women at low risk (t(106)=5.92,p<0.001) and moderate risk (t(443)=12.13, p<0.001), but not at high risk. Satisfaction: Significantly lower in high-risk group (p<0.001). Perception of risk: Marginally significant trend to increased perceived risk in high- risk women in the trial group. Interest in genetic testing: Effect of risk information not significant.	Specialists other than geneticists might provide assessment of breast cancer risk, reassuring those at reduced risk and targeting high-risk women for specialist genetic counseling and testing services. Low-risk women: Anxiety and cancer concerns were reduced with personal risk information. High levels of satisfaction, whether or not information based on detailed genetic analysis. High-risk women: Risk information, even unfavorable, does not appear to create significant anxiety. Concerns about breast cancer risk remained and they were less satisfied with consultation in either group. Implication: breast cancer worry may impact quality of life for women who recognize they are at high risk.	The Medical Research Council, National Assembly for Wales, NHS R&D (Wales), and Imperial Cancer Research Fund Dr. Gray is supported by Tenovus, the cancer charity
Brain et al., 2011[132] NA Moderate-risk group from Brain et al., 2002[137]	**A vs. B** Mean perceived risk post risk assessment: 3.83 (SD 0.51) vs. 3.97 (SD 0.38), p=0.01 All other outcomes were NS between groups	Women's cancer worry decreased over time regardless of intervention group, though there was a significant affect immediately after risk assessment this affect was gone by 9 months followup.	Wales Office for Research and Development in Health and Social Care
Braithwaite et al., 2005[133] Fair	**A vs. B** Mean baseline cancer worry (scale of 1 to 4): 1.92 vs. 1.81 Mean baseline STAI-state anxiety (scale of 20 to 80): 35.73 vs. 40.00 (p<0.01) Perceptions of risk information Participants were positive about risk information from both interventions on credibility, trustworthiness, accuracy, clarity, and helpfulness. Nurse counseling scored significantly higher than GRACE for all; significant differences in participants' satisfaction with risk information Clinical nurse specialist arm was 'very satisfied' with risk information (p<0.01)	No significant differences between GRACE and nurse counseling in risk perception or cancer worry. Nurse counseling was superior to GRACE on patient attitudes and satisfaction indicators.	Cancer Research U.K. (CUK), grant no. C1345/A169

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Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Burke et al., 2000[67] Fair	Cancer worry Risk perception	To assess whether modified traditional genetic counseling causes women with an intermediate risk of breast cancer to have a more realistic view of their risk, of genetic testing, and to decrease breast cancer worry	RCT	Eligible: 793 Enrolled: 356 Randomized: 243 (120 to genetic counseling, 123 to control group) Analyzed: 237 (116 to genetic counseling, 121 to control group)	U.S.	Sources for solicitation include women who live within 60 miles of Seattle: 2 studies at Fred Hutchinson Cancer Research Center, an oncologist's practice at University of Washington, mass media announcements.
Cull et al., 1998[68] Good	Psychological factors Risk perception	To evaluate use of video for education on the genetic basis of breast cancer and on strategies for breast cancer risk management in a breast cancer family clinic	RCT	Eligible: 159 Enrolled: 144 Randomized: 128 (66 to video before group, 62 to video after) Analyzed: 95 (53 to video before group, 42 to video after group)	U.K.	A consecutive series of women newly referred to the breast cancer family clinic were invited by mail to participate. 24% of the video before (VB) and 30% of the video after (VA) group were referred by another hospital clinic. One subject in each group had been referred from another genetic clinic. The remaining were referred by general practitioners.

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Burke et al., 2000[67] Fair	**Genetic counseling vs. control** Average age (years) 43 (SD 12) vs. 42 (SD 12) White: 94% vs. 93%	Inclusion: Women aged 18 to 74, lived within 60 miles of Seattle, and had ≥1 biological relative who has been diagnosed with breast cancer Exclusion: A personal history of breast or ovarian cancer and a family history indicative of autosomal dominant inheritance of breast cancer	Intermediate family history of breast cancer: 1 or more biological relative(s) with breast cancer but whose pedigree suggests a low likelihood of autosomal dominant transmission. Family history indicative of autosomal dominant inheritance of breast cancer: ≥2 first degree or 1 first degree and 1 second degree relative with either breast cancer before age 50 or ovarian cancer at any age, or ≥2 paternal second degree relatives with either breast cancer before age 50 or ovarian cancer at any age. The Claus model showed that these women would have ≥20% breast cancer risk by age 79.
Cull et al., 1998[68] Good	Mean age of 39 years (SD 8)	NR	NR

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Burke et al., 2000[67] Fair	Random assignment to 3 groups: individual genetic counseling (120 women), psychosocial group counseling (113 women, reported elsewhere, Bowen 1999), control (123 women). A) Adapted genetic counseling protocol for women with intermediate risk included precounseling telephone call, baseline questionnaire, individual genetic counseling session, immediate followup questionnaire, 6-month followup questionnaire, mailed summary letter B) Control group was offered group counseling following completion of the study	NSI: Questionnaire to assess breast cancer worry, opinions on genetic testing, and risk perception	Years: NR 6 months
Cull et al., 1998[68] Good	A) Subjects sent information about study with initial clinic appointment 4 weeks before the appointment. They were asked to return baseline questionnaire and forms within 2 weeks if wanting to participate. Those who did so were randomized either to the VB (Video Before) group, and were sent a copy of the educational video about 10 days before the clinic consultation, or to the VA (Video After) group, taking the video home after the postclinic assessment. B) Clinic consultation: individual meeting with geneticist to discuss individual risk and with breast surgeon to discuss risk management. Clinicians noted session length and rated assessment of it. Post clinic assessment included completion of instruments. Followup assessment by mail 4 weeks later.	GHQ: 30-item questionnaire to screen individuals for psychiatric disorders NSI: 12 response category assessment of risk perception 4-point scale to assess genetic risk Multiple choice questionnaire to assess objective risk STAI: Measures an individual's current anxiety feelings	Years: NR 1 month following clinic consultation

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Burke et al., 2000[67] Fair	Significant differences between counseling and control groups in mean perceived risk of breast cancer (F=27.9, p<0.009). Significant differences over time in perceived risk for the counseling group (F=65.9, p<0.001). Interaction between group and time for perceived risk was significant (F=50.6, p<0.001). Low overestimators of breast cancer risk reduced risk estimates by an average of 19 percentage points after counseling, compared with high overestimators who reduced risk estimates by an average of 36 percentage points (F=13.41,p<0.00001). After counseling, those who perceived themselves as candidates for testing decreased from 82% to 60%; interest in testing was reduced from 91% to 60%. 70% (82) liked the counseling very much, 56% (65) found the counseling very useful, and 22% (26) found it moderately useful. After receiving risk estimates, 33% (39) were a lot less worried and 32% (37) were a little less worried.	Most participants saw a benefit to counseling and afterward had a more accurate understanding of their risk. Counseling reduced interested in genetic testing.	The National Institutes of Health (HGO1190)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
Cull et al., 1998[68] Good	Duration of Consultation: VB group spent less time with surgeon (mean 11.8 min vs. 14.6, p<0.05), but their time with geneticist was not significantly shorter. Risk Assessment: No significant difference between VB or VA in accuracy of estimate at baseline. VB retained accuracy from clinic to followup. VA were more likely to underestimate at followup (p<0.05). Understanding of Risk Information: Subjective: At baseline and at followup, no significant difference. Objective: VB had higher scores (p<0.01) and a higher proportion of correct responses to more items. Followup: no significant differences after adjusting for education level (t =0.34). Emotional Distress: No significant difference in groups in anxiety or distress levels. Use of Video and Family Discussion: VB: 94% watched video at least 1 time from start to finish. 76% reported it offered new information. VA: 41/42 who gave followup data watched the video at least once and 41% of them said it gave new information. In both VA and VB, most (66% and 65%, respectively) watched it alone and most discussed it with a partner.	Women who saw the video before their clinic visit were not deterred from attending. Compliance with the study and satisfaction with the clinic visit were higher among those who viewed the video beforehand.	The NHS R&D (Cancer) Programme and the Imperial Cancer Research Fund

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Fry et al., 2003[134] Fair	Perceived risk Cancer worry	To compare the psychological outcomes of two models of breast cancer genetics services.	RCT	Eligible: 574 Enrolled: 373 Analyzed: 244	Scotland	Women referred by GP for breast cancer genetic risk counseling
Gurmankin et al., 2005[135] NA	Risk perception	To examine the risk perception derived from a risk communication with a health care provider during genetic counseling for breast cancer and *BRCA1/2* mutation risks.	Before and after	Eligible: NR Enrolled: 58 Analyzed: NR	U.S.	New patients at university cancer evaluation program

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Fry et al., 2003[134] Fair	Mean age (SD) Standard service: 37.3 (9.4) Novel service: 39.1 (9.6)	Inclusion: Women who lived in the region and were able to give informed consent, and complete a baseline questionnaire. Exclusion: Women who were symptomatic or diagnosed with breast and/or ovarian cancer, or women who had previously consulted with another clinic about their family history of cancer.	Criteria for significantly increased risk: Having a FDR with breast cancer diagnosis before age 40; having 2 FDRs or SDRs on the same side of the family with breast cancer diagnosis before age 60, or with ovarian cancer; having 3 FDRs or SDRs on the same side of the family with breast or ovarian cancer; having a FDR with breast cancer in both breasts; and having a male relative with breast cancer.
Gurmankin et al., 2005[135] NA	Mean age of 45.9 years (SD 10.5) 88% White 10% Black 2% Other 42% Ashkenazi Jewish	Inclusion: Females only Exclusion: Health care provider indicated they were too ill to participate	NR

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Fry et al., 2003[134] Fair	A) Standard (regional) service: Self-report family history and baseline questionnaire; genetics consultant and genetics nurse specialist assigned categorical risk via Cancer Research Campaign. Women at low risk receive informative letter; women at moderate/high risk offered appointment at familial breast cancer clinic where a genetics consultant discusses risk status and breast surgeon discusses risk management. Where appropriate, clinical exams and mammography included. Patients' GPs receive summary data, and patients receive followup questionnaires 4 weeks and 6 months later. B) Novel (Community-based) service: Women sent an appointment for a community-based clinic near their residence. Meetings run by genetics nurse specialist where family history collected and compared to published criteria (Cancer Research Campaign) to determine risk. Women at low risk offered information, reassurance, and discharged. Women at moderate/high risk offered appointment at a regional center with a geneticist and genetics nurse specialist, and asked to complete followup questionnaires at 4 weeks and 6 months.	Cancer Worry Scale (scale 5 to 24) GHQ-30	Years: NR 6 months
Gurmankin et al., 2005[135] NA	A) Precounseling interview assessed patient's breast cancer risk perception, *BRCA1/2* mutation risk perception, worry about breast cancer, family history of cancer, breast cancer risk reduction behaviors, and demographic information B) Postcounseling interview assessed patient's breast cancer risk, *BRCA1/2* mutation risk, recall of actual risk information, worry about breast cancer, completion of the Spielberger Trait Anxiety Inventory (20 to 80 score range) and the Life Orientation Test-Revised (0 to 32 measure of optimism)	NSI: Scale of 0 to 100 to assess risk perception scale of 1 to 7 to asses cancer worry STAI: Measures an individual's current anxiety feelings	October 2002 to February 2004 1 week

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Fry et al., 2003[134] Fair	**A vs. B** Cancer worry Baseline: 11.5 (3.2) vs. 11.3 (3.0) 4 weeks: 10.3 (2.4) vs. 10.2 (2.7) 6 months: 9.9 (2.5) vs. 9.7 (2.7) GHQ-30 Total score: median (IQR) Baseline: 2(9) vs. 2(7.3) 4 weeks: 1(8) vs. 2(8.5) 6 months: 0(4) vs. 0(5) GHQ-30 Case-level distress: % (n) Baseline: 36 (66) vs. 31 (58) 4 weeks: 21 (32) vs. 22 (27) 6 months: 21 (29) vs. 23 (28)	All women experienced a significant reduction in CWS scores, with greatest reductions from baseline to 4 weeks ($p<0.000$), and a smaller, but still significant reduction from 4 weeks to 6 months ($p=0.003$). Women experienced a significant drop in case level distress from baseline to four weeks ($p=0.004$), but there were no other significant differences in numbers of women with case level distress between trial arms, or time points.	Chief Scientist's Office and cancer Research U.K.

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
Gurmankin et al., 2005[135] NA	Mean breast cancer risk perception: 44% Risk perception change from baseline: +17%, (p<0.001) Accuracy of recall Risk information patients recalled was higher than risk communicated to them (+6%, p=0.02 vs. 8%, p=0.001) Patients' belief in recall was positive for breast cancer, showing postcounseling risk perceptions higher than risk information they recalled being told (+9%, p=0.001)	Patients' breast cancer risk perceptions following risk communication were higher than corresponding actual risk communicated to them (+19%, p<0.001) Inaccurate risk perception (high or low) can lead patients to make different medical decisions than they would with accurate risk perception. They could engage in interventions or experience unnecessary stress if perceived risks are inaccurately high.	The American Cancer Society and a Robert Wood Johnson Faculty Scholar Award

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Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Helmes et al., 2006[136] Fair	Cancer worry Risk perception	To assess whether women participating in either in-person or telephone counseling sessions would have a more accurate perception of their personal breast cancer risk, increase their intentions for breast screening, have reduced levels of cancer worry, and have less interest in genetic testing	RCT	Eligible: 898 Enrolled: 340 Randomized: 340 (104 to the in-person arm, 121 to the telephone arm, 115 to control) Analyzed: 335 (102 in the in-person arm, 119 in the telephone arm, 114 control arm)	U.S.	Physicians network in Washington state
Hopwood et al., 2004[138] NA	Cancer worry Psychological factors	To assess changes in risk perception, psychological distress, health care behaviors, and use of health care resources, to assess satisfaction with services, to describe regional variations in outcomes	Before and after	Eligible: 271 Enrolled: 256 Analyzed: 234 (1 month), 202 (12 months), 192 (precounsel, 1 month and 12 months)	U.K.	Cancer genetic services centers

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Helmes et al., 2006[136] Fair	**Mean age (years)** In-person counseling: 39.9 (SD 9.2) Telephone counseling: 40.4 (SD 9.7) Delayed counseling: 41.8 (SD 10.1)	Inclusion: Women aged 18-64 years, within 60 miles of research institute, planning to live in area for 1 year, spoke English, telephone in home, covered by commercial health insurance plan Exclusion: Women with personal history of breast/ovarian cancer, personal history of genetic counseling or testing for cancer risk	14.7% had family history of breast cancer
Hopwood et al., 2004[138] NA	Average across all five cancer genetics services: Mean age of 41 years (range: 22 to 72) 94% Female 2% Ethnic minority	Inclusion: Women seen at a cancer genetics services center Exclusion: Women who had been diagnosed with cancer, under 18 years	NR

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Helmes et al., 2006[136] Fair	A) In-person counseling: board certified genetic counselor conducted counseling consisting of a review of family history, discussion of breast cancer risk, and education about breast cancer genes. Also discussed genetic testing considerations, including implications of results, testing strategies, potential risks and benefits of test, cost of test, and psychological effects of test. Information packet was provided that contained personal risk information comparing the woman's risk with average-woman's risk; personal computer- drawn 3-generation pedigree; brochures on self-breast exams, pap-smear, and mammography; genetics visual aids; list of community resources; and cover letter. B) Telephone counseling: information packet was sent in the mail with instructions to open at the beginning of the telephone counseling which was identical in content and structure to in person counseling. C) Control group did not receive counseling.	NSI: Scale of 0 to 100 to assess risk perception Scale of 1 to 4 to measure intention to obtain breast cancer screening 4-item questionnaire to assess interest in genetic testing	Years: NR 3 months
Hopwood et al., 2004[138] NA	Genetic counseling, otherwise not described	GHQ: 60-item questionnaire to screen individuals for psychiatric disorders NSI: 5-response category assessment of perceived cancer risk	Years: NR At 1 month and 1 year following precounseling

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Helmes et al., 2006[136] Fair	**A vs. B vs. C (change from baseline to followup)** Mean risk perception (scale of 0 to 100): -10.29 vs. -8.65 vs. +1.14 (p<0.001) Mean cancer worry (scale of 4 to 16): -0.9 vs. -0.82 vs. -0.38 (p=0.002) Breast health intentions (score of 1 to 4): 0 vs. +0.01 vs. +0.02 (NS) Interest in genetic testing (score of 1 to 4): -0.61 vs. -0.52 vs. +0.51 (p<0.001)	There were no differences between in-person and telephone counseling, however both intervention groups decreased risk perception, cancer worry, and interest in genetic testing compared to the group that did not receive counseling. Counseling and no counseling had no effect on breast health intentions.	National Human Genome Research Institute grant HG01190
Hopwood et al., 2004[138] NA	**Precounseling vs. 1 month followup vs. 12 months followup** Underestimated risk: 30% (49/162) vs. 23% (37/162) vs. 22% (36/162) Mean GHQ (scale 0 to 28): 3.4 vs. 3.0 vs. 3.4 (NS) Mean CWS (scale 1 to 16): 11.6 vs. 10.9 vs. 10.8 (p<0.001)	Cancer distress decreased after counseling and continued to be low 1 year later.	NHS Research and Development Directorate, Programme for Cancer; Project NCP/B42

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Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Hopwood et al., 1998[137] Fair	Psychological factors	To understand psychological support needs for women at high genetic risk for breast cancer	Cohort	Eligible: 176 Enrolled: 174 Analyzed: 158	U.K.	All were consecutive first-time attendees at the Family History Clinics (Manchester, U.K.).
Kelly et al., 2008[139] NA	Risk perception	To examine change in subjective risk of ovarian cancer over time in response to genetic counseling and testing in the short- and long-term; and the discrepancy between subjective and objective estimates of ovarian cancer risk; and new methods for conceptualizing subjective risk derived from the Common Sense Model.	Before and after	Eligible: 78 Enrolled: 78 (40 to no personal history of breast cancer, 38 to personal history) Analyzed: NR	U.S.	Women were recruited from the community

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Hopwood et al., 1998[137] Fair	Mean age of 36.19 years (range: 22.63 to 46.35)	Inclusion: Women aged 18 to 45 living within a 25-mile radius of the FHC with risk ≥2 fold greater than the population for breast cancer Exclusion: Not reported	Risk was ≥2 fold greater than the population for breast cancer (i.e., 1:6 lifetime risk or greater as assessed using the Claus model).
Kelly et al., 2008[139] NA	Mean age of 48.64 years (SD 12.69) 100% Ashkenazi Jewish women	Inclusion: Ashkenazi Jewish women with personal or family histories suggestive of an inherited predisposition to breast and/or ovarian cancer Exclusion: Prior history of ovarian cancer, men, women having prophylactic oophorectomies	≥1 Ashkenazi Jewish grandparent

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Hopwood et al., 1998[137] Fair	A) Postal questionnaire prior to counseling B) At attendance for risk counseling, women were asked to complete GHQ together with several other self-report measures C) Questionnaires completed again at 3, 6, 9, and 12 months later D) Three months after Family History Consultation, home visit conducted with research interviews, including administration of the Psychiatric Assessment Schedule. Additional structured questions assessed attitude to risk information, reaction and concerns about cancer.	GHQ: 60-item questionnaire to screen individuals for psychiatric disorders NSI: 5-item questionnaire to assess risk perception PAS: Semi-structured clinical interview designed for use with respondents who have learning disability	Years: NR 3, 6, 9 and 12 months following genetic counseling

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
Kelly et al., 2008[139] NA	Genetic counseling included review of family cancer history, personal risk factors for breast and ovarian cancer, mechanisms of cancer inheritance, meaning of a positive and negative test result, and risks and benefits associated with testing.	CWS: 3-item questionnaire to measure how frequently an individual worries about getting breast cancer	Years: NR 6 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Hopwood et al., 1998[137] Fair	GHQ scores: Compliance at baseline was 85% (n=34), and 94% at 3 months (n=148). Prevalence of psychological distress, with a cut-off score >5, was 31% at baseline and 26% at 3 months. An examination of the 4 subscales of GHQ showed that 9.7% scored ≥5 on the somatic scale, 14% on the anxiety subscale and 3% each on the depression and suicidal ideation subscales at baseline. At 3 months, proportions were 12%, 15%, 6.8%, and 3.4%, respectively. When analysis was restricted to 105 women with evaluable assessments on all occasions, prevalence was 31% and 25% respectively. Baseline scores compared with pre-counseling risk estimates showed no significant difference (p=0.087). Significant difference between psychological distress and perceived risk postcounseling (p=0.0053). Women with accurate risk knowledge postcounseling had significantly lower scores than those who underestimated (p=0.0034) or who overestimated (p=0.0447). Psychiatric Assessment Schedule: Psychiatric disorder was confirmed in 21 (13.3%) of the study participants at 3 months. Most women had multiple concerns, but none reported risk counseling as a precipitant for their distress. Estimation of risk: Prior to risk counseling, 10% accurately estimated risk of breast cancer, while 50% accurately estimated after (p=0.0000). More women continued to overestimate (17%) than underestimate (11%). In general, giving women an accurate estimate of their probability of breast cancer when they perceived it to be much lower did not appear to trigger clinical anxiety or depression.	Prevalence rate for psychological distress when measured by a self-report questionnaire was double that ascertained by psychiatric interview, which is regarded as the gold standard. Interview data suggests that psychiatric morbidity was not apparently caused by the genetic counseling. This suggests that routine genetic risk consultations do not facilitate disclosure of distress or unresolved grief, and the use of a screening instrument together with a second-stage assessment interview should be explored further.	The Cancer Research Campaign
Kelly et al., 2008[139] NA	**Precounseling vs. postcounseling (ovarian cancer)** Accuracy of risk perception (estimated from graph): 1 vs. -5 Mean risk assessment (0 to 100%): 30.81 (SD 3.84) vs. 25.45 (SD 3.45) **Postcounseling vs. postresult vs. 6-month followup** Mean risk assessment (0 to 100%) Those with positive result (n=7): 27.86 (SD 8.01) vs. 31.43 (SD 7.46) vs. 22.14 (SD 7.23) Those with informative negative result (n=5): 27.00 (SD 6.63) vs. 11.00 (SD 2.45)	All women underestimated their risk of developing ovarian cancer.	The New Jersey Commission on Cancer Research and the Mid- Atlantic Region Human Genetics Network

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
	vs. 15.00 (SD 5.00) Those with uninformative negative result (n=28): 24.50 (SD 4.48) vs. 19.76 (SD 4.29) vs. 17.82 (SD 3.20)		

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Lerman et al., 1996[140] Fair	Cancer worry Risk perception	To study effect of individualized breast cancer risk counseling	RCT	Eligible: 438 Enrolled: 227 Randomized: 227 (group randomization NR) Analyzed: 200 (90 to risk counseling, 110 to control group)	U.S.	Subjects identified by relatives under treatment for breast cancer at either Fox Chase Cancer Center or Duke Comprehensive Cancer Center.
Lerman et al., 1999[69] Fair	Cancer worry Interest in genetic testing	To investigate racial differences in response to two alternate pretest education strategies for *BRCA1* genetic testing: a standard education model and an education plus counseling model	RCT	Eligible: 581 Enrolled: 364 Randomized: 364 (group randomization NR) Analyzed: 298 (157 to education only, 141 to education plus counseling)	U.S.	Subjects were recruited from two cancer centers (Georgetown University Medical Center or Washington Hospital Center).
Lobb et al., 2004[141] Good	Psychological factors	To examine the effect of different consultant communication styles on a variety of outcomes	Longitudinal cohort	Eligible: NR for unaffected group Enrolled: NR for unaffected group Analyzed: 89	Australia	Women from high-risk breast cancer families attending their first consultation before genetic testing

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Lerman et al., 1996[140] Fair	Aged 35 to 40 years: 18% Aged 41 to 49 years: 41% Aged ≥50 years: 42% White: 90% Black: 10%	Inclusion: Women aged 35 and older and a family history of breast cancer Exclusion: A personal history of cancer and younger than 35	≥1 FDR with breast cancer Breast cancer risk estimates for individual women were calculated using subject's Gail model variables and estimated the lifetime probability of developing breast cancer, the 95% CIs, and the estimated lifetime risk for a woman of the same age with the lowest risk of disease.
Lerman et al., 1999[69] Fair	Black: 24% -<40 years of age: 34% -≥40 years of age: 66% White: 76% -<40 years of age: 41% -≥40 years of age: 59%	Inclusion: White and Black women with a family history of breast cancer or ovarian cancer Exclusion: Personal history of cancer (except basal cell or squamous cell skin cancers)	≥1 FDR affected with breast cancer and/or ovarian cancer

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
Lobb et al., 2004[141] Good	Mean age of 38.7 years (range: 19 to 60)	Inclusion: Women attending their first consultation before genetic testing with no prior testing for or carrier of *BRCA1* or *BRCA2* Exclusion: Unable to give informed consent, under the age of 18, showed evidence of severe mental illness, and non-fluent in English	NR

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Lerman et al., 1996[140] Fair	A) Study group: 1) discussion of individual factors contributing to elevated risk, 2) presentation of individualized risk data, 3) recommendations for annual mammography and clinical breast exams, 4) instruction in breast self-exam B) Control group: 1) interview assessment of current health practices, 2) age-specific recommendations for variety of cancer screening tests, 3) encouragement to quit smoking, 4) suggestions for reducing dietary fat to 30% or less, 5) recommendations for regular aerobic exercise	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	Years: NR 3 months
Lerman et al., 1999[69] Fair	A) Education only: topics discussed included individual risk factors for breast cancer and ovarian cancer and patterns of inheritance for breast and ovarian cancer susceptibility. Subjects given qualitative estimates of their risk of developing breast cancer and ovarian cancer. Pedigrees were reviewed. Potential benefits, limitations, and risks of genetic testing for inherited breast cancer and ovarian cancer susceptibility also reviewed. B) Education plus counseling: provided the same education and materials described above. Subjects guided through a set of questions that explored personal issues related to cancer and genetic testing. Subjects discussed the emotional impact of having a family history of cancer, psychosocial implications of genetic testing for inherited breast cancer and ovarian cancer susceptibility, anticipated reactions to a positive and negative test result, and intentions to communicate test results to family members and friends.	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	Years: NR 1 month
Lobb et al., 2004[141] Good	A) Self-administered questionnaires were mailed 2 weeks before and 4 weeks after their genetic consultation. Consultations were taped and retained for analysis. Questionnaires included Breast Cancer Genetics Knowledge, Expectations, Perceived Risk, IES, HADS, and Satisfaction with Genetic Counseling Scale. B) Women came to the center for their genetic consultation. The consultation was recorded, analyzed, and coded to capture 10 aspects of genetic counseling. Not all counselors incorporated all aspects and this was the basis for the study.	HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients IES: 15-item scale measuring intrusion and avoidance responses in relation to a specific stressor NSI: Scale of 0 to 7 to assess genetic clinic expectations Scale of 0 to 9 to assess information sought Scale of 0 to 100 to assess risk perception	Years: NR 4 weeks

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Lerman et al., 1996[140] Fair	Breast cancer preoccupation: IES average score on measure of breast cancer preoccupation was 6.9+ 0.71 (means +SE). No significant baseline difference in risk comprehension between groups; however, significant change in risk comprehension at 3-month followup due to movement in risk-counseling group from overestimation to accurate or underestimation.	Among women with less formal education, counseling led to significant reductions in distress by the 3-month followup, suggesting a possible increased adherence to mammography.	Public Health Service grants ROICA57767 and K07CAOI604 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services
Lerman et al., 1999[69] Fair	Genetic testing intention: Family history and baseline genetic testing intentions both made significant independent contributions to 1-month genetic testing intentions. Women with stronger family history of cancer had greater increases in intentions. Only in Black, education plus counseling led to greater increases in intentions than education only (p=0.003). IES scores: All groups evidenced a reduction in distress from baseline to 1 month. However, this decrease, although not a significant difference, was smallest among Black women who received education plus counseling.	Overall: Black women were found to differ significantly from White women in the effects of the interventions on testing intentions and provision of a blood sample. Effects were independent of socioeconomic status and referral mechanism.	The National Institutes of Mental Health and National Human Genome Research Institute grant MH/HG54435
Lobb et al., 2004[141] Good	Anxiety: Women who had more aspects of genetic testing discussed had a decrease in anxiety after 4 weeks (p=0.03). Women receiving a letter summarizing their consultation had lower anxiety (p=0.012) and a trend toward less anxiety about breast cancer (p=0.089). Women who received four or more supportive communications were more anxious about breast cancer (p=0.000). Depression: Women whose consultants facilitated understanding more had a decrease in depression (p=0.052). Risk Accuracy: Women receiving a letter summarizing their consultation had increased risk accuracy (p=0.023).	Women who understand what is being presented to them have decreased depression. This can imply that women may feel overwhelmed with the amount of information they receive and may feel worse if they are not helped to understand it. Providing a written summary of the consultation helped with accurate risk perception.	The University of Sydney Cancer Research Fund

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Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Matloff et al., 2006[142] Fair	Risk perception	To examine if a personalized risk assessment and genetic counseling intervention would affect knowledge, risk perception, and decision making in a group of women who had 1 FDR with breast cancer compared with a control group	RCT	Eligible: NR Enrolled: NR Randomized: 64 (32 in each group) Analyzed: 54 completed 1 month followup (28 control and 26 intervention), 48 completed 6 month followup (25 control and 23 intervention)	U.S.	Women recruited through advertisements in New Haven.
Mikkelsen et al., 2007[143] Fair Same population as Mikkelsen et al., 2009[144]	Risk perception	To explore the impact of genetic counseling on perceived personal lifetime risk of breast cancer, the accuracy of risk perception, and possible predictors of inaccurate risk perception 1 year following counseling	Prospective cohort	Eligible: 3257 (568 in counseling group, 689 in reference group 1, 2000 in reference group 2) Enrolled: 1971 (319 in counseling group, 381 in comparison group 1, and 1271 in group 2) Analyzed: 1602 (213 in counseling group, 319 in comparison group 1, and 1070 in group 2)	Denmark	Danish women at risk of hereditary breast and ovarian cancer
Mikkelsen et al., 2009[144] Fair Same population as Mikkelsen et al., 2007[143]	Psychological factors Cancer worry Quality of life changes	To clarify the psychosocial impact of genetic counseling for hereditary breast and ovarian cancer.	Prospective cohort	Eligible: 3257 (568 in counseling group, 689 in reference group 1, 2000 in reference group 2) Enrolled: 1971 (319 in counseling group, 381 in comparison group 1, and 1271 in group 2) Analyzed: 1602 (213 in counseling group, 319 in comparison group 1, and 1070 in group 2)	Denmark	Danish women at risk of hereditary breast and ovarian cancer

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Matloff et al., 2006[142] Fair	Mean age of 49 years (range: 41 to 55) 21% Ashkenazi Jewish	Inclusion: Women ≥40 years with ≥1 FDR with breast cancer, had gone through natural menopause Exclusion: Taking menopausal therapy, having had cancer, atypical hyperplasia, or LCIS, being a known carrier of a *BRCA1/2* mutation, having heart disease, women with family history that placed them at >10% risk of carrying a mutation	≥1 FDR with breast cancer
Mikkelsen et al., 2007[143] Fair Same population as Mikkelsen et al., 2009[144]	Median age (years): Counseling: 39 (range: 18 to 72) Group 1: 56 (range: 28 to 76) Group 2: 45 (range: 18 to 75)	Inclusion: Women aged ≥18 years who attended an initial genetic counseling session for breast or ovarian cancer Exclusion: Women affected with breast or ovarian cancer at baseline or who developed cancer during the followup period	NR
Mikkelsen et al., 2009[144] Fair Same population as Mikkelsen et al., 2007[143]	Median age (years): Counseling: 39 (range: 18 to 72) Group 1: 56 (range: 28 to 76) Group 2: 45 (range: 18 to 75)	Inclusion: Women aged ≥18 years who attended an initial genetic counseling session for breast or ovarian cancer Exclusion: Women affected with breast or ovarian cancer at baseline or who developed cancer during the followup period	NR

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Matloff et al., 2006[142] Fair	A) Counseling session with personalized letter summarizing patient data B) Controls who received no counseling	NSI: Reviewed detailed information about menopause, the risks and benefits of each menopause therapy option and a disease risk factor assessment	August 2002 to January 2004 6 months
Mikkelsen et al., 2007[143] Fair Same population as Mikkelsen et al., 2009[144]	A) Genetic counseling: information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer B) Comparison group 1: women referred for mammography C) Comparison group 2: random sample of women	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition	2003 to 2004 1 year
Mikkelsen et al., 2009[144] Fair Same population as Mikkelsen et al., 2007[143]	A) Genetic counseling: information on incidence of sporadic breast cancer, genetics, inheritance patterns, and estimated personal lifetime risk of inherited cancer B) Comparison group 1: women referred for mammography C) Comparison group 2: random sample of women	HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients	2003 to 2004 1 year

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Matloff et al., 2006[142] Fair	**A vs. B** <u>Mean discrepancy between perceived risk for self and average woman</u> Baseline: 16.3 (SD 17.9) vs. 22.3 (SD 24.3) 1 month: 0.8 (SD 22.3) vs. 21.1 (SD 25.4) 6 months: 3.6 (SD 20.1) vs. 18.3 (SD 23.0) **A only** <u>Mean discrepancy between perceived risk for self and actual risk</u> Baseline: 36.9 (SD 20.4) 1 month: 18.9 (SD 28.6) 6 months: 17.1 (SD 25.9)	After counseling accuracy of perceived risk of breast cancer increased.	Susan G. Komen Foundation
Mikkelsen et al., 2007[143] Fair Same population as Mikkelsen et al., 2009[144]	**A vs. B vs. C** <u>Perceived absolute lifetime risk of breast cancer (%)</u> Mean within group changes from baseline to 1 year followup: -6.6 (95% CI -3.0 to -10.2) vs. 1.6 (95% CI 3.6 to -0.5) vs. 1.1 (95% CI 2.2 to 0.0) Mean between group changes: -8.2 (95% CI -12.2 to -4.1) counseling vs. group 1; -7.7 (95% CI -11.4 to -4.0) counseling vs. group 2 Change in risk accuracy of perceived lifetime risk of breast cancer (%) overestimate: -12 vs. 5 vs. 2 Accurate at 1 year followup: 16 vs. -5 vs. -2 (p=0.03 A vs. B and p=0.07 A vs. C)	Genetic counseling helped to increase risk accuracy even 1 year after counseling.	Danish Cancer Society, Grant Number PP 02 010, the Center of Innovation and Development in Nursing Education in the County of Aarhus and Aarhus University Research Foundation
Mikkelsen et al., 2009[144] Fair Same population as Mikkelsen et al., 2007[143]	**A vs. B vs. C** HADS-A score decreased from baseline to 1 year: 4.7% (95% CI -3.5 to 12.8) vs. 2.5% (95% CI -4.5 to 9.5) vs. 1.1% (95% CI -2.3 to 4.7); decrease in anxiety in group 1 was in women in nonsystematic screening (7.0%, 95% CI: -4.1 to 18.1) with a slight increase in women in systematic screening (1.1%; 95% CI -7.5 to 9.8) <u>Baseline vs. 2 weeks followup vs. 6 months followup vs. 12 months followup</u> Cancer specific distress: 52% vs. 50% vs. 41% vs. 41% Comparing women referred for mammography vs. no genetic counseling: (41% to 35%), or to a random sample from the general population (from 32% to 30%) with no counseling. More women with genetic counseling experienced decrease in cancer-specific distress; difference statistically significant when compared to general population (p=0.006), and subgroup of women with mammography screening (p=0.05)	A 11% (95% CI 1.4 to 20.8) decrease in cancer-specific distress in genetic counseling group from baseline to 1 year followup exceeded decrease in groups 1 and 2 with significance in group 2 (p=0.006) and in subgroup of group 1 in systematic screening (p=0.05).	Danish Cancer Society, Grant Number PP 02 010, the Center of Innovation and Development in Nursing Education in the County of Aarhus and Aarhus University Research Foundation, and the Danish Nurses' Organization

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Pieterse et al., 2011[145] NA	Risk perception accuracy, correct knowledge, perceived personal control Generalized state anxiety Cancer- related distress.	To assess changes in cognitions (accurate risk perception, correct knowledge, perceived personal control) and distress (state anxiety, cancer-related stress reactions) from before to immediately and six months after concluding breast cancer genetic counseling in female counselees, and whether changes in cognitions and distress were similar in affected versus unaffected women.	Before and after	Eligible: 204 Enrolled: 77 Randomized: N/A Analyzed: 77	The Netherlands	Women seeking counseling for hereditary cancer, University Medical Center in The Netherlands, surveys exchanged through the mail
Roshanai et al., 2009[146] Fair	Risk perception Psychological factors	To investigate the effect of an informational intervention on counselees' knowledge, risk perception, communication of information to at-risk relatives and satisfaction with the service.	RCT	Eligible: 210 Randomized: 163 (85 in intervention, 78 in control group) Analyzed: 147 at precounseling (73 in intervention, 74 in control); 144 for risk perception (71 in intervention, 73 in control); 147 two weeks postcounseling (73 in intervention, 74 in control); 139 at eight months postcounseling (68 in intervention, 71 in control)	Sweden	Swedish women visiting a university cancer genetic clinic, mainly referred due to breast cancer or family history of breast, ovarian or colorectal cancer (groups separated for analysis)

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Pieterse et al., 2011[145] NA	18 years or older	Inclusion: Patients sought counseling for hereditary cancer; were first among their first and second degree relatives to request counseling; were first time attendees; and age >18 years. Exclusion: Not reported	Seeking counseling for hereditary cancer
Roshanai et al., 2009[146] Fair	Female: 90.5% (n=133) Male: 9.5% (n=14) Median age, females (years): 56 (range: 23 to 84)	Inclusion: Women aged ≥18 years; able to read, write, and speak Swedish Exclusion: Suffered from any mental illness	Risk estimated by geneticist: Intervention % (n) vs. control % (n) ≤20%: 15 (5) vs. 23 (3) 21 to 40%: 72.5 (29) vs. 77 (37) >40%: 9 (3) vs. 4 (1)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Pieterse et al., 2011[145] NA	A) First session topics included family's occurrence of breast and other cancers, inheritance, and criteria on probability of inherited breast cancer. Likelihood of hereditary breast cancer running in family was estimated. Genetic testing was offered to counselees or affected relatives when they have an a priori chance (≥10%) of carrying BRCA gene. Counselees eligible for testing informed of medical consequences and options. Periodic surveillance recommended to all counselees at increased risk (>20%). Counselees and referring physician receive summary letter about genetic and risk information. Counselors distributed postcounseling questionnaire after last session and asked participants to complete it within a day. Six months later, counselees were sent a followup questionnaire. All three of these questionnaires assessed cognitions and distress. Counselors completed a questionnaire after counselee's last visit. Counseling spanned 1 to 4 visits over 6 to 24 months; STAI, IES, and VAS were used to measure anxiety levels	IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition NSI: Scale of 0 to 100 to assess risk perception; Scale of 0 to 7 to assess hereditary breast cancer knowledge PPC: Construct reflecting the degree to which a person believes that a situation is under their control STAI: Measures an individual's current anxiety feelings VAS: Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale	Years: NR 24 months (6 months after last counseling session)
Roshanai et al., 2009[146] Fair	A) Genetic counseling from specialist nurse: pedigree explanation; Buckman's Breaking Bad News model to inform at-risk relatives; pamphlet, videotape, copies of pedigree and medical records B) Control group received standard care given at the clinic: genetic counseling from a specialist nurse, no additional information, and no help in identify at-risk relatives	HADS: 14-item self-report scale for the detection of depression and anxiety in hospitalized patients SPIKES: A 6-step protocol for delivering bad news	2003 to 2005 At 2 weeks and at 8 months postcounseling

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Pieterse et al., 2011[145] NA	**Risk perception accuracy: % (n), Precounseling vs. immediately postcounseling vs. 6 months post-counseling** Underestimation: 3 (1) vs. 16 (5) vs. 24 (8) Correct estimation: (-) (0) vs. 32 (10) vs. 18 (6) Overestimation: 97 (29) vs. 52 (16) vs. 57 (19) Total number of counselees: 3 (unaffected group)	Counseling educates women on lifetime breast cancer risk; correct knowledge on breast cancer genetics decreased over time. Benefits gained immediately after counseling seem to remain over time.	Dutch Cancer Society supported original study (Grant number NIVEL 1999-2090); author supported by a postdoctoral fellowship from the Dutch Cancer Society.
Roshanai et al., 2009[146] Fair	The only significant difference between intervention and control was immediately after counseling, and at 2 weeks, when controls showed more accurate estimation of risk; groups showed the same results at 8-month followup.	At 8 month followup, 74% of counselees in control and intervention groups had informed relatives; 96% of relatives of intervention counselees and 89% of relatives of controls reported being	The Swedish Cancer Society

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
	No significant difference for anxiety or depression between control and intervention at any time point both groups significantly decreased over time ($p<0.01$).	informed. The majority (75% of intervention relatives and 67% of controls) reported receiving sufficient information.	

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Watson et al., 1998[148] Good	Cancer worry Psychological factors Risk perception	To look at recall of risk information after genetic counseling, and to determine impact of receiving an audiotape of the genetic consultation on level of recall, cancer-related worry, and uptake of risk management methods	RCT	Eligible: 135 Enrolled: 115 Randomized: 115 (60 cases, 55 controls) Analyzed: 107 (56 cases, 51 controls)	U.K.	First time attendees at the cancer family clinics of 2 London hospitals--Royal Marsden, Sutton and London, and St. George's Hospitals.

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Watson et al., 1998[148] Good	-Median age of 37 years (range: 28 to 56) for participants from the Royal Marsden Hospital -Median age of 41 years (range: 23 to 71) for participants from St. George's Hospital	Inclusion: Women with a family history of breast cancer, first visit to genetic clinic, never having been clinically affected with cancer, no known mental illness and aged ≥18 years Exclusion: Not reported	Not reported

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Watson et al., 1998[148] Good	All subjects were referred for genetic counseling with a clinical geneticist who provided a consultation (randomized at clinic immediately after consultation to minimize bias), including pedigree based on risk calculation and information regarding management options based on risk level. All were as part of consultation. A) Consultation plus audiotape group offered instructions on self-exam and clinical exam and received an audiotape of the consultation B) Consultation only group offered instructions on self-exam and clinical exam	CWS: 3-item questionnaire to measure how frequently an individual worries about getting breast cancer GHQ-12: 12-item questionnaire to screen individuals for psychiatric disorders VAS: Any of a number of pain self-assessment tools where subjects indicate their level of pain in response to a continuous visual scale	Years: NR 6 months

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Watson et al., 1998[148] Good	CWS scores: For both groups, median score was 11 (range 6 to 22). 95% CI 10 to12 for cases and 95% CI 10 to11 for controls; mean 11.14 (SD 3.23) for cases and mean 11.39 (SD 3.37) for controls. Scores fell in subjects given a tape of consultation from median 11 at baseline to 10 at 1 month, then 9 at 6 months. Relative risk scores: At 1-month followup 41% accurately recalled their risk of developing cancer, 25% overestimated, 11% underestimated, 23% didn't know/didn't remember. Results suggest that risk figure, regardless of accuracy, doesn't reflect more general view about risk compared with average women. Risk figure given as odds ratio compared with other formats (percentage or descriptive terms): odds ratio--71% were accurate in recall compared with 25% when given in other formats. Risk questionnaire scores: Usefulness of information rated on a visual analog scale. Average ratings were high, ranging from 8.5 (population risk) to 9.1 (risk of gene in family). Risk of gene in family, lifetime risk, and risk < age 50 were rated significantly more useful than population risk, risk of no cancer by age 50, and risk of disease over next 5 years. Medical management uptake: No significant correlation between cancer worry change scores and either level of breast clinical exam (p=0.8) or mammography (p=0.8), no difference between cases and controls for rate of self-exam, doctor exam, or mammography at 6-month followup, no difference between groups for other health behaviors unaffected by whether consultation tape was received or not.	Overall: GHQ-12 scores: For combined groups, median score was 1 (range 0 to 11). 36 subjects had a score indicative of psychological morbidity (>3) at baseline and 31 at 1-month and 6-month followup.	Not reported

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
2013 Review						
Watson et al., 1999[149] Good	Psychological factors	To investigate perception of genetic risk and the psychological effects of genetic counseling in women with a family history of breast cancer	Prospective cohort	Eligible: 303 Enrolled: 282 Analyzed: 282	England	First time genetic clinic attendees recruited from four South London genetic counseling centers (Royal Marsden NHS Trust Hospital [2 separate clinics], Mayday University Hospital, and St. Georges' Hospital)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Watson et al., 1999[149] Good	Median age of 37 years (range: 19 to 76)	Inclusion: Women with a family history of breast cancer, never clinically affected by cancer, no known serious mental illness, age 18 or older, and able to complete a questionnaire Exclusion: Not reported	Breast cancer risk calculated using CASH model based on the number of breast cancer cases in first and second degree relatives, age of family members at disease onset, and age of woman presenting for genetic counseling.

Author, year Quality	Interventions	Measures	Duration of followup
2013 Review			
Watson et al., 1999[149] Good	Self-administered questionnaires given at genetic clinic immediately, pre-, and postgenetic consultation, and by postal survey at 1-, 6-, and 12-month followup	GHQ: 12-item questionnaire to screen individuals for psychiatric disorders IES: 17-item questionnaire to measure an individual's level of distress in relation to a specific event or condition NSI: Lifetime risk perception assess as a 1 in x odds ratio Relative risk assessed on a 5-point scale Breast cancer incidence assessed as 1 in x STAI: Measures an individual's current anxiety feelings	Years: NR 12 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Watson et al., 1999[149] Good	GHQ: One-third had notable levels of distress. There was no statistically significant change in general mental health at each followup compared with pre-counseling level. Cancer Anxiety and Helplessness / IES: No statistically significant changes in levels of cancer-specific distress. Followup assessment revealed that 13% (35/268) had received some psychological intervention during the 12 months since attending the clinic. Of these, 7% (n=19) had received psychotropic medication, 4% (n=10) had engaged in psychological counseling, and 2% (n=6) had received both forms of intervention. Levels of state anxiety: Anxiety levels at precounseling were at similar levels to those reported in healthy women attending for breast cancer screening (mean 38.7), with a significant downward shift immediately postcounseling (mean 35.2, p<0.001). Perception of risk: Specific figures about risk, provided within genetic counseling, tend not to be remembered. Continual overestimators may be worrying unnecessarily and excessively about breast cancer risk and under-estimators appear undisturbed by the information that their risk is greater than they thought. Underestimators were not significantly different from the rest of the sample in	High levels of cancer-related worry compare unfavorably to previously gathered data on general population risk samples. Genetic counseling does not alleviate cancer-specific distress in a substantial minority of women; this contradicts previous U.S. findings. A single counseling session may not shift worries in some women. General levels of psychological morbidity unaffected by genetic counseling. Substantial minority of women who do not benefit from counseling and continue to overestimate risk, and worry was unrelieved. Study highlights problems with genetic	The Cancer Research Campaign (CRC project CP1026)

Appendix B Table 7. Evidence Table of Genetic Counseling Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
	terms of their scores for intrusive and avoidant thoughts about breast cancer risk when assessed precounseling. However, at 12 months, their scores were significantly lower than the rest on each of the scales (avoidance p=0.02; intrusion p=0.006), indicating that in the long-term they are less likely to report having intrusive thoughts about breast cancer risk. High levels of cancer-specific distress were found in pregenetic counseling, with 28% reporting that they worried about breast cancer "frequently or constantly" and 18% that worry about breast cancer as a "severe or definite" problem. Following genetic counseling, levels of cancer-specific distress were unchanged. General mental health remained unchanged over time (33% psychiatric cases were detected pregenetic counseling, and 27% 12 months after genetic counseling).	counseling, e.g. some women continue to overestimate risk despite being told otherwise. Anxiety is not alleviated by genetic counseling, and women who continue to overestimate their risk and worry about breast cancer are likely to go on seeking unnecessary screening.	

Abbreviations: aOR=adjusted odds ratio; BRCA=breast cancer susceptibility gene; BRCAPRO= breast cancer susceptibility gene prediction model; BCSC=Breast Cancer Surveillance Consortium; BSI=Brief Symptom Inventory; CASH=Cancer and Steroid Hormone Study; CG=control group; CGSW=Cancer Genetics Service for Wales; CI=confidence interval; CUK=Cancer Research UK; CWS=Cancer Worry Scale; CWS-R=Cancer Worry Scale-Revised; DUKE-SSQ=DUKE Social Support Questionnaire; FDR=first-degree relative; FHC=family history clinic; GHQ=General Health Questionnaire; GHQ-30=General Health Questionnaire 30; GP=general practitioner; GRACE=Genetic Risk Assessment in the Clinical Environment; HADS=Hospital Anxiety and Depression Scale; HADS-Anxiety=Hospital Anxiety and Depression Scale-Anxiety; HADS-D=Hospital Anxiety and Depression Scale-Depression; IES=Impact of Events Scale; IES-A=Impact of Events Scale-Avoidance; IES-I=Impact of Events Scale-Intrusion; IGC=Individual genetic counseling; IQR=interquartile range; LCIS=lobular carcinoma in situ; MCMQ=Medical Coping Modes Questionnaire; NA=not applicable; NHS=National Health Service; NR=not reported; NS=not significant; NSI=Neuropsychological Symptom Inventory; PAS=Psychiatric Assessment Schedule; PC=psychosocial counseling; PCP=primary care provider; PGC=psychological group counseling; PPC=Perceived personal control; R&D=research and development; RCT=randomized control trial; RST=referral screening tool; SD=standard deviation; SDR=second-degree relative; SD=standard deviation; SPIKES=Setting up, Perception, Invitation, Knowledge, Emotions-Protocol for delivering bad news; STAI=State/Spielberger Trait Anxiety Index; TRACE=trial of genetic assessment in breast cancer; U.K.=United Kingdom; U.S.=United States; VA=video after; VAS=Visual Analogue Scale; VB=video before

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Sub-category	Purpose	Study type	N
Current Review				
Andrews et al., 2004[150] Fair	Psychological	Explore characteristics of those who choose to receive their testing results.	Prospective cohort	Eligible: 65 Enrolled: 60
Godard et al., 2007[157] Good	Psychological	To determine why people decline genetic testing.	Prospective cohort	364 who withdrew before or after genetic testing

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
Current Review				
Andrews et al., 2004[150] Fair	Australia	Women of Ashkenazi Jewish ancestry, who underwent genetic testing, at a hospital clinic in Sydney	Mean age (years): 50.9	Inclusion: Ashkenazi Jewish women ages ≥20 years with and without prior breast/ovarian cancer who agreed to provide information about post-test anxiety; study evaluated anxiety in those who received testing results and those who did not.
Godard et al., 2007[157] Good	Canada	Individuals from high risk breast and ovarian cancer families who declined genetic testing	Mean age: not reported -Age <40 years: 16.9% -Age 40 to 59 years: 43.3% -Age ≥60 years: 39.8% Female: 85.9% Male:14.1%	1,220 individuals from 385 high-risk families; 886 received results and 364 withdrew either before or after genetic testing. 234 of these voluntarily explained their withdrawal.

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
Current Review				
Andrews et al., 2004[150] Fair	**Using the National Guidelines on Familial Aspects of Breast Cancer** Average risk (lifetime risk of 1:8 to 1:12): 45% High risk (lifetime risk of 1:2 to 1:4 or higher): 22% **Using BRCA PRO:** Score < 10%: 29 Score > 10%: 31	BRCA carriers and noncarriers	Impact of Event Scale (15-item) State Component of the State-Trait Anxiety Inventory (STAI-State) Beck Depression Inventory (BDI) Satisfaction with the Decision to Undergo Testing (pleasure, unsure or regretted having had the test at 12 months after result disclosure)	Years: NR 12 months
Godard et al., 2007[157] Good	Individuals were recruited if family met one of the following characteristics: 1) >4 individuals with breast and/or ovarian cancer diagnosed in 1st or 2nd degree relatives; 2) families with 3 individuals with breast and/or ovarian cancer in 1st degree relatives; and 3) families with an identified *BRCA1/2* mutation.	BRCA mutation carriers and noncarriers. Of those who withdrew after testing: 45.8% (87/190) had no mutation and 54.2% (103/190) had a mutation.	Those who declined to receive results voluntarily submit reasons for withdrawal; recorded in notes and comments received from the research subjects or taken by genetic counselors and genetic nurses.	Years: NR Through completion of genetic counseling and testing.

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Results	Conclusions	Funding source
Current Review			
Andrews et al., 2004[150] Fair	**Baseline vs. 4 months vs. 12 months, among those without prior breast cancer (n=50)** Carriers (n=4) Breast cancer worry: 23.0 vs. 12.8 vs. 11.5 Anxiety: 42.7 vs. 33.5 vs. 35.5 Depression 7.3 to 5.0 to 7.0 Noncarriers (n=28) Breast cancer worry: 11.5 vs. 7.6 vs. 6.3 Anxiety: 39.7 vs. 45 vs. 39.6 Carriers and noncarriers combined Breast cancer worry for all non affected women: p=0.018 for 4 months vs. baseline and p=0.002 for 12 months vs. baseline Anxiety and depression scores were not significantly different from baseline Decline to be tesed: 34% (17/50) **Baseline vs. 4 months vs. 12 months, among those with prior breast cancer (n=10)** Carriers (n=3) Breast cancer worry: 21.7 vs. 15.5 vs. 10.5 Anxiety: 25.1 vs. 31.5 vs. 26.5 Depression: 9.3 vs. 10.0 vs. 7.0 Noncarriers (n=6) Breast cancer worry: 23.3 vs. 17.3 vs. 16.8 Anxiety: 34.1 vs.40.9 vs. 33.3 Depression: 6.3 vs. 6.6 vs. 4.8	Breast cancer anxiety declined significantly for both the carrier and noncarrier groups. No significant change from baseline in generalized anxiety or depression. No significance testing done on the affected women because of small numbers.	NIH
Godard et al., 2007[157] Good	**Prior to 1st counseling session vs. after 1st counseling session vs. after 1st blood draw** Timing of withdrawal: 48.8% (163/334) vs. 37.4% (125/334) vs. 12.8% (46/334) Concerns/reasons for withdrawal prior to 1st counseling session Expected psychological impact: 19 vs. 66 Saw no advantage to genetic counseling: 11 vs. 23 Did not want to discuss cancer or preferred testing in clinical setting: 19 vs. NR Concern about insurance: 3 vs. 11 Logistical constraints: NR vs. 14 Relative's refusal to participate or difficulty contacting family: NR vs. 20	Anxiety was the most common reason for withdrawing from genetic testing. Confidentiality did not come up as a concern. Cost was not an issue in this study because testing was provided as part of the study (no charge).	Canada Institutes of health for the INHERITS BRCAs research program.

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Author, year Quality	Sub-category	Purpose	Study type	N
Current Review				
Lieberman et al., 2017[161] Good	Testing approaches	To compare streamlined BRCA screening via proactive recruitment in medical settings with self-referral.	Prospective cohort	Eligible: NR Enrolled: 1771 (1027 recruiter enrolled vs. 744 self-referred) Analyzed: 845 1 week after testing prior to result disclosure, 623 6 months after testing, after receiving results

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
Current Review				
Lieberman et al., 2017[161] Good	Israel	Unclear, recruiter enrolled patients recruited from mammography center, ambulatory clinics, and an executive screening clinic	Mean age (years): 52 (SD 13); 54 recruiter enrollees vs. 48 self-referred enrollees, p<0.001 79% female	Inclusion: Ashkenazi Jewish, age ≥25 years, previously unaffected with cancer, and without a known familial BRCA mutation. Exclusion: Not reported

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
Current Review				
Lieberman et al., 2017[161] Good	Ashkenazi Jewish, self-defined as 4 grandparents of Ashkenazi Jewish origin	BRCA carriers and noncarriers	General satisfaction with participation and testing (scale 1 to 5, very dissatisfied to extremely satisfied) Impact of Events Scale (IES, scale 0 to 75) Knowledge of breast cancer genetics and genetic testing (scale 0 to 10) Perceived Personal Control (PPC, scale 0 to 2) Satisfaction with Health Decision scale (SWD, scale 6 to 30) State-Trait Anxiety Inventory (STAI, scale 6 to 24)	Years: NR 6 months

Author, year Quality	Results	Conclusions	Funding source
Current Review			
Lieberman et al., 2017[161] Good	**Recruiter enrolled vs. self-referred** *Mean on psychological scale* IES before result disclosure: 5.4 vs. 6.2, p=0.02 IES after result disclosure, non carriers only: 4.8 vs. 5.6, p=NS IES score >30 (indicating high post-event distress): 0.7% vs. 2.7% , p=0.02 PPC before result disclosure: 1.00 vs. 1.10, p<0.001 PPC after result disclosure, non carriers only: 1.18 vs. 1.28, p=0.006 STAI before result disclosure: 9.8 vs. 10.2, p=NS	Overall 90% of participants reported being satisfied or very satisfied both 1 week and 6 months after testing, with increased satisfaction over time. Most participants (71%) and 40% of carriers did not have relevant family history.	Breast Cancer Research Foundation

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Results	Conclusions	Funding source
	STAI after result disclosure: 9.8 vs. 10.2, p=NS Knowledge before result disclosure: 6.8 vs. 7.4, p<0.001 Knowledge after result disclosure: 6.8 vs. 7.5, p<0.001 SWD before result disclosure: 25.2 vs. 26.3, p<0.001 SWD after result disclosure: 26.2 vs. 26.8, p=0.01 Very satisfied before result disclosure: 40% vs. 55%, p<0.001 Satisfied before result disclosure: 48% vs. 40% Very satisfied after result disclosure: 53% vs. 61%, p=0.02 Satisfied after result disclosure: 37% vs. 35% **Carriers vs. noncarriers** *Mean on psychological scale* IES: 19.9 vs. 4.9, p<0.001 PPC: 1.43 vs. 1.23, p=NS STAI: 12.6 vs. 9.9, p=0.016 Knowledge: 8.7 vs. 7.1, p<0.001 SWD: 25.3 vs. 26.5, p=NS Very satisfied: 63% vs. 57%, p=NS Satisfied: 26% vs. 36%		

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Author, year Quality	Sub-category	Purpose	Study type	N
Current Review				
Lumish et al., 2017[163] Fair	Psychological	To describe patient understanding, psychological outcomes and utilization of genetic information among patients with a personal or family history of breast or ovarian cancer who were offered panel gene testing.	Cohort	Eligible: 367 Enrolled: 232 Analyzed:103 without prior personal history of cancer
Manchanda et al., 2015[164] Good	Testing approaches	To assess the benefits/disadvantages of a population-based approach to genetic testing for high penetrance- dominant gene mutations compared with the conventional family history-based approach.	RCT	Eligible: NR Enrolled: 1042 Randomization: 1034 (530 population screening, 504 family-history based) Analyzed: 1017 (520 population screening, 497 family-history based)
Smith et al., 1999[170] Good	Psychological	To compare psychological distress among individuals tested for *BRCA1* based on siblings' test results	Cohort	Eligible/Invited: 759 Enrolled 87 males and 125 females who completed baseline interview (n=408) and were tested for *BRCA1*, received results in person from genetic counselor (n=230) and completed a follow- up interview 1-2 weeks after the receipt of their test results (n=212) and had completed data on all variables

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
Current Review				
Lumish et al., 2017[163] Fair	U.S.	Patients with family history of breast or ovarian cancer Columbia University Cancer Genetics Clinic	Mean age: 41.6 years (SD 13.0) Female: 93.2% (96/103)	Inclusion: All patients referred to the clinic for counseling for hereditary breast and ovarian cancer between June 2013 and May 2015. Exlusion: Non-English, deceased, no current contact information, no personal or fam history of breast or ovarian cancer or did not undergo genetic testing at the time of consultation.
Manchanda et al., 2015[164] Good	U.K.	North-London Jewish community	Mean age (years): 54.30 (SD: 14) 66.8% female	Inclusion: Age >18 years and Ashkenazi Jewish ethnicity Exclusion: Known BRCA mutation, first-degree relatives of a BRCA carrier or previous BRCA testing
Smith et al., 1999[170] Good	U.S.	Participants are all part of larger main study of Kindred 2082, the largest known kindred identified with a *BRCA1* mutation (750 living members); all were invited to participate including those affected with breast and ovarian cancer	Mean age: men 46 years; women 46 years Men, n = 87 Women, n=125	Inclusion: All members of Kindred 2082; Utah and Idaho; all members of the Church of Jesus Christ of Latter-day Saints, primarily White and of northern European descent. Exclusion: Unable to consent to participate or unable to attend two in-person genetic counseling sessions at the University of Utah.

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
Current Review				
Lumish et al., 2017[163] Fair	Any family history of breast or ovarian cancer	13.5% (14/103) *BRCA1/2* positive 66.9% (69/103) negative 19.4% (20/103) VUS	IES (event related distress) Multidimensional Impact of Cancer Risk Assessment (MICRA, scale) SWD (Satisfaction with Decision Instrument)	June to December 2015 Mean of 12.5 months after genetic testing (range 3 to 27 months
Manchanda et al., 2015[164] Good	Ashkenazi Jewish, self-defined as 4 grandparents of Ashkenazi Jewish origin	BRCA carriers and noncarriers	Health Anxiety Inventory (HAI, scale) Hospital Anxiety and Depression Scale (HADS, scale) Short Form 12-item (SF-12, both MSC [Mental Health Component] and PCS [Physical Health Component Scale] subscales) Multidimensional Impact of Cancer Risk Assessment (MICRA, scale)	2008 to 2010
Smith et al., 1999[170] Good	All members of known *BRCA1* mutation carrier kindred.	Known and unknown mutation status but all at risk for *BRCA1* Mutation carrier status: Men 33%; Women 38%.	Baseline State Anxiety Scale Test-related Distress: IES (event related distress) Carrier/noncarrier and sibling status (all siblings test positive; all siblings tested including both positive and negative; all siblings tested negative; no other siblings with results yet)	1 to 2 weeks after testing result

Author, year Quality	Results	Conclusions	Funding source
Current Review			
Lumish et al., 2017[163] Fair	**Positive vs. negative vs. VUS** Mean IES total score: 18.1 (SD 12) vs. 8.8 (SD 11) vs. 6.7 (SD 11), p<0.05 for positive vs. others Mean IES-I score: 1 (SD 0.8) vs. 0.4 (SD 0.5) vs. 0.3 (SD 0.5), p=0.006 for positive vs. others and p=0.008 for VUS vs. negative Mean IES-A score: 1 (SD 0.6) vs. 0.5 (SD 0.6) vs. 0.4 (SD 0.7), p=NS Mean IES-H score: 0.5 (SD 0.7) vs. 0.2 (SD 0.4) vs. 0.2 (SD 0.4), p=NS Mean MICRA total score: 29.6 (SD 14.0) vs. 19.0 (SD 10.8) vs. 12. 4 (SD 8.6), p=0.002 for positive vs. negative and p=0.001 for VUS vs. negative Mean MICRA-distress score: 10.9 (SD 5.7) vs. 3.3 (SD 5.8) vs. 1.5 (SD 3.1), p<0.05 for positive vs. others Mean MICRA-uncertainty score: 9.6 (SD 7.7) vs. 6.0 (SD 7.3) vs. 4.3 (SD 5.3), p=NS Mean MICRA-positive experience score: 9.1 (SD 4.6) vs. 9.7 (SD 7.1) vs. 6.6 (SD 7.3), p=0.04 for positive vs. negative and p=0.01 for VUS vs. negative Mean SWD score: 21.7 (SD 3.3) vs. 23.1 (SD 2.2) vs. 22.2 (SD 4.2), p=NS	Patients without personal history of breast or ovarian cancer, who tested positive for a mutation tended to have higher levels of post-testing distress and some intermediate levels of distress among those receiveing a VUS.	NIA Grant T35 AG 044303

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Results	Conclusions	Funding source
Manchanda et al., 2015[164] Good	13 carriers were detected in teh PS arm, and of these only 3 had a clinically significant FH. 9 carriers were detected in the FH arm 5 more carriers were detected among FH-negative FH-arm participants following study completion. Overall decrease in anxiety, distress and uncertainty with time. The overall *BRCA1/2* prevalence detected was 2.45%. Of the 1034 participants, 12.4% (128) were FH positive. The most decrease in anxiety was baseline to 7 days (-0.64) compared to 7 days to 3 mo (-0.24). Positive experience scores increased by QOL and health anxiety did not change with time (after testing). For 27 BRCA carriers in the population, the sensitivity of FH-based approach is 44.4% (95% CI=26.4 to 63.9); positive likelihood ratio is 3.86 (95% CI=2.2 to 5.81) and negative-likelihood ratio is 0.63 (95% CI = 0.41 to 0.84). No signficant short-term differences between FH and population-based approaches with respect to levels of anxiety, depression, health anxiety, physical/mental well-being, distress, and uncertainty linked to genetic testing.	Overall anxiety decreases in both groups. No difference between groups in terms of psychological outcomes. FH-strategy failed to detect some mutation carreiers who had negative FH.	Cancer Charity The Eve Appeal
Smith et al., 1999[170] Good	Relative to noncarriers, men who tested positive and who were the first sibling tested experienced more distress than those who tested positive when all of their siblings were negative. Noncarrier males whose siblings all tested positive also experienced distress. For women, distress was greatest among those who learned they were carriers. Carrier women whose siblings were negative or mixed had attenuated levels of elevated distress.	Siblings' reaction to testing results varies by whether siblings have been tested and what their results were.	NCI

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Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Arver et al., 2004[151] NA	Psychological	To prospectively evaluate the psychological consequences during the 1st year following pre-symptomatic testing with respect to anxiety, depression, and QOL in self-referred individuals tested for breast/ovarian or colon cancer genes known in their families.	Before and after	Eligible: NR Enrolled: 66 Analyzed: 63 at week 1 and 2 months, 61 at 6 months, 59 at 12 months
Dagan and Shochat, 2009[152] Fair Same population as Shochat and Dagan, 2010[169]	Psychological Cancer worry	To investigate the association between *BRCA1/2* status and HR-QOL in Ashkenazi asymptomatic women.	Case-control	Eligible: 152 (39 carriers, 77 noncarriers, 36 controls) Enrolled: 73 (17 carriers, 20 noncarriers, 36 controls) Analyzed: 73 (17 carriers, 20 noncarriers, 36 controls)
Ertmanski et al., 2009[153] NA	Psychological	To predict which women might suffer from abnormally high levels of anxiety and depression after receiving a positive genetic test result.	Before and after	Eligible: NR Analyzed: 56

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Arver et al., 2004[151] NA	Sweden	Clinical Genetic Unit, Karolinska University Hospital, Stockholm	Mean age of 40.5 years (SD 11.1)	Inclusion: Healthy females belonging to a family with a known mutation in 1 of the genes *(BRCA1, BRCA2, MLH1* , or *MSH2*), wishing for genetic testing, aged ≥18 years, Swedish speaking Exclusion: Individuals with cancer and men
Dagan and Shochat, 2009[152] Fair Same population as Shochat and Dagan, 2010[169]	Israel	Rambam Health Care Campus oncogenetic clinic	Mean age of 51.5 years (SD 8.9) Carriers: 51.4 years (SD 9.1) Noncarriers: 54.5 years (SD 9.4) Controls: 50.0 years (SD 8.3)	Inclusion: Asymptomatic *BRCA1/2* carriers and noncarriers who had undergone genetic testing at Rambam Health Care Campus click *Control:* Age-matched low-risk community control, with no family history of breast/ovarian cancer and not tested for *BRCA1/2* mutations Exclusion: Major chronic illnesses, pregnancy, aged ≤1 year
Ertmanski et al., 2009[153] NA	Poland	Women seeking genetic testing at cancer genetics center in Poland. Women who tested positive for BRCA were included in analysis.	NR for women without breast cancer	Inclusion: Women who tested positive for BRCA mutation and completed both baseline and followup measures Exclusion: Not reported

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Arver et al., 2004[151] NA	Women with a 50% or 25% risk of being gene carriers	BRCA carriers and non-carriers	Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) Swedish SF-36 Health Survey (SF-36, scale NR)	1995 to 1999 At 1 week, 2, 6, and 12 months
Dagan and Shochat, 2009[152] Fair Same population as Shochat and Dagan, 2010[169]	FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer	BRCA carriers and noncarriers	The Brief Symptom Inventory (BSI, scale NR) Cancer Related Worry (CRW, scale NR) Health-Related Quality of Life (HR-QOL, scale NR)	January 2006 to November 2007 Mean followup of 8.0 years (SD 1.9)
Ertmanski et al., 2009[153] NA	Positive family history of early onset breast or ovarian cancer	BRCA positive	Impact of Events Scale (IES, scale 0 to 75) State-Trait Anxiety Inventory (STAI, scale 1 to 10)	January 2005 to December 2007 At 1 month and 1 year

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Arver et al., 2004[151] NA	**Pretest vs. 1 week posttest vs. 2 months posttest vs. 6 months posttest vs. 1 year post-test** <u>Mean on psychological scale</u> HADS-A (estimated from graph): 5.6 vs. 4.6 vs. 4.0 vs. 4.0 vs. 4.2; p<0.001 over time, only pretest is above normal value HAD-D (estimated from graph): 2.4 vs. 2.4 vs. 2.4 vs. 2.4 vs. 2.6; p=NS SF-36 general health: 78.7 (SD 19.2) vs. 78.8 (18.1) vs. 79.6 (20.2) vs. 81.0 (20.1) vs. 81.0 (20.3); p=NS SF-36 vitality: 67.0 (21.9) vs. 66.4 (19.8) vs. 71.9 (21.8) vs. 68.2 (25.4) vs. 69.3 (23.4); p=NS SF-36 social function: 87.3 (15.6) vs. 86.5 (20.0) vs. 91.1 (17.5) vs. 89.1 (19.4) vs. 89.0 (18.2); p=NS SF-36 role emotional: 83.8 (30.5) vs. 82.5 (34.8) vs. 79.2 (38.6) vs. 88.0 (29.2) vs. 86.2 (33.1) SF-36 mental health: 77.4 (18.7) vs. 74.9 (20.0) vs. 80.1 (19.5) vs. 78.6 (17.9) vs. 78.3 (19.6); p=NS	Anxiety went down over time, however depression and QOL were not affected. The results were not separated out by carriers and noncarriers though.	King Gustav V's Jubilee Fund and the Swedish Cancer Society

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Author, year Quality	Results	Conclusions	Funding source
Dagan and Shochat, 2009[152] Fair Same population as Shochat and Dagan, 2010[169]	**Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)** Mean on psychological scale (SD) CRW: 0.75 (0.5) vs. 0.67 (0.5) vs. 0.45 (0.4); p=NS BSI total: 0.66 (0.7) vs. 0.35 (0.4) vs. 0.50 (0.4); p=NS HR-QOL total: 74.4 (19.2) vs. 80.3 (13.7) vs. 83.0 (10.2); p=NS HR-QOL role limitation due to emotional problems subscale: 74.5 (36.4) vs. 91.7 (21.3) vs. 97.2 (9.3); p<0.01 HR-QOL role limitation due to physical problems subscale 79.4 (30.9) vs. 85.0 (28.6) vs. 95.1 (13.1); p=0.05	Carriers had higher QOL distress regarding role limitation due to emotional problems and physical problems compared to noncarriers and controls.	NR
Ertmanski et al., 2009[153] NA	**Pretest vs. 1 month posttest vs. 1 year posttest** Mean STAI-Anxiety: 6.6 vs. 6.5 vs. 6.5 At 1 month posttest, IES mean score was 23.8, this is considered a low level of negative psychological reaction	For women not affected by breast cancer themselves, testing positive for the BRCA mutation did not increase anxiety and did not have a negative psychological impact.	Polish Ministry of Science and Higher Education grant number 2 PO5 D 12929

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Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Foster et al., 2007[154] Fair	Cancer worry	To assess long-term impact of genetic testing for breast/ovarian cancer predisposition in a clinical cohort.	Prospective cohort	Eligible: NR Analyzed: 154
Geirdal et al., 2005[156] Good Same population as Geirdal and Dahl, 2008[155]	Psychological	To explore psychological distress in women at risk of FBOC and HNPCC cancers and without access to genetic testing, and to compare them with mutation carriers and with healthy women from the general population.	Prospective cohort	Eligible: 10,321 (253 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers) Enrolled: 10,244 (176 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers) Analyzed: 10,244 (176 FBOC, 10,000 normal controls, 68 *BRCA1* mutation carriers)
Geirdal and Dahl, 2008[155] Good Same population as Geirdal et al., 2005[156]	Psychological	To examine how coping strategies used by women with FBOC were associated with caseness of anxiety disorder and to explore if a similar pattern of associations were observed in the carrier group.	Prospective cohort	Eligible: 333 (253 FBOC, 80 *BRCA1* mutation carriers) Enrolled: 242 (174 FBOC, 68 *BRCA1* mutation carriers) Analyzed: 242 (174 FBOC, 68 *BRCA1* mutation carriers)

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Foster et al., 2007[154] Fair	U.K.	Recruited from 9 U.K. centers between 1997 to 2000	Median age: 42 years (range: 23 to 72)	Inclusion: Unaffected by cancer and from families with a *BRCA1/2* mutation identified in an affected blood relative Exclusion: Not reported
Geirdal et al., 2005[156] Good Same population as Geirdal and Dahl, 2008[155]	Norway	Section for Genetic Counseling, Department of Cancer Genetics, The Norwegian Radium Hospital	**Mean age (years)** FBOC: 40.5 (SD 9.7) *BRCA1* carriers: 42.0 (SD 10.6) Controls: 42.5 (SD 10.9)	Inclusion: Self-referred or referred from doctors to Section for Genetic Counseling, at risk for FBOC or BRCA positive Controls: random sample of age-matched women completing same questionnaires Exclusion: Not reported
Geirdal and Dahl, 2008[155] Good Same population as Geirdal et al., 2005[156]	Norway	Section for Genetic Counseling, Department of Cancer Genetics, The Norwegian Radium Hospital	**Mean age (years)** FBOC: 40.5 (SD 9.7) *BRCA1* carriers: 42.0 (SD 10.6)	Inclusion: FBOC: Women aged ≥18 years, had been to genetic counseling at Section for Genetic Counseling *BRCA1* positive: Women aged ≥18 years, had been to genetic counseling and testing at Section for Genetic Counseling, carried a demonstrable mutation Exclusion: FBOC: Any identifiable mutation in family, diagnosed with breast or ovarian cancer *BRCA1* positive: Diagnosed with breast or ovarian cancer

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Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Foster et al., 2007[154] Fair	50% risk of inheriting a *BRCA1/2* mutation, this was lower if an intervening relative had died	BRCA carriers and non-carriers	Cancer worry scale-revised (CWS-R, scale 6 to 24) General Health Questionnaire (GHQ-28, scale 0 to 28)	1997 to 2000 3 years
Geirdal et al., 2005[156] Good Same population as Geirdal and Dahl, 2008[155]	Family history of ≥2 FDR (or SDR though males) with early onset (<50 years) breast cancer and/or multiple cases of breast cancers in the same lineage compatible with dominant inheritance in the family and/or a combination of early onset breast cancer and ovarian cancer in the family	BRCA positive FBOC, mutation status unknown	Beck Hopelessness Scale (BHS, scale 0 to 20) General Health Questionnaire (GHQ-28, scale 0 to 84) Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) Impact of Event Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40)	January 2000 to December 2001
Geirdal and Dahl, 2008[155] Good Same population as Geirdal et al., 2005[156]	Family history of ≥2 FDRs (or SDRs though males) with early onset (<50 years) breast cancer and/or multiple cases of breast cancers in the same lineage compatible with dominant inheritance in the family and/or a combination of early onset breast cancer and ovarian cancer in the family	BRCA positive FBOC, mutation status unknown	Coping Orientation to Problems Experienced Scale (COPE, scale varied for each coping strategy) Hospital Anxiety and Depression Scale (HADS, anxiety subscale 0 to 21)	January 2000 to December 2001

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Foster et al., 2007[154] Fair	**Carriers (n=53) vs. noncarriers (n=101)** Mean on psychological scales (SD) GHQ at baseline: 2.7 (4.6) vs. 2.6 (3.8); p=NS GHQ at 3 year posttest: 4.5 (6.3) vs. 3.7 (5.3); p=0.03 for carriers baseline vs. posttest; p=NS for between groups differences CWS-R at baseline: 11.7 (3.1) vs. 11.5 (3.4); p=NS CWS-R at 3 year posttest: 10.4 (3.6) vs. 9.3 (2.1); p=0.03 for carriers baseline vs. post-test; p=NS for between groups differences	Overtime cancer worry decreased for both carriers and noncarriers, while general distress increased for both groups, with 18% of carriers and 17% of noncarriers identified as cases using the GHQ-28 at 3 year followup.	Award C1226/A137 from Cancer Research U.K.
Geirdal et al., 2005[156] Good Same population as Geirdal and Dahl, 2008[155]	**FBOC (n=176) vs. carriers (n=68) vs. controls (n=10,000)** Mean differences on psychological scales (SD) HADS-D: 2.4 (2.9) vs. 1.7 (2.4) vs. 3.2 (2.9); p<0.05 FBOC vs. carriers HADS-A: 5.2 (3.8) vs. 4.2 (3.6) vs. 4.5 (3.5); p<0.05 FBOC vs. carriers GHQ-28: 3.3 (5.4) vs. 2.3 (4.0) vs. NR; p<0.05 FBOC vs. carriers IES-I: 10.2 (8.7) vs. 9.8 (7.6) vs. NR; p=NS IES-A: 8.3 (7.9) vs. 8.4 (7.6) vs. NR; p=NS BHS: 3.7 (2.5) vs. 3.8 (2.6) vs. NR; p=NS	Women in FBOC group, but who had not undergone genetic testing were more anxious, more depressed, and higher general distress than women who were known to be BRCA mutation carriers.	The Norwegian Foundation for Health and Rehabilitation, the National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo

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Author, year Quality	Results	Conclusions	Funding source
Geirdal and Dahl, 2008[155] Good Same population as Geirdal et al., 2005[156]	**FBOC (n=174) vs. carriers (n=68)** Mean HADS-A: 5.3 (SD 3.9) vs. 4.2 (SD 3.6); p=0.04 Prevalence of HADS-defined anxiety: 24% vs. 24%; p=NS Mean (SD) on subscales of COPE with significant differences, higher scores=strategy used more often Active coping: 10.2 (3.2) vs. 8.7 (3.2); p=0.002 Planning: 9.1 (3.5) vs. 7.9 (3.7); p=0.01 Suppression of competing activities: 6.7 (2.7) vs. 5.2 (2.3); p<0.001 Focus on and venting of emotions: 8.1 (3.6) vs. 6.2 (2.7); p<0.001 Seeking instrumental support: 10.2 (3.6) vs. 7.4 (3.1); p<0.001 Seeking emotional support: 9.4 (3.3) vs. 7.9 (2.7); p=0.003 Acceptance: 12.4 (3.1) vs. 13.3 (2.9); p=0.01 Mental disengagement: 6.7 (2.8) vs. 6.0 (2.2); p=0.03 NS COPE subscales: positive reinterpretation and growth, restraint coping, denial, behavioral disengagement, turning to religion, and use of humor	Women in FBOC group, but who had not undergone genetic testing were more anxious than *BRCA1* mutation carriers. FBOC groups used many more coping strategies compared with *BRCA1* mutations carriers, however mutation carriers were more accepting of their breast cancer risk than those in the FBOC group and therefore may not have used other coping strategies.	The Norwegian Foundation for Health and Rehabilitation, the National Council for Mental Health, Norway, and a donation from Edith Kongshe, Oslo

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Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Graves et al., 2012[158] NA	Psychological	To examine long-term psychosocial outcomes in a large U.S. sample	Case-series	Eligible: 655 Enrolled: 464 Analyzed: 107 (unaffected)
Julian-Reynier et al., 2011[159] Good	Risk perception	To describe the sequences of preventive decisions made by women up to 5 years after disclosure of their test results and the surveillance/surgical options chosen by various age groups.	Prospective cohort	Eligible: 331 Analyzed: 246
Kinney et al., 2005[160] Poor	Psychological	To evaluate the effect of receiving genetic test results on general and cancer-specific psychological distress among African Americans at high-risk for carrying a deleterious *BRCA1* mutation.	Prospective cohort	Eligible: NR Analyzed: 52

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Graves et al., 2012[158] NA	U.S.	Women at the Lombardi Comprehensive Cancer Center Familial Cancer Registry	NR for women without breast cancer	Inclusion: Women ages 25 to 75 years, received *BRCA1/2* test results, and were at least 3 years post disclosure at the time of the study Exclusion: Not reported
Julian-Reynier et al., 2011[159] Good	France	French Cancer Genetic Network	**Mean age (years)** Carriers: 37.2 Noncarriers: 41.7	Inclusion: *BRCA1/2* mutation carriers and non- carriers in the same families Exclusion: Not reported
Kinney et al., 2005[160] Poor	U.S.	Members of a high-risk African American kindred that was identified previously with the *BRCA1* mutation	NR for women without breast cancer	Inclusion: Women aged ≥18 years and members of the family identified in the genetic linkage study as having *BRCA1* mutation Exclusion: Not reported

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Graves et al., 2012[158] NA	Not reported	43.9% (47/107) BRCA positive 56.1% (60/107) BRCA true negative	Impact of Events Scale (IES, scale 0 to 75) State-Trait Anxiety Inventory (STAI, scale 20 to 80)	Years: NR Median of 5 years posttest
Julian-Reynier et al., 2011[159] Good	*BRCA 1/2* mutation carriers or members of families where a mutation was identified	41% (101/246) *BRCA 1/2*	Perception of personal risk of cancer (6- point Likert scale) Preventive health behaviors	2000-2006 5 years
Kinney et al., 2005[160] Poor	All women from *BRCA1* mutation positive family	*BRCA 1* carriers and noncarriers	Center for Epidemiologic Studies- Depression (CES-D, scale NR) Impact of Events Scale (IES, scale 0 to 75) State-Trait Anxiety Inventory (STAI, scale 1 to 10)	Years: NR 4 months

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Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Graves et al., 2012[158] NA	**Logistic regression bivariate analysis (statistically significant associations)** Positive genetic test with genetic testing distress: p=0.03 Negative genetic test with positive experiences: p=0.008 **Multiple regression analysis (statistically significant associations)** Genetic testing distress Model 1 adjusting for marital status, pretest cancer distress, and receipt of RRM accounted for 13% of variance in genetic testing distress; p=0.003 Model 2 adjusting for model 1 and genetic test result (positive or true negative) accounted for an additional 12% of variance in genetic testing distress; p=0.00001 Positive experiences Model 1 adjusting for income and pretest cancer distress accounted for 8% of variance in positive; p=0.04 Model 2 adjusting for model 1 and genetic test result (positive or true negative) accounted for an additional 6% of variance in positive experiences; p=0.008	Among unaffected women, *BRCA1/2* carriers reported higher genetic testing distress and lower positive experiences compared with *BRCA1/2* true negatives.	Department of Defense grant DAMD BC021733, Jess and Mildred Fisher Center for Familial Cancer Research, and Lombardi Comprehensive Cancer Center's Familial Cancer Registry and Clinical and Molecular Epidemiology Shared Resources
Julian-Reynier et al., 2011[159] Good	**Carriers (n=101) vs. noncarriers (n=145)** Change from before test result to after test result of those who perceived personal risk as high Breast cancer risk: +18% vs. -47%; p=0.016 for carriers change and p<0.001 for noncarriers change Ovarian cancer risk: +20% vs. -27%; p=0.007 for carriers change and p<0.001 for noncarriers change	Carriers' perception of risk increased after receiving genetic test results, while noncarriers perception of risk decreased.	Institute National du Cancer
Kinney et al., 2005[160] Poor	Noncarriers unaffected with breast cancer decreased anxiety from baseline to 1 month followup; p=0.001, data not shown	Noncarriers' anxiety went down after receiving genetic test results.	National Human Genome Research Institute, National Institute of Nursing Research and the National Cancer Institute

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Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Low et al., 2008[162] Fair	Psychological	To examine the relationship between mutation carrier status, personal cancer history, and the potential positive impact of genetic testing.	Prospective cohort	Eligible: NR Analyzed: 47
Meiser et al., 2002[165] Good	Psychological	To study the psychological adjustment of women who have undergone testing for *BRCA1/2* breast and ovarian cancer susceptibility	Prospective cohort	Eligible: NR Enrolled: 143 (30 carriers, 60 noncarriers, and 53 controls) Analyzed: 140 (30 carriers, 59 noncarriers, and 51 controls)

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Low et al., 2008[162] Fair	U.S.	UCLA Familial Cancer Registry and Genetic Evaluation Program	NR for women without breast cancer	Inclusion: Aged ≥18 years with family history of breast, ovarian, or other cancer consistent with *BRCA1/2* heredity and/or 10% prior probability of carrying a *BRCA1/2* mutation based on published risk assessment data Exclusion: Did not complete followup data
Meiser et al., 2002[165] Good	Australia	Women in outreach clinics who had *BRCA1/2* testing, were healthy with a family history of breast or ovarian cancer, and approached 1 of 14 familial cancer clinics (FCC) and 6 associated clinics	Mean age of 40 years (SD 11.1)	Inclusion: Eligible for genetic testing and at risk for developing hereditary breast cancer with an affected living relative to provide blood sample Exclusion: History of breast or ovarian cancer, limited English literacy, and being tested for founder mutations only

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Low et al., 2008[162] Fair	Personal and/or family history consistent with *BRCA1/2* heredity and/or 10% prior probability of carrying a *BRCA1/2* mutation	BRCA positive and negative Variant of uncertain significance was grouped with negative results	Brief COPE (scale NR) Emotional Approach Coping Scale (scale NR) Impact of Events Scale-Revised (IES- R, scale NR) Post-Traumatic Growth Inventory (PTGI, scale 0 to 105)	September 1998 to Fall 2003 Average of 20.9 months

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
Meiser et al., 2002[165] Good	25% mutation (*BRCA1/2*) carrier risk: Subjects from high-risk family with closest affected relative or relative with a *BRCA* mutation is 2nd degree 50% risk: Subjects from high-risk family who has either a 1st degree affected relative or unaffected relative with a known pathogenic *BRCA1/2* mutation	BRCA carriers and non-carriers	Beck Depression Inventory (BDI, scale 0 to 63) Impact of Events Scale (IES, scale 0 to 75) Miller Behavioural Style Scale (scale NR) State-Trait Anxiety Inventory (STAI, scale 20 to 80)	November 1996 to October 2000 12 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Low et al., 2008[162] Fair	**Carriers (n=7) vs. noncarriers (n=40)** Mean on psychological scale (SE) PTGI total score (estimated from graph): 14 vs. 22; p=NR IES-R at 1-month posttest: 5.83 (2.47) vs. 1.37 (0.10); p<0.05 Approach coping score: 2.32 (0.18) vs. 2.37 (0.14); p=NS	Women with BRCA positive mutations reported greater distress after testing than non-carriers, but did not report differences in positive life changes.	STOP CANCER Research Career Development Award
Meiser et al., 2002[165] Good	**Carriers (n=30) vs. noncarriers (n=59) vs. controls (n=51)** Baseline mean scores (SD); p=NS for all Breast cancer worry: 13.1 (13.1) vs. 13.4 (14.6) vs. 16.0 (14.8) STAI: 36.1 (11.2) vs. 33.6 (12.1) vs. 33.6 (10.7) BDI: 5.5 (5.7) vs. 6.3 (6.7) vs. 5.9 (5.6) 7-10 day followup mean scores (SD) Breast cancer worry: 21.2 (14.4) vs. 13.9 (16.1) vs. 14.9 (12.3); p=0.005 carriers vs. controls, p=NR carriers vs. noncarriers STAI: 38.5 (13.8) vs. 31.6 (11.1) vs. 36.8 (12.1); p=0.024 noncarriers vs. others BDI: 5.3 (6.2) vs. 5.7 (7.0) vs. 7.2 (6.8); p=NS 4 month followup mean scores (SD) Breast cancer worry: 17.7 (18.6) vs. 8.1 (13.5) vs. 13.1 (13.5); p=NS carriers vs. controls; p=NR carriers vs. noncarriers STAI: 36.8 (15.3) vs. 32.2 (10.8) vs. 36.3 (14.2); p=NS BDI: 6.2 (8.7) vs. 3.6 (5.4) vs. 6.4 (6.3); p=0.024 noncarriers vs. others 12 month followup mean scores (SD) Breast cancer worry: 16.1 (14.9) vs. 8.2 (14.2) vs. 12.3 (14.8); p=0.045 carriers vs. controls, p=NR carriers vs. noncarriers STAI: 31.7 (10.5) vs. 36.2 (12.9) vs. 39.0 (12.2); p=0.007 noncarriers vs. control BDI: 4.0 (5.1) vs. 5.4 (6.4) vs. 6.9 (7.00); p=NS	Those without deleterious BRCA mutations derive psychological benefits from genetic testing. Those who test positive for deleterious BRCA mutations may anticipate a sustained increase in breast cancer distress following disclosure, although no other adverse effects were found in this group	Project Grants Nos. 970929 and 113877 from National Health and Medical Research Council of Australia

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Metcalfe et al., 2012[166] NA	Psychological	To report on cancer-related distress levels, uptake of cancer risk reduction options, and the resulting breast and ovarian cancer risk in Jewish women 2 years after receiving a postive BRCA mutation result	Before and after	Eligible: 22 Enrolled: 19 Analyzed: 17
Reichelt et al., 2004[167] Good	Psychological	To examine the short-term psychological impact of receiving definite results concerning *BRCA1* mutation status in a clinical setting.	Prospective cohort	Eligible: 301 Enrolled: 244 Analyzed: 209
Reichelt et al., 2008[168] NA	Psychological	To examine the levels of psychological and cancer-specific distress at 18 months after getting genetic test results in women with demonstrated *BRCA1* mutations and to explore associations with baseline characteristics.	Before and after	Eligible: NR Analyzed: 181

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Metcalfe et al., 2012[166] NA	Canada	Jewish women responding to a newspaper ad	Mean age: 46 years (range: 28-67)	Inclusion: Women self-identified as Jewish, ages 25 to 70 years, residing in Ontario, and positive for a BRCA mutation Exclusion: Not reported
Reichelt et al., 2004[167] Good	Norway	Unit of Medical Genetics, The Norwegian Radium Hospital	**Mean age (years)** Tested: 43.9 (SD 11.7) Not tested: 33.0 (SD 11.7)	Inclusion: Aged ≥18 years and risk based on clinical criteria Exclusion: None
Reichelt et al., 2008[168] NA	Norway	Section for Hereditary Cancer, Department of Medical Genetics, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway	NR for women without breast cancer	Inclusion: Women aged ≥18 years, with a known *BRCA1* mutation in a close relative Exclusion: None

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Metcalfe et al., 2012[166] NA	All were positive for BRCA mutation	42% (8/19) *BRCA1* 58% (11/19) *BRCA2*	Impact of Events Scale (IES, scale 0 to 75, IES-I subscale 0 to 35, IES-A subscale 0 to 40)	Years: NR 2 years
Reichelt et al., 2004[167] Good	50% risk for FDRs to carriers 25% risk for SDRs through males to carriers	BRCA carriers and noncarriers Unknown status, for those who refused testing	Beck Hopelessness Scale (BHS, scale 0 to 20) General Health Questionnaire (GHQ- 28, scale 0 to 84) Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 21) Impact of Event Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40)	September 1997 to October 1999 6 weeks

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
Reichelt et al., 2008[168] NA	Known *BRCA1* mutation in close relative	BRCA positive and negative	Hospital Anxiety and Depression Scale (HADS, scale 0 to 42) Impact of Events Scale-Intrusive subscale (IES-I, scale 0 to 35)	September 1997 to October 1999 At 6 weeks and 8 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Metcalfe et al., 2012[166] NA	**Pretest vs. 1 year posttest vs. 2 years posttest** Mean IES-I (SD): 1.1 (1.9) vs. 10.9 (8.6) vs. 6.9 (6.2); p=0.02 Mean IES-A (SD): 4.1 (8.7) vs. 12.9 (8.2) vs. 10.4 (9.4); NS Mean IES-total (SD): 5.2 (10.5) vs. 23.8 (14.5) vs. 17.2 (14.5); p=0.05 **2 years posttest clinical distress levels** 11% (2/19) severe distress (score ≥44) 21% (4/19) moderate distress (score 26-43) 37% (7/19) mild distress (score 9-25) 32% (6/19) subclinical distress (score <9)	Intrusive behaviors increased 1 year posttest but decreased by 2 years, with most women (69%) scoring in the mild or subclinical distress level at 2 years	Not reported
Reichelt et al., 2004[167] Good	**Carriers (n=141) vs. noncarriers (n=68)** Mean on psychological scales (SD) at followup; all p=NS IES-I: 9.8 (7.6) vs. 9.3 (8.0) IES-A: 8.4 (7.6) vs. 7.6 (7.4) HADS-A: 4.2 (3.6) vs. 4.1 (3.9) HADS-D: 1.7 (2.4) vs. 2.3 (2.7) GHQ-28: 2.3 (4.0) vs. 2.4 (4.5) BHS: 3.8 (2.6) vs. 4.0 (2.8) **Tested (n=244) vs. not tested (n=57)** Mean on psychological scales (SD) at baseline IES-I (subscale 0 to 35): 8.8 (7.5) vs. 8.9 (7.3); p=NS IES-A (subscale 0 to 40): 8.0 (7.1) vs. 7.7 (7.3); p=NS HADS-A (subscale 0 to 21): 4.4 (3.8) vs. 4.1 (3.2); p=NS HADS-D (subscale 0 to 21): 2.0 (2.6) vs. 1.3 (1.8); p<0.05 GHQ (scale 0 to 84): 2.5 (4.2) vs. 2.0 (3.2); p=NS BHS (scale 0 to 20): 4.0 (2.7) vs. 3.7 (2.1); p=NS	Women who chose to get tested had higher baseline depression than those who decided not to get tested. There were no differences at followup between women who were tested and found to be mutation carriers and those who were not mutation carriers.	A grant from the Norwegian Research Council
Reichelt et al., 2008[168] NA	**Pretest vs. 6 weeks posttest vs. 18 months posttest** Mean psychological scales (SD) HADS: 6.6 (6.1) vs. 6.2 (6.1) vs. 6.9 (6.9); p=NS IES-I: 9.3 (7.8) vs. 9.0 (7.8) vs. 8.7 (7.9); p=NS	This study did not separate out women without cancer by carrier status. The results show no differences in distress before testing or up to 18 months after testing.	Norwegian Research Council grant number 115586/320

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
Shochat and Dagan, 2010[169] Fair Same population as Dagan and Schochat, 2009[152]	Insomnia	To investigate the association between positive genetic diagnosis for *BRCA1/2* founder mutations and symptoms of insomnia in Ashkenazi asymptomatic women.	Case-control	Eligible: 152 (39 carriers, 77 noncarriers, 36 controls) Enrolled: 73 (17 carriers, 20 noncarriers, 36 controls) Analyzed: 73 (17 carriers, 20 noncarriers, 36 controls)

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
Shochat and Dagan, 2010[169] Fair Same population as Dagan and Schochat, 2009[152]	Israel	Rambam Health Care Campus oncogenetic clinic between 1996 to 2006	Mean age: 51.5 years (SD 8.9) -Carriers: 51.4 years (SD 9.1) -Noncarriers: 54.5 years (SD 9.4) -Controls: 50.0 years (SD 8.3)	Inclusion: Asymptomatic *BRCA1/2* carriers and noncarriers who had undergone genetic testing at Rambam Health Care Campus click *Control:* Age-matched low-risk community control, with no family history of breast/ovarian cancer and not tested for *BRCA1/2* mutations Exclusion: Major chronic illnesses, pregnancy, aged ≤1 year

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
Shochat and Dagan, 2010[169] Fair Same population as Dagan and Schochat, 2009[152]	FDR and/or SDR with breast or ovarian cancer and/or relative with other cancer	BRCA carriers and noncarriers	The Brief Symptom Inventory (BSI, scale NR) Cancer Related Worry (CRW, scale NR) Daily sleep log Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF, scale 0 to 120) Pittsburgh Sleep Quality Index (PSQI, each subscale 4-point Likert) Wrist activity monitors	January 2006 to November 2007 Mean followup of 8.0 years (SD 1.9)

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Shochat and Dagan, 2010[169] Fair Same population as Dagan and Schochat, 2009[152]	**Carriers (n=17) vs. noncarriers (n=20) vs. controls (n=36)** Reported sleep problems (PSQI >5): 53% vs. 20% vs. 28%; p=0.03 for carriers vs. other groups <u>Mean on sleep measures (SD)</u> PSQI total: 7.29 (4.34) vs. 3.94 (2.49) vs. 4.21 (2.80); p=0.013 for carriers vs. noncarriers Sleep latency (minutes, recorded by wrist monitor): 12.23 (14.36) vs. 5.41 (5.93) vs. 9.44 (8.05); p=NS Sleep duration (minutes, recorded by wrist monitor): 435.96 (47.68) vs. 407.46 (55.56) vs. 434.40 (52.19); p=NS Sleep efficiency (%, recorded by wrist monitor): 94.46 (10.65) vs. 96.80 (2.43) vs. 97.26 (2.85); p=NS Wake after sleep onset (minutes, recorded by wrist monitor): 18.08 (23.90) vs. 12.82 (10.64) vs. 11.51 (10.03); p=NS <u>Correlations between PSQI total score and other measures</u> CRW: 0.417 vs. 0.125 vs. 0.029; p=NS BSI: 0.437 vs. 0.546 vs. 0.057; p=0.013 for noncarriers MFSI-SF: 0.418 vs. 0.315 vs. 0.430; p=0.009 for controls <u>Linear regression model predictors of PSQI total score (poor sleep quality)</u> Menopausal symptoms and lower level of education combined accounted for 12.6% of the variance; p=0.019 Menopausal symptoms, lower level of education, and fatigue combined accounted for 23.0% of the variance; p=0.001 Menopausal symptoms, lower level of education, fatigue, and carrier status combined accounted for 28% of the variance; p<0.001	Carriers reported more sleep problems compared to noncarriers and healthy controls. However, actual sleep duration, latency and wakefulness after sleep onset were not significantly different between groups.	Not reported

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Sub-category	Purpose	Study type	N
2013 Review				
van Dijk et al., 2006[171] Good	Cancer worry	To assess whether the pedigree-based familial risk estimation and the personal cancer history can explain cancer worry and distress among women who receive an uninformative DNA test result.	Prospective cohort	Eligible: NR Enrolled: 133 Analyzed: 132

Author, year Quality	Country	Population and setting	Demographics	Inclusion and exclusion criteria
2013 Review				
van Dijk et al., 2006[171] Good	The Netherlands	Department of Clinical Genetics in Leiden or Rotterdam The Netherlands between 1995 to 2002, in families where a BRCA mutation was already detected	NR for women without breast cancer	Inclusion: Women from a family with a previously detected BRCA mutation, aged ≥18 years, and had not previously received genetic counseling elsewhere Exclusion: Not reported

Author, year Quality	Risk level definition	Population/mutation status	Measures	Duration of followup
2013 Review				
van Dijk et al., 2006[171] Good	BRCA mutation previously detected in family and individuals with a probability of mutation detection of ≥10% Women with an uninformative result were separated into 2 risk groups, 1) <30% personal risk estimate for low-risk and 2) ≥30% personal risk estimate for high-risk	BRCA positive, true negative, and uninformative results	Breast cancer worry question of "During the last 2 weeks, how often did you worry about developing breast cancer?" (Likert scale ranging from 1=almost never to 4=almost all the time) Impact of Events Scale (IES, scale 0 to 75)	1998 to 2002 At 1 and 7 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
van Dijk et al., 2006[171] Good	**Positive (n=22) vs. true negative (n=41) vs. uninformative low risk (n=35) vs. uninformative high-risk (n=34)** Mean on psychological scales (SD) IES at pretest: 21.55 (14.70) vs. 14.85 (11.99) vs. 13.54 (11.97) vs. 22.53 (14.22); p<0.05 for uninformative low risk group vs. positive and true negative groups IES at 1 month following test result: 24.14 (13.21) vs. 10.85 (13.62) vs. 7.40 (8.57) vs. 14.38 (12.41); p<0.05 for positive group vs. other groups IES at 7 months following test result: 24.09 (15.57) vs. 8.32 (13.30) vs. 6.31 (8.44) vs. 14.00 (14.51); p<0.05 for positive group vs. other groups and p<0.05 for uninformative high-risk group vs. uninformative low risk group Breast cancer worry at pretest: 2.41 (0.73) vs. 1.88 (0.87) vs. 1.94 (0.73) vs. 2.21	Women unaffected with breast cancer but with a positive mutation had higher levels of distress and cancer worry. However, at times they were similar in their level of distress and cancer worry as those who received an uninformative test result but were at high-risk.	The Dutch Cancer Society Grant number UL 98-1740

Appendix B Table 8. Evidence Table of Genetic Testing Studies

Author, year Quality	Results	Conclusions	Funding source
	(0.81); p<0.05 positive group vs. true negative and uninformative low risk groups Breast cancer worry at 1 month following test result: 2.64 (1.00) vs. 1.29 (0.75) vs. 1.51 (0.66) vs. 1.68 (0.81); p<0.05 for positive group vs. other groups Breast cancer worry at 7 months following test result: 2.18 (0.96) vs. 1.24 (0.70) vs. 1.37 (0.55) vs. 1.59 (0.66); p<0.05 for positive group vs. other groups		

Abbreviations: BDI=Beck Depression Inventory; BHS=Beck Hopelessness Scale; BRCA=breast cancer susceptibility gene; BRCAPRO=breast cancer susceptibility gene prediction model; BSI=Brief Symptom Inventory; CES-D=Center for Epidemiologic Studies-Depression Scale; COPE=Emotional Approach Coping Scale; CRW=Cancer-Related Worry; CWS-R=Cancer Worry Scale-Revised; DNA=deoxyribonucleic acid; FBOC=familial breast ovarian cancer; FCC=family cancer clinic; FDR=first degree relative; GHQ=General Health Questionnaire; HADS= Hospital Anxiety and Depression Scale; HADS-A=Hospital Anxiety and Depression Scale- Anxiety; HADS-D=Hospital Anxiety and Depression Scale- Depression; HAI=Health Anxiety Inventory; HNPCC=hereditary non-polyposis colorectal cancer; HR-QOL=Health Related-Quality of Life; IES=Impact of Events Scale; INHERITS BRCA=Interdisciplinary Health Research International Team on Breast Cancer susceptibility; MCS=Mental Health Component Scale; MFSI-SF=Multidimensional Fatigue Symptom Inventory-Short Form; MICRA=Multidimensional Impact of Cancer Risk Assessment; NCI=National Cancer Institute; NIH=National Health Institute; NR=not reported; NS=not significant; PCS=Physical Component Summary; PPC=Perceived Personal Control; PSQI=Pittsburgh Sleep Quality Index; PTGI=Post-Traumatic Growth Inventory; QOL=quality of life; RCT=randomized control trial; SD=standard deviation; SDR=second degree relative; SF-36=Swedish SF-36 Health Survey; STAI=State-Trait Anxiety Inventory; SWD=Satisfaction With Decision Instrument; UCLA=University of California, Los Angeles; U.K.=United Kingdom; U.S.=United State

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/setting	Inclusion/exclusion criteria
Breast Cancer				
Current Review				
Vreeman et al., 2018[215] NA	Retrospective cohort	To evaluate the performance of a breast cancer screening program with multiple followup rounds for women with different categories of increased breast cancer risk	The Netherlands Academic hospital Women with increased risk of breast cancer	Inclusion: Women at increased risk of breat cancer undergoing screening breast MR or mammogram Exclusion: NR
2013 Review				
Cortesi et al., 2006[218] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	Prospective cohort (Expected incidence ratio derived from registry data)	To describe the results of an intensive surveillance program and document effectiveness of the program in selecting individuals at risk of breast cancer.	Italy Women with increased risk of breast cancer	Inclusion: Women ages >18 years with *BRCA1* or *BRCA2* mutations discovered through genetic testing or increased risk for breast cancer relative to the general population based on Gail model, Claus tables and modified BRCAPRO model (adapted to the Italian population) and study defined criteria: ≥3 relatives diagnosed with breast cancer or ovarian cancer in 2 different generations; ≥1 of these 3 relatives must be FDR of one of the other 2, in case of male interposition, a relationship of different degree is allowed; ≥1 breast cancer diagnosed at <35 years of age regardless of family history; ≥1 breast cancer and 1 ovarian cancer in the same woman, regardless of family history; ≥1 male breast cancer, regardless of family history; 1 sporadic breast cancer or ovarian cancer Exclusion: Women with symptoms suggestive of breast cancer; women with a personal history of breast cancer

Author, year Quality	Risk level definitions	N	Baseline demographics
Breast Cancer			
Current Review			
Vreeman et al., 2018[215] NA	*BRCA1*, *BRCA2*, family history of breast cancer, personal breast cancer history, other (e.g. history of chest wall radiation or of high-risk lesions like atypical ductal hyperplasia or lobular carcinoma in situ)	2773 women included 8818 breast MRIs 6245 mammograms 471 *BRCA1* 299 *BRCA2*	**Mean age at start of screening (range), years** *BRCA1*: 39 (23 to 75) *BRCA2*: 41 (23 to 73)
2013 Review			
Cortesi et al., 2006[218] NA Modena Study Group for Familial Breast and	Risk level was defined by Gail model, Claus tables, modified BCAPRO model, and study defined criteria (see inclusion) Carrier (Gail model lifetime risk of 50 to 85%): presence of mutant BRCA genes High-risk (Gail model lifetime risk of 30 to 50%): ≥3 relatives with breast cancer	1325 enrolled 48 mutation carriers (37 *BRCA1* and 11 *BRCA2*) 674 high-risk	**Mean age at surveillance (range), years** Carrier: 42 (20 to 75) High-risk: 42 (15 to 75) Intermediate-risk: 43 (19 to 67)

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Risk level definitions	N	Baseline demographics
Ovarian Cancer participants	(or ovarian cancer) in 2 different generations; 1 breast cancer/ovarian cancer case is a FDR of the other 2; ≥1 case has been diagnosed at age <40 years or with bilateral breast cancer; breast cancer diagnosed <35 years, regardless of family history; breast and ovarian cancer in same woman, regardless of family history Intermediate risk (Gail model lifetime risk of 18 to 29%): male breast cancer, regardless of family history Slightly increased risk (Gail model lifetime risk of 6 to 18%): breast/ovarian cancer without any of the described criteria	257 intermediate-risk 346 slightly increased- risk	Slightly increased-risk: 40 (18 to 75)

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
Breast Cancer			
Current Review			
Vreeman et al., 2018[215] NA	A) Mammography: annual from age 30 years in BRCA carriers B) MRI: annual from age 25 years in BRCA carriers	Screen-positive for cancer: BIRADS 0, 3, 4, or 5 (biopsy conducted for BIRADS 4, 5, and some BIRADS 3)	2003 to 2014 Followup not reported (retrospective study)
2013 Review			
Cortesi et al., 2006[218] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	From 1994 to September 2000 all women underwent: A) Mammography B) Ultrasonography C) CBE D) Transvaginal ultrasound and serum CA-125 levels Testing interval varied by assessed risk (see below) From October 2000 mutation carrier surveillance modified to include: E) CE MRI BRCA risk: Started at age 25 with annual mammography and MRI, bi-annual CBE and ultrasound plus transvaginal ultrasound and serum CA-125 levels High-risk: started at age 30 with mammography every 2 years until age 36 and then annually, bi-annual CBE and ultrasound plus annual transvaginal ultrasound and serum CA-125 levels Intermediate risk: Started at age 30 with mammography every 2 years until age 40 and then annually, bi-annual CBE and ultrasound plus annual transvaginal ultrasound and serum CA- 125 levels Slightly increased risk: Started at age 30 with one mammogram before 40 years then every 18 to 24 months, and annual CBE and ultrasound	Not reported	1992 to 2005 Median 55 months (range 1 to 151 months)

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
	Note: if possible, all exams performed on the same day during the second week of the menstrual cycle in premenopausal women; additional investigation using fine needle aspiration or core biopsy performed as required.		

Author, year Quality	Outcome: test characteristics	Cancer incidence
Breast Cancer		
Current Review		
Vreeman et al., 2018[215] NA	**Sensitivity (95% CI), A vs. B vs. A+B** *BRCA1*, all cancers: 45% (32 to 59) vs. 63% (50 to 74) vs. 66% (53 to 77) *BRCA1*, excluding occult: 51% (37 to 65) vs. 77% (64 to 87) vs. 81% (68 to 90) *BRCA2*, all cancers: 36% (21 to 53) vs. 67% (50 to 80) vs. 70% (53 to 83) *BRCA2*, excluding occult: 44% (27 to 63) vs. 88% (70 to 96) vs. 92% (75 to 98) **Specificity (95% CI), A vs. B vs. A+B** *BRCA1*: 98% (98 to 99) vs. 95% (94 to 96) vs. 94% (93 to 95) *BRCA2*: 98% (97 to 98) vs. 94% (93 to 96) vs. 94% (92 to 95) **PPV of recall (95% CI), A vs. B vs. A+B** *BRCA1*: 0.49 (0.35 to 0.63) vs. 0.32 (0.25 to 0.42) vs. 0.30 (0.23 to 0.38) *BRCA2*: 0.32 (0.19 to 0.49) vs. 0.26 (0.18 to 0.36) vs. 0.24 (0.17 to 0.34)	**Breast cancers (invasive + DCIS) in study population (screen-detected, interval with symptoms, and occult found at prophylactic mastectomy)** *BRCA1* (n=471): 39, 9, 11 *BRCA2* (n=299): 23, 2, 8 All patients (n=2463): 129, 16, 25 All patients, invasive cancers only: 104, 16, 7
2013 Review		
Cortesi et al., 2006[218] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	44 breast cancers detected; 64% (n=28) invasive, 36% (n=16) DCIS 36 screen-detected Carriers: n=5 cancers (4 invasive, 1 DCIS) High-risk: n=23 (14 invasive, 9 DCIS) Intermediate-risk: n=11 (8 invasive, 3 DCIS) Slightly increased-risk: n=5 (2 invasive, 3 DCIS) **Sensitivity, A vs. B vs. A+B vs. E** All: 78% (28/36) vs. 50% (18/36) vs. 97% (35/36) vs. 100% (4/4) Carriers: 50% (2/4) vs. 75% (3/4) vs. 75% (3/4) vs. 100% (4/4) High-risk: 90% (19/21) vs. 52% (11/21) vs. 100% (21/21) Intermediate-risk: 50% (4/8) vs. 450% (4/8) vs. 100% (8/8) Slightly increased-risk: 100% (3/3) vs. 0% (0/3) vs. 100% (3/3)	**Breast cancer incidence in study population vs. expected incidence** All: SIR 4.9, 95% CI 1.6 to 7.6, p<0.001 Carriers: SIR 20.3, 95% CI 3.1 to 83.9, p<0.001 High-risk: SIR 4.5, 95% CI 1.5 to 8.3, p<0.001 Intermediate-risk: SIR 7.0, 95% CI 2.0 to 17.1, p=0.0018 Slightly increased-risk: SIR not significantly increased Note: SIR = ratio of observed to expected number of cancers; expected number of cancers based on Modena Cancer Registry rates from 1998 to 2002 in 5 year age groups from age 25 to >85 years old; observed women years at risk were multiplied by expected cancer incidence to estimate total number of cancers expected

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: cancer characteristics Interval cancers	Outcome: disease-free survival Mortality	Conclusions	Funding source
Breast Cancer				
Current Review				
Vreeman et al., 2018[215] NA	Characteristics of 16 interval cancers (all patients): Invasive: 100% (16/16) Mean size: 15.5 mm (range 5 to 26) Nodal status: 31% (5/16) node-positive	Survival not reported	Screening performance depended on risk category. Sensitivity was lowest in *BRCA1* carriers. Specificity improved at followup rounds.	Netherlands Organisation for Health Research and Development and European Union's 7th Framework Programme
2013 Review				
Cortesi et al., 2006[218] NA Modena Study Group for Familial Breast and Ovarian Cancer participants	Staging: 61% (n=17) stage I; 25% (n=7) stage II; 7% (n=2) stage III; 7% (n=2) stage IV Size: 29% (n=8) <10 mm in diameter; 36% (n=10) were 10-15 mm in diameter; 32% (n=9) >15 mm in diameter; one was inflammatory breast cancer Nodal status: 36% (n=10) node positive Interval cancers: n=8; all identified with CBE; interval cancer rate 1.3 per 1000; diagnosed with CBE only (n=4); CBE plus ultrasound (n=3); CBE plus ultrasound plus mammography (n=1); time interval from last negative screen to diagnosis ranged from 1-14 months DCIS: Screening sensitivity for DCIS increased with age; low rate (65%) in women <50 years; high rate (93%) in oldest age group	Posttreatment, 4 recurrences and 3 deaths (2 for disease progression, 1 from heart failure). Actuarial 5 year survival rate was 93%	Rate of cancers detected in women at high-risk for breast cancer was significantly higher than expected in an age-matched general population. Results support increased screening surveillance program to identify and monitor high-risk individuals.	Italian consortium for Hereditary Breast and Ovarian Cancer; COFIN-MURST 2003 to 2005; Fondazione Cassa di Risparmio di Modena; Associazione Angela Serra per la ricerca sul Cancro

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/setting	Inclusion/exclusion criteria
Breast Cancer				
2013 Review				
Leach, 2005[203] NA MARIBS study	Prospective cohort, one-arm	To compare contrast enhanced MRI with mammography for breast cancer screening in women genetically predisposed to breast cancer.	U.K. Women attending one of 22 participating centers in the U.K. with increased breast cancer risk	Inclusion: Asymptomatic women aged 35 to 49 years fulfilling one of the following: known carrier of a deleterious *BRCA1*, *BRCA2*, or *TP53* mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome Aim was to include women whose affected FDRs had ≥60% chance of being a *BRCA1* or *BRCA2* mutation carrier or women with an annual risk of at least 0.9% Exclusion: Women with previous breast cancer, those with any cancer such that prognosis was <5 years, participants who underwent predictive genetic testing during study and whose results were negative, women who developed cancer during study period

Author, year Quality	Risk level definitions	N	Baseline demographics
Breast Cancer			
2013 Review			
Leach, 2005[203] NA MARIBS study	Known carrier of a deleterious *BRCA1, BRCA2,* or *TP53* mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome	649 analyzed -13% (82) with known *BRCA1* mutation -6% (38) with known *BRCA2* mutation	Median age at entry, years: 40 (range: 31 to 55; only one woman aged >50 years)

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
Breast Cancer			
2013 Review			
Leach, 2005[203] NA MARIBS study	All women underwent: A) Annual mammography from age 35 years (or younger if FDR developed cancer at age <35 years) B) Annual CE MRI Note: if possible, exams done on same day, between days 6-16 of menstrual cycle Note: In women with equivocal results, high specificity MRI exam or repeat screening MRI done 2-6 weeks later followed by ultrasound, fine needle aspiration, localization	Scoring system based on morphological and dynamic contrast uptake characteristics validated against histology (area under receiver operating characteristic curve =0.88, 95% CI 0.83 to 0.94) and diagnostic accuracy tested using subset of present study and 100 symptomatic cases (sensitivity=91%, 95% CI 83 to 96; specificity=81%,	Study recruitment 1997 to 2003 Variable screening episodes per individual but screening continued until each women had at least 2 annual scans (in 2004)

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
	and tissue sampling by conventional methods as appropriate Note: 93% of mammographic examinations were 2-view, 7% 1- view	95% CI 79 to 83) Note: All scoring was double reported; in statistical analysis, scoring system was paired to BIRADS as follows: for MRI; score of B, suspicious = BIRADS 0,3, or 4 and score of A, malignant = BIRADS 5; for mammography; score M3, indeterminate = BIRADS 0 to 3, M4, suspicious = BIRADS 4, and M5, malignant = 5	

Author, year Quality	Outcome: test characteristics	Cancer incidence
Breast Cancer		
2013 Review		
Leach, 2005[203] NA MARIBS study	**All cancers (n=35)** Sensitivity (95% CI), A vs. B: 40% (24 to 58) vs. 77% (60 to 90), p=0.01 Sensitivity (95% CI), A + B: 94% (81 to 99) Specificity (95% CI), A vs. B: 93% (92 to 95) vs. 81% (80 to 83), p<0.0001 Specificity (95% CI), A plus B: 77% (75 to 79) PPV (95% CI), A vs. B: 10% (5.8 to 17) vs. 7.3% (4.9 to 10) NPV (95% CI), A vs. B: 99% (98 to 99) vs. 99% (99 to 100) AUC (95% CI), A vs. B: 0.70 (0.68 to 0.72) vs. 0.85 (0.84 to 0.87), p=0.035 **Excluding DCIS (n=6)** Sensitivity (95% CI), A vs. B: 31% (15 to 51) vs. 86% (68 to 96), p=0.0009 Sensitivity (95% CI), A plus B: 97% (82 to 100) ***BRCA1* carriers or relative with *BRCA1* mutation (n=139)** Sensitivity (95% CI), A vs. B: 23% (5 to 54) vs. 92% (64 to100), p=0.004 Sensitivity (95% CI), A plus B: 92% (64 to 100) Excluding 1 DCIS case: 25% (5.5 to 57) vs. 100% (74 to 100) Specificity (95% CI), A vs. B: 92% (88 to 94) vs. 79% (75 to 83), p<0.0001 Specificity (95% CI), A plus B: 74% (69 to 78) PPV (95% CI), A vs. B: 9.1% (1.9 to 24) vs. 14% (7.2 to 23) ***BRCA2* carriers or relative with *BRCA2* mutation (n=86)** Sensitivity (95% CI), A vs. B: 50% (21 to 79) vs. 58% (28 to 84), p=1.0 Sensitivity (95% CI), A plus B: 92% (62 to 100) Sensitivity (95% CI), excluding 3 DCIS cases: 33% (7.5 to 70) vs. 67% (30 to 93), p=0.45 Specificity (95% CI), A vs. B: 94% (91 to 97) vs. 82% (77 to 87), p=0.0001 Specificity (95% CI), A plus B: 78% (72 to 83)	15 incident cancers, observed incidence rate was 1.9% per year

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: test characteristics	Cancer incidence
	PPV (95% CI), A vs. B: 9.1% (1.9 to 24) vs. 14% (7.2 to 23) Note: Anonymous testing was restricted to women with breast cancer so that women with BRCA positive relatives but no breast cancers themselves, were not tested; Sensitivities refer only to tested mutation carriers, specificities are only preliminary estimates **Incident screens (n=15 cancers, n=1217 non-cancers)** **Observed incidence rate: 1.9% per year** **Sensitivity (95% CI), A vs. B** Any cancer: 40% (16 to 68) vs. 80% (52 to 96), p=0.11 Excluding 6 DCIS cases: 31% (15 to 51) vs. 86% (68 to 96), p=0.0009 A plus B: 97% (82 to 100) Any cancer, excluding *BRCA1* carriers/relatives: 50% (28 to 72) vs. 68% (45 to 86), p=0.45 Any cancer, excluding *BRCA2* carriers/relatives: 35% (16 to 57) vs. 87% (66 to 97); A plus B: 96% (78 to 100) **Specificity (95% CI), A vs. B** All cancers: 94% (92 to 95) vs. 81% (79 to 83), p<0.0001	

Author, year Quality	Outcome: cancer characteristics Interval cancers	Outcome: disease-free survival Mortality	Conclusions	Funding source
Breast Cancer				
2013 Review				
Leach, 2005[203] NA MARIBS study	Grade: 10% (3/29) grade1; 24% (7/29) grade 2; 66% (19/29) grade 3 Size: 38% (11/29) were <10 mm in greatest dimension; 14% (4/29) were 10 to 14 mm in greatest dimension; 17% (5/29) were 15 to 19 mm; 31% (9/29) were ≥20 mm in greatest dimension; average tumor size = 15 mm Nodal status: 81% (21/26) cancers node-negative Interval cancers: n=2 (one considered benign on MRI and one considered benign on mammography; method of detection NR)	Not reported	Contrast enhanced MRI is more sensitive than mammography for breast cancer detection in women with familial risk for breast cancer. Specificity was acceptable for both. Detected tumors were small, and mostly node negative, suggesting that annual screening with mammography and contrast enhanced MRI would detect most tumors in this risk group.	Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/setting	Inclusion/exclusion criteria
Breast Cancer				
2013 Review				
Le-Petross et al., 2011[204] NA	Retrospective analysis of prospective cohort, one-arm	To investigate the efficacy of alternating screening mammography and breast MRI every 6 months in women with a genetically high risk of developing breast cancer for breast cancer detection	United States Women at increased genetic risk of breast cancer at single-institution	Inclusion: Women aged ≥18 years, having undergone alternating screening mammography and breast MRI every 6 months at study institution, either confirmed *BRCA1/2* carriers or FDR of confirmed *BRCA1/2* carrier Exclusion: Women with history of breast cancer, who had calculated lifetime risk of breast cancer >20%, or who did not undergo a screening MRI, women who used chemoprevention or underwent bilateral prophylactic mastectomy, those with metastatic disease, undergoing treatment, or high BMI preventing MRI, women lost to followup, or died during original trial

Author, year Quality	Risk level definitions	N	Baseline demographics
Breast Cancer			
2013 Review			
Le-Petross et al., 2011[204] NA	Based on BRCA status	321 screened 73 analyzed (51% (37) *BRCA1;* 49% (36) *BRCA2*)	Median age at entry, years: 44 (range 23 to 75) Mean age at diagnosis, years: 51 (range 43 to 64)

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
Breast Cancer			
2013 Review			
Le-Petross et al., 2011[204] NA	All women underwent CBE every 6 months plus: A) Mammography every 6 months alternating with, B) MRI every 6 months Note: Ultrasound used to evaluate abnormal screen findings, biopsy as required	BIRADS	Records from 1997 to 2009 Median followup 2 years (range 1 to 6 years) Median number of screening cycles was 2 (range 1 to 6 cycles); 29% completed 1 cycle, 31% completed 2 cycles, 25% completed 3 cycles, 15% completed 4, 5 or 6 cycles

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: test characteristics	Cancer incidence
Breast Cancer		
2013 Review		
Le-Petross et al., 2011[204] NA	**Sensitivity, (95% CI), A vs. B** Not able to report vs. 92% (0.76 to 1.00) **Specificity, (95% CI), A vs. B** 82% (0.72 to 0.92) vs. 87% (0.79 to 0.95) 12/13 cancers identified on MRI (1/13 on prophylactic mastectomy), but not mammography 6 months prior; no cancer detected by mammography alone; no cancer palpable by CBE 5/13 cancers detected on targeted US post MRI detection	13 cancers detected (10 invasive, 3 DCIS) in 11 patients 5/13 cancers detected on first screening cycle (likely prevalent), 8/13 incident cancers **No. of cancers detected by cycle in 11 patients** Post cycle 1: 5 cancers Post cycle 2: 2 cancers Post cycle 3: 3 cancers Post cycle 4: 1 cancer

Author, year Quality	Outcome: cancer characteristics Interval cancers	Outcome: disease-free survival Mortality	Conclusions	Funding source
Breast Cancer				
2013 Review				
Le-Petross et al., 2011[204] NA	Size on MRI: Mean 14 mm (range 1 to 30 mm) Nodal status: 9% (1/11) women node-positive Interval cancers: n=0	Not reported	Screening women at increased genetic risk of breast cancer by alternating mammography with MRI every 6 months has a higher cancer yield than studies that screened using both modalities at the same time point.	Not reported

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/setting	Inclusion/exclusion criteria
Breast Cancer				
2013 Review				
Rijnsburger et al.,2010[219] See also Kriege et al., 2004[201] NA Dutch MRISC study	Prospective cohort (Registry data/data from another prospective study used for cancer characteristics comparison)	To evaluate the long term results of the Dutch MRI screening (MRISC) study, including separate analyses of *BRCA1/2* mutation carriers and survival results	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion: Women aged 25 to 75 years with cumulative lifetime risk of breast cancer ≥15% due to genetic or familial predisposition (women could be tested at age younger than 25 if family member diagnosed before age of 30 years) Exclusion: Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation

Author, year Quality	Risk level definitions	N	Baseline demographics
Breast Cancer			
2013 Review			
Rijnsburger et al.,2010[219] See also Kriege et al., 2004[201] NA Dutch MRISC study	Based on cumulative lifetime risk determined using modified Claus tables: *BRCA1/2* carriers, or other mutations: 50 to 85% risk High-risk: 30 to 50% risk Moderate-risk (no documented gene mutation): 1 to -30% risk	Enrolled: 2275 Analyzed: 2157 (422 *BRCA1* , 172 *BRCA2* , 5 other mutation, 1069 high-risk, 489 moderate-risk)	Mean age at entry, years: Cohort: 40.1 (range 19 to 75) *BRCA1* : 38.7 *BRCA2* : 40.0 High-risk: 40.8 Moderate-risk: 40.0

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
Breast Cancer			
2013 Review			
Rijnsburger et al.,2010[219] See also Kriege et al., 2004[201] NA Dutch MRISC study	All women underwent: A) Biannual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: Both imaging investigations performed on same day or time period when possible, between day 5 and day 15 of menstrual cycle Note: When one of the examinations reported "probably benign finding" or "need additional imaging evaluation" (BIRADS 3 or 0), further investigation undertaken by ultrasonography Malignancy diagnosis based on histological findings	BIRADS	1999 to 2006 Median 4.9 years, mean 4.0 years (range 0.1 to 6.3 years), followup post diagnosis for mortality Relapse: Median 5.0 years (range 1.7 to 8.4 years)

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: test characteristics	Cancer incidence
Breast Cancer		
2013 Review		
Rijnsburger et al.,2010[219] See also Kriege et al., 2004[201] NA Dutch MRISC study	**Number of screen detected breast cancers; total, invasive, DCIS** *BRCA1*: 21/35, 19/31, 2/4 *BRCA2*: 15/18, 12/13, 3/5 Other mutation: 1/5, 0/0, 1/1 High-risk: 26/27, 22/23, 4/4 Moderate-risk: 15/16, 11/11, 4/5 Total: 78/97, 64/78, 14/19 ***Screening method comparisons based on 75 breast cancers with data that included results for both imaging methods*** **Sensitivity (95% CI), A vs. B vs. C** Any breast cancer: 21% (12 to 32) vs. 41% (30 to 53) vs. 71% (59 to 81), p=0.0016 for B vs. C Invasive: 22% (11.8 to 32) vs. 36% (24 to 49) vs. 77% (65 to 87), p<.00005 for B vs. C DCIS: 15% (1.9 to 45) vs. 69% (39 to 91) vs. 39% (14 to 68), p=0.388 for B vs. C Mutation (any breast cancer) *BRCA1*: 13% (2.8 to 34) vs. 25% (9.8 to 47) vs. 67% (45 to 84), p=0.0129 for B vs. C *BRCA2*: 7.7% (0.2 to 36) vs. 62% (33 to 86) vs. 69% (39 to 91), p=1.0 for B vs. C Risk group (any breast cancer) High: 32% (13 to 56) vs. 46% (24 to 68) vs. 77% (55 to 92) Moderate: 33% (9.9 to 65) vs. 47% (21 to 73) vs. 67% (38 to 88) *BRCA1* vs. *BRCA2* sensitivity of methods compared Mammography, p=.04; all other comparisons between groups and screening methods were nonsignificant. Specificity of methods did not differ between groups. **Specificity (95% CI), A vs. B vs. C** Any breast cancer: 98% (97.5 to 98.2) vs. 95% (94.0 to 95.1) vs. 90% (88.9 to 90.4) Mutation (any breast cancer) *BRCA1*: 97% (95.7 to 97.9) vs. 95% (93.0 to 95.9) vs. 91% (89.1 to 92.6) *BRCA2*: 98% (96.4 to 99.4) vs. 94% (90.9 to 96.0) vs. 92% (88.7 to 94.5) Risk group (any breast cancer) High: 98% (97.7 to 98.7) vs. 95% (93.8 to 95.3) vs. 89% (87.9 to 90.1) Moderate: 98% (96.9 to 98.6) vs. 95% (93.5 to 95.9) vs. 90% (87.8 to 91.0) **PPV (95% CI), A vs. B vs. C** Any breast cancer: 10% (5.7 to 17) vs. 8.5% (5.8 to 12) vs. 7.7% (5.8 to 9.9) Mutation (any breast cancer) *BRCA1*: 8.8% (1.8 to 24) vs. 9.5% (3.6 to 20) vs. 14% (8.5 to 22) *BRCA2*: 14% (0.4 to 58) vs. 26% (12 to 45) vs. 23% (11 to 39) Risk group (any breast cancer) High: 9.8% (3.7 to 20) vs. 5.3% (2.6 to 9.5) vs. 4.5% (2.6 to 7.1) Moderate: 12% (3.4 to 28) vs. 8.5% (3.5 to 17) vs. 6.2% (3.0 to 11)	**Incidence of cancer per population group; total, invasive, DCIS** *BRCA1*: 35, 31, 4 *BRCA2*: 18, 13, 5 Other mutation: 5, 0, 1 High-risk: 27, 23, 4 Moderate-risk: 16, 11, 5 Total: 97, 78, 19

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: cancer characteristics Interval cancers	Outcome: disease-free survival Mortality	Conclusions	Funding source
Breast Cancer				
2013 Review				
Rijnsburger et al.,2010[219] See also Kriege et al., 2004[201] NA Dutch MRISC study	**Characteristics of detected breast cancers, includes 78 screen detected cancers and 11 interval cancers** Tumor size, cm: 40% (30/76) <1, 39% (29/76) 1 to 2, 20% (15/76) >2, p1=0.003, p2=0.0045 Nodal status negative: 69% (50/72), p1=0.42, p2=1 Histology: 29% (21/72) grade 1, 32% (23/72) grade 2, 39% (28/72) grade 3, p1<0.001, p2=0.15 p1=overall comparison between subgroups p2=comparison between *BRCA1* and *BRCA2* Note: Age at diagnosis, number of interval cancers, estrogen and progesterone receptor status significantly different between subgroups **Number of interval cancers; total, invasive, DCIS** *BRCA1*: 10/35, 10/31, 0/4 *BRCA2*: 1/18, 1/18, 0/5 Other mutation: 0/0, 0/0, 0/0 High-risk: 1/27, 1/23, 0/4 Moderate-risk: 1/16, 0/11, 1/5 Total: 13/97, 12/78, 1/19 Note: denominator includes 6 breast cancers detected at prophylactic mastectomy Kriege, 2004: Breast cancer characteristics, study group vs. control1 vs. control2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, 45 in control group 2) No. of DCIS: 6 vs. 120 vs. 0 Invasive tumor size <1 cm: 19/44 vs. 193/1380 vs. 5/45, p<0.001 vs. control 1, p<0.04 vs. control 2 Nodal status negative: 28/44 vs. 657/1380 vs. 17/45, p<0.001 vs. control 1, p=0.001 vs. control 2 Histological grade 1: 19/44 vs. 99/1380 vs. 4/45, p<0.001 vs. control 1, p=0.01 vs. control 2 Note: Control 1 = National Cancer Registry data of women with breast cancer diagnosed in 1998, Control 2 = participants diagnosed with breast cancer between 1996-2002, participating in a prospective study of gene mutation	**Disease-free and overall survival in 89 patients** 11/93 patients with breast cancer had relapse, 7/11 were mutation carriers 5 patients had distant metastasis, all were mutation carriers 4 patients died, 9.7% (3/31) *BRCA1* and 6.3% (1/16) *BRCA2* Cumulative metastasis-free and overall survival at 6 years in 43 mutation carriers with invasive cancer were 84% and 93%, other groups had 100% cumulative survival	Sensitivity of MRI superior to mammography for detection of breast cancer in women at increased risk. *BRCA1*- associated cancers have younger age at diagnosis, lower mammographic sensitivity, high number of interval cancers, low number of DCIS, and unfavorable tumor size at diagnosis.	Dutch government; Cancer Genomics Center

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Design	Purpose	Population/setting	Inclusion/exclusion criteria
Ovarian Cancer				
Current Review				
Evans, 2008[32] NA	Prospective cohort, 1-arm (for staging and survival, prevalent and post-prevalent cases compared)	To assess the effectiveness of annual ovarian cancer screening with TVUS and CA-125 in reducing mortality from ovarian cancer in women at increased genetic risk	Five cancer genetics centers in the U.K., the Netherlands, and Norway Women at increased risk of ovarian cancer	Inclusion: All women with ≥10% lifetime risk of ovarian cancer based on family history were offered genetic testing and screening Exclusion: NR
Rosenthal et al., 2013[217] UK FOCSS Phase I NA	Prospective cohort, 1-arm (for staging and survival compared women diagnosed within a year of screening to those diagnosed later)	To establish the performance characteristics of annual TVUS and CA-125 screening for women at high risk of ovarian or fallopian tube cancer	U.K. High-risk women recruited at 37 regional centers	Inclusion: Women with estimated minimum 10% lifetime ovarian cancer risk based on family history of ovarian and breast cancer or mutation in predisposing genes including BRCA Exclusion: History of BSO, age <35 years, or participating in another ovarian cancer screening trial
Rosenthal et al., 2017[218] UK FOCSS Phase II NA	Prospective cohort, 1-arm (for staging compared women diagnosed within a year of screening to those diagnosed later)	To establish the performance of screening with CA-125 and TVUS for women at high risk of ovarian or fallopian tube cancer.	U.K. Recruited at 42 National Health Service centers	Inclusion: Women ≥35 years old at high risk for ovarian cancer, based on personal or family history of cancer or genetic predisposition to cancer Exclusion: History of bilateral oophorectomy, or negative result for a pathologic mutation found in affected family member
2013 Review				
Hermsen et al., 2007[198] NA	Prospective cohort, 1-arm (staging vs. 2 external comparison groups; unscreened family members with cancer and combined data from multiple studies)	To assess efficacy of annual gynecological screening, accounting for compliance to protocol.	The Netherlands Women with BRCA mutation screened at 6 University Family Cancer Clinics	Inclusion: Women with *BRCA1/2* mutation screened at one of participating centers Exclusion: Women with symptoms at first visit, who had only one visit, or who were found to have cancer at first screening visit

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Risk level definitions	N	Baseline demographics
Ovarian Cancer			
Current Review			
Evans, 2008[32] NA	All estimated ≥10% lifetime ovarian cancer risk, based on family history	981 *BRCA1/2* 3532 overall	Not reported Screening offered starting at 30 or 35 years of age
Rosenthal et al., 2013[217] UK FOCSS Phase I NA	All estimated ≥10% lifetime ovarian cancer risk, based on BRCA and other predisposing mutations in patient or family, or history of ovarian, breast, and colorectal cancer in family	282 *BRCA1* 250 *BRCA2* 3563 overall	Median age, years (all participants): 44.6 (range 35 to 81)
Rosenthal et al., 2017[218] UK FOCSS Phase II NA	Some results reported separately for BRCA carriers; other indicators of risk include mutations in other cancer-related genes, family history of ovarian, breast, and other cancers, and Ashkenazi Jewish ethnicity	804 *BRCA1/2* 4348 overall	Median age, years (all participants): 45.5 (range 34.2 to 84.8)
2013 Review			
Hermsen et al., 2007[198] NA	Based on BRCA status	883 (683 *BRCA1,* 200 *BRCA2*) 459 for analysis of screening/compliance (data available for all screening visits)	**Median age, years** *BRCA1:* 40 (range 21 to 76) *BRCA2:* 44 (range 25 to 77)

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Screening method and interval	Scoring criteria	Duration/followup
Ovarian Cancer			
Current Review			
Evans, 2008[32] NA	A) Annual CA-125 B) Annual TVUS	Not reported	Enrolled 1991 to 2007 Followup not reported Screened for up to 16 years
Rosenthal et al., 2013[217] UK FOCSS Phase I	UK Familial Ovarian Cancer Screening Study (UK FOCSS), Phase I: A) Annual CA-125 B) Annual TVUS	CA-125: premenopausal 35 IU/mL, postmenopausal 30 IU/mL	Recruited 2002 to 2008 11,366 women-years for 3563 women, mean followup 3.2
Rosenthal et al., 2017[218] UK FOCSS Phase II NA	UK Familial Ovarian Cancer Screening Study (UK FOCSS), Phase II: A) CA-125 every 4 months, interpreted using risk of ovarian cancer algorithm (ROCA) B) TVUS annually, or within 2 months of an abnormal ROCA result	CA-125: Normal, Intermediate, or Elevated; no fixed threshold; initial ROC based on initial CA-125 level and age-specific ovarian cancer incidence; later ROC based on both CA-125 level and rate of change; menopausal status incorporated as well TVUS: Normal, Unsatisfactory, or Abnormal	2007 to 2012 13,728 women-years for 4,348 women; median followup 4.8 years
2013 Review			
Hermsen et al., 2007[198] NA	All women underwent: A) Annual serum CA-125 measurement B) Annual TVUS Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted	CA-125: >35kU1-1 abnormal if resulted in extra screen visit or diagnostic operation TVUS: Abnormal or normal	1993 to 2005 1473 person-years

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: test characteristics	Cancer incidence
Ovarian Cancer		
Current Review		
Evans, 2008[32] NA	Not reported	49 ovarian cancers diagnosed among 981 BRCA carriers (21 prevalent, 28 post-prevalent, 9 interval) 64 ovarian cancers diagnosed overall
Rosenthal et al., 2013[217] UK FOCSS Phase I NA	Based on 538 BRCA carriers, incident cancers only **Test characterstics (95% CI), A+B** Sensitivity: 76.9 (46.2 to 95.0) Specificity: 99.2 (97.9 to 99.8) PPV: 71.4 (41.9 to 91.6) NPV: 99.4 (98.2 to 99.9) Note: estimates reported here include occult cancers as false negatives	20 cancers diagnosed among 538 BRCA carriers (6 prevalent, 10 incident screen-detected, 2 screen-negative, 2 occult). Note: These include only cancers detected within 365 days of last screening test and included in test performance analysis.
Rosenthal et al., 2017[218] UK FOCSS Phase II NA	Based on 804 BRCA carriers **Test characterstics (95% CI), A+B** Sensitivity: 64.3 (35.1 to 87.2) Specificity (occults NA): 99.3 (98.9 to 99.6) PPV: 36.0 (18.0 to 57.5) NPV: 99.8 (99.5 to 99.9) Note: estimates reported here include occult cancers as false negatives	14 cancers diagnosed among 804 BRCA carriers (1 prevalent, 8 incident, 5 occult)
2013 Review		
Hermsen et al., 2007[198] NA	15 cancers diagnosed in cohort Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) **Sensitivity (95% CI), A vs. B vs. A+B** All cancers: 42% (14 to 70) vs. 25% (1 to 50) vs. 42% (14 to 70) Excluding occult cancers: 71% (38 to 100) vs. 43% (6 to 80) vs.71% (38 to 100) **Specificity (95% CI) A vs. B vs. A+B** All cancers: 99% for all (CI range 98 to 100) Excluding occult cancers: 99% for all (CI range 98 to 100) **PPV (95% CI), A vs. B vs. A+B** All cancers: 33% (9 to 57) vs. 20% (0 to 40) vs. 23% (5 to 40) Excluding occult cancers: 33% (9 to 57) vs. 20% (0 to 40) vs. 23% (5 to 40) **NPV (95% CI), A vs. B vs. A+B** All cancers: 99% (99 to 100) for all Excluding occult cancers: 100% for all (CI range 99 to 100)	10 cancers diagnosed during followup 5 screen detected 6.5 cases expected Based on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) **SIR (95% CI)** Overall: 1.5 (0.7 to 2.8) *BRCA1*: 1.7 (0.8 to 3.1) *BRCA2*: unable to estimate, no event observed Optimally screened women-years (interval between screen visits <13 months): 1.6 (0.5 to 3.6) Note: Expected number of cases based on data from population-based studies of breast cancer cases, families of *BRCA1/2* carriers; SIR =expected/observed cases based on reference curves derived from refitting BOADICEA model of genetic susceptibility to breast cancer and including data from population-based studies of breast cancer families and cases

Appendix B Table 9. Evidence Table of Studies of Intensive Screening Interventions

Author, year Quality	Outcome: cancer characteristics Interval cancers	Outcome: disease-free survival Mortality	Conclusions	Funding source
Ovarian Cancer				
Current Review				
Evans, 2008[32] NA	**Stage 3 or 4**: *BRCA1*: 71% (30/42) *BRCA2*: 71% (5/7) *BRCA1/2* prevalent: 81% (17/21) *BRCA1/2* post-prevalent: 61% (17/28) **Interval**: n=9 among BRCA carriers	Among 49 BRCA carriers diagnosed with ovarian cancer: 5-year survival: 59% (95% CI 51% to 66%) 10-year survival: 36% (95% CI 27% to 45%) Deaths among prevalent cases: 57% (12/21)1 Deaths among post-prevalent cases: 39% (11/28)	Annual surveillance by TVUS and CA-125 in women at increased familial risk of ovarian cancer is ineffective in detecting tumors at an early enough stage to affect survival in BRCA carriers	National Institute for Health Research, Central Manchester Foundation Trust
Rosenthal et al., 2013[217] UK FOCSS Phase I NA	Among all participants excluding those with Lynch Syndrome: **Stage**: 26% (6/23) of cancers in women screened in the year before diagnosis were stage IIIc to IV, vs. 86% (6/7) of those in women not screened in year before diagnosis Among BRCA carriers: **Interval cancers**: n=2 screen-negative cancers within one year of screening.	Survival (all participants): 71.9 months (95% CI 60.7 to 83.2) in women screened in year before diagnosis 48.4 months (95% CI 39.4 to 57.4) in women not screened in year before diagnosis, p=0.233 Based on 11 deaths from ovarian, fallopian tube, or peritoneal cancer	Screening more frequently than annually in a high-risk population with prompt surgical intervention offers a better chance of early-stage detection of ovarian cancer	Cancer Research UK, the UK Department of Health, the Eve Appeal, the National Cancer Institute, the UK National Institute for Health Research, and University College London
Rosenthal et al., 2017[218] UK FOCSS Phase II NA	Based on 4,348 participants **Stage**: 37% (7/19) stage IIIb to IV of cancers diagnosed within a year of last UK FOCSS Phase II screening, vs. 94% (17/18) of those diagnosed later **Interval cancers**: n=0 clinically presenting interval cancers	Survival analysis not performed 3 deaths among 37 women with invasive cancer at end of study (including those diagnosed within one year of screening and later)	ROCA-based screening is an option for women at high risk of ovarian cancer who defer or decline RRSO, given its high sensitivity and significant stage shift. Effects on survival are unknown.	Cancer Research UK, The Eve Appeal, and the UK National Institute for Health Research
2013 Review				
Hermsen et al., 2007[198] NA	**Stage:** 80% (8/10) stage III/IV (4/5 incident, 4/5 interval cancers) vs. 77% (20/26) in unscreened family members with cancer **Interval cancers**: n=5	After mean followup 28 months from diagnosis 3/15 cases died of ovarian cancer	Annual screening with TVUS and serum CA-125 is an ineffective method for detecting ovarian cancer in women at increased risk due to family history	Biocare Foundation

*Incident plus interval cancer

Abbreviations: BIRADS=Breast Imaging Reporting and Data System; BMI=Body mass index; BOADICEA=Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; BRCA=breast cancer susceptibility gene; BRCAPRO= breast cancer susceptibility gene prediction model; CA-125=cancer antigen-125; CBE=clinical breast exam; CE=contrast enhanced; CI=confidence interval; cm=centimeter; DCIS=ductal carcinoma in situ; FDR=first degree relative; MARIBS=Magnetic Resonance Imaging for Breast Screening; mm=Millimeter; MRI=magnetic resonance imaging; MRISC=Magnetic resonance imaging screening study; NA=not applicable; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; ROCA=Risk of Ovarian Cancer Algorithm; SIR=standard incidence ratio; TP53=tumor protein 53; TVUS=transvaginal ultrasound; U.K.=United Kingdom; UK FOCSS=United Kingdom Familial Ovarian Cancer Screening Study; U.S.=United States

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Mastectomy					
Current Review					
Flippo-Morton et al., 2016[174] Fair	Retrospective cohort	To analyze the uptake and outcomes of surgery and surveillance in *BRCA1/2* patients.	Eligible patients without cancer diagnosis: 100 Analyzed: 87	1996 to 2011 All patients testing positive for a BRCA mutation at a single center in the U.S. (North Carolina).	Age at BRCA testing among 87 women analyzed: 59% >35 years, 41% ≤ 35 years
Heemskerk-Gerritsen et al., 2013[177] Fair	Prospective cohort	To prospectively assess the effect of BRRM when compared with surveillance on breast cancer risk and mortality in healthy *BRCA1/2* mutation carriers.	Eligible patients: 570 *BRCA1* : 405 *BRCA2* : 165	1994 to 2011 All patients testing positive for a BRCA mutation and with no cancer history at a single center in the Netherlands.	Age at BRCA testing, years: BRRM: 33 (range 18 to 64) Surveillance: 36 (range 18 to 75)

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Mastectomy			
Current Review			
Flippo-Morton et al., 2016[174] Fair	Inclusion: All patients testing positive for a BRCA mutation. Study included patients with breast cancer or a combination of breast and ovarian cancers (n=118, not reported here), as well as women without a diagnosis of cancer at the time of testing (n=87). Exclusion: Male patients, patients with a malignancy other than breast, and patients without complete followup data.	BRCA status	Median followup 30.4 months among 87 patients analyzed RRM: median followup 36 months (range 12 to 132 months), no invasive breast cancers developed Surveillance: median time to cancer development 30 months (range 3 to 76 months)
Heemskerk-Gerritsen et al., 2013[177] Fair	Inclusion: *BRCA1* or *BRCA2* carrier, no history of cancer at the time of DNA testing, both breasts and both ovaries in situ at the time of DNA testing, and followup at one site in the Netherlands. Exclusion: Women with symptomatic breast cancer at baseline.	BRCA status	Median followup, years: BRRM: 8.5 (range 0.6 to 17.8), 6.3 after surgery (range 0.1 to 17.4), 1379 PYO Surveillance: 4.1 (range 0.1 to 16.1), 2037 PYO

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
Current Review			
Flippo-Morton et al., 2016[174] Fair	**RRM ± RRSO (n=38) vs. RRSO alone (n=13) vs. surveillance (n=36)** Number of invasive breast cancers: 0 vs. NR vs. 14% (5/36) Note: 13% (5/38) of women undergoing RRM had breast neoplasia identified on pathology (DCIS or atypical hyperplasia).	Bilateral prophylactic mastectomy is an effective means of breast cancer prevention.	Carolinas Medical Center/Levine Cancer Institute; no outside funding
Heemskerk-Gerritsen et al., 2013[177] Fair	**BRRM (n=212) vs. surveillance (n=358)** Number of incident breast cancers: 0 vs. 57 (20% in *BRCA1,* 7% in *BRCA2*) Incidence rate per 1000 PYO: 0 vs. 28	In healthy *BRCA1/2* mutation carriers, BRRM when compared with	The Dutch Cancer Society and the Dutch Pink Ribbon Foundation.

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
	10-year breast cancer-free survival: 100% vs. 74% (p<0.001) All-cause mortality, BRRM vs. surveillance: HR 0.20 (95% CI 0.02 to 1.68) Breast cancer mortality: HR 0.29 (95% CI 0.03 to 2.61) Note: one patient in BRRM group described as presenting with metastases in 2001 and dying of breast cancer in 2006; not clear why she was not included in analyses.	surveillance reduces breast cancer risk substantially, while longer followup is warranted to confirm survival benefits.	

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Mastectomy					
2013 Review					
Domchek et al., 2010[98] Fair	Prospective cohort	To assess the relationship of RRM or RRSO with cancer outcomes.	Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 *BRCA1* , 523 *BRCA2*)	1974 to 2008 U.K., Europe and North America Women from 22 centers in the PROSE consortium.	Not reported
Evans et al., 2009[173] all sites Fair	Prospective cohort, one-arm	To assess effectiveness of risk-reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of *BRCA1/2* mutation.	All RRM enrolled: 550 Bilateral (unaffected): 57% (314/550) *BRCA1/2*: 37% (202/550)	1987 to 1992 Europe Multidisciplinary family history clinics established at 10 centers.	Age range of women undergoing mastectomy, years: 21 to 72 Mean age: NR

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Mastectomy			
2013 Review			
Domchek et al., 2010[98] Fair	Inclusion: Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. Exclusion: Women with cancer diagnosis within first 6 months of followup, women who had undergone RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points.	BRCA status	Patients followed until end of 2009. Median followup 3.65 years for those who had surgery and 4.29 years for those who did not. **Mastectomy & breast cancer outcomes** *BRCA1* followed mean 2.7 years to censoring *BRCA2* followed mean 2.5 years to censoring
Evans et al., 2009[173] all sites Fair	Inclusion: Eligible for bilateral RRM if lifetime breast cancer risk in excess of 25% or eligible for unilateral RRM if already had a diagnosis of in situ or invasive breast cancer in the contralateral breast. Paris center offered surgery to *BRCA1/2* carriers only. Exclusion: Not reported	Lifetime risk of breast cancer >25% based on family history with or without mutation or diagnosis of breast cancer in contralateral breast.	Followup among all women with RRM, years: Median 7.5; Mean 6.1; 3,334 women years Followup among women undergoing bilateral RRM: 2,155 women years

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
2013 Review			
Domchek et al., 2010[98]	Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery	Among a cohort of women with BRCA	Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
Fair	Risk-reducing mastectomy and risk of first occurrence of breast cancer Total: 0% (0/75) vs. 5.8% (34/585) *BRCA1*: 0% (0/43) vs. 5.1% (19/372) *BRCA2*: 0% (0/32) vs. 7.0% (15/213)	mutations, RRM was associated with a lower risk of breast cancer.	Research Fund; SPORE grant from the Dana-Farber/Harvard Cancer Center; the U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade received funding as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles received funding from the National Institute for Health Research
Evans et al., 2009[173] all sites Fair	Bilateral RRM: N=307 among women with followup (314 total) Expected cancers: 21.30 Cancers diagnosed: 0	Risk-reducing surgery is highly effective.	NR

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Mastectomy					
2013 Review					
Evans et al., 2009[173] Manchester site Fair	Prospective cohort	To assess effectiveness of risk-reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of *BRCA1/2* mutation.	All RRM enrolled: 245 Bilateral (unaffected): 73% (179/245) *BRCA1/2:* 36% (87/245)	1987 to 1992 United Kingdom Multidisciplinary family history clinic in Manchester.	Mean age of women undergoing mastectomy, years: 41 (range: 21 to 60)
Hartmann et al., 1999[175] Fair	Retrospective cohort	To define the effect of RRM on incidence of breast cancer and risk of death from breast cancer.	Eligible: 639 Analyzed: 639	1960 to 1993 U.S. Mayo Clinic medical records of women who underwent RRM.	Mean age at surgery 42 (range: 18 to 79)

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Mastectomy			
2013 Review			
Evans et al., 2009[173] Manchester site Fair	Inclusion: Eligible for bilateral RRM if lifetime breast cancer risk in excess of 25% or eligible for unilateral RRM if already had a diagnosis of in situ or invasive breast cancer in the contralateral breast. Exclusion: Not reported	Lifetime risk of breast cancer >25% based on family history with or without mutation or diagnosis of breast cancer in contralateral breast.	Followup among all women with RRM, years: Median 7.3; 1,673 women years Followup amongst women undergoing bilateral RRM: 1,274 women years Followup among control women; 2,438 women years
Hartmann et al., 1999[175] Fair	Inclusion: Women with a family history of breast cancer who underwent bilateral RRM. Exclusion: Breast cancer detected in surgically treated breast; Surgery undertaken for augmentation of reduction. High-risk Comparison Group Inclusion: Sisters of high-risk subjects were recruited to the study.	High risk: ≥2 first-degree relatives with breast cancer; 1 first-degree relative and ≥2 second-degree or third-degree relatives with breast cancer; 1 first-degree relative with breast cancer before the age of 45 years and 1 other relative with breast cancer; 1 first-degree relative with breast cancer and ≥1 relatives with ovarian cancer; 2 second-degree or third-degree relatives with breast cancer and ≥1 with ovarian cancer; 1 second-degree or third-degree relative with breast cancer and ≥2 with ovarian cancer; ≥3 second-degree or third-degree relatives with breast cancer; 1 first-degree relative with bilateral breast cancer; Breast cancer in male family members Moderate risk: Women who did not meet these criteria.	Median 14 years, with a minimum of 2 years for 99% of the subjects.

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
2013 Review			
Evans et al., 2009[173] Manchester site Fair	**Bilateral RRM (N=179) vs. no mastectomy (N=367)** Breast cancers expected based on life tables: 12.12 vs. 20.8 Cancers diagnosed: 0 vs. 21	Risk-reducing surgery is highly effective.	Not reported
Hartmann et al., 1999[175] Fair	Overall: 425 subjects were classified moderate risk, 214 subjects high risk. 95% were alive at the time of the study. 7 were diagnosed with breast cancer (4 moderate risk, 3 high risk); all cases occurred after subcutaneous mastectomy. Cancer Diagnosis: 37 in the moderate-risk group (based on Gail model estimates) and 53 in the high-risk group (based on the high-risk comparison group) were expected to develop breast cancer had they not undergone mastectomy. RRM reduced risk in the moderate-risk group by 89.5% ($p<0.001$) and in the high-risk group by 90% to 94% (depending on adjusted analysis). 2 women in the high-risk group were diagnosed with ovarian cancer. Death Reduction: 10 in the moderate-risk group (based on Gail model estimates) and 31 in the high-risk group (based on the high-risk comparison group) were expected to die from breast cancer had they not undergone mastectomy. Death was reduced in the moderate-risk group by 100% (no deaths) (95% CI 70 to 100) and in the high-risk group by 81% to 94% (depending on adjusted analysis) (2 deaths).	In women with high risk of breast cancer on the basis of family history, RRM can significantly reduce the incidence of breast cancer.	Department of Defense; National Cancer Institute; Donaldson Charitable Trust

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Mastectomy					
2013 Review					
Hartmann et al., 2001[176] Fair	Retrospective cohort	To report the effect of RRM on breast cancer risk in *BRCA1/2* carriers identified from a high-risk cohort.	18 *BRCA1/2*	*BRCA1/2* mutation carriers undergoing RRM and enrolled as high-risk participants in prior study (Hartmann, 1999).	Mean age at surgery 41 (range 20 to 75)
Skytte et al., 2011[183] Good	Prospective cohort	To compare incidence of breast cancer after RRM in healthy BRCA mutation carriers versus non-operated mutation carriers and background population.	Eligible: 307 with mutation (201 *BRCA1*, 106 *BRCA2*)	January 1996-February 2008 Denmark Women from clinical genetics departments at multiple sites with mutation status diagnosed.	Median age at entry into study, years: 36.2 (range: 17.9 to 86.3) Mean age at group entry, years (mastectomy vs. no mastectomy): 37.1 vs. 37.7 <40 years: 67% (64/96) vs. 60% (127/211) Note: age at group entry = age at mastectomy for mastectomy group and age at BRCA diagnosis for no mastectomy group.

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Mastectomy			
2013 Review			
Hartmann et al., 2001[176] Fair	Inclusion: Women with *BRCA1/2* mutations who underwent bilateral RRM mastectomy.	BRCA status	13.1 years
Skytte et al., 2011[183] Good	Inclusion: *BRCA1* or *BRCA2* mutation positive and women who did not undergo mastectomy or salpingo-oophorectomy prior to study. Exclusion: Diagnosis of breast or ovarian cancer before BRCA testing and women who opted for risk- reducing surgery before receiving test result.	BRCA status	Median time from study entry to mastectomy: 7.7 years Total at-risk time in mastectomy group: 378.7 years Total at-risk time in no mastectomy group: 934.6 years

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
2013 Review			
Hartmann et al., 2001[176] Fair	**Expected risk reduction** Easton model (a high-penetrance model): 6.1 cases Struewing model (a low-penetrance model): 4.5 cases **Mastectomy resulted in risk reduction** Eastern model: 89.5% or 100% (95% CI 41.4 to 99.7 and CI 68 to 100) Struewing model: 85% or 100% (95% CI 15.6 to 99.6 and CI 54.1 to 100)	Risk-reducing mastectomy is associated with a substantial reduction in the incidence of breast cancer in known *BRCA1/2* mutation carriers.	Not reported
Skytte et al., 2011[183] Good	**Number of breast cancer cases (incidence per person-year)** Mastectomy vs. no mastectomy: 3/96 (0.8%) vs. 16/211 (1.7%); HR 0.394 (95% CI 0.115 to 1.355) p=0.14 Note: 3/3 women with breast cancer in the mastectomy group and 12/16 women in no mastectomy group were *BRCA1* positive. Note: all women diagnosed with cancer in mastectomy group had also undergone bilateral salpingo-oophorectomy; 1 woman diagnosed with breast cancer on date of mastectomy, contributed to the "no mastectomy" group at risk time and cancer incidence. Adjusting for age did not change significance (HR 0.455, p=0.224) Effect of age was significant (p=0.008), in both groups, 1 year age difference was associated with 4.2% increase in breast cancer risk Annual incidence of breast cancer after mastectomy by carrier status: 1.1% for *BRCA1* (n=67); 0 for *BRCA2* (n=29)	Study of 307 healthy *BRCA1/2* carriers suggests bilateral RRM reduces risk of breast cancer but does not completely eliminate it. Study size too small to show a significant difference.	Not reproted

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
Current Review					
Heemskerk-Gerritsen et al., 2015[178] HEBON Study Fair	Retrospective cohort and prospective cohort	To assess potential bias in estimated breast cancer risk reduction after RRSO. Multiple analytic methods tested and a new one proposed.	Eligible patients: 822 *BRCA1* : 589 *BRCA2* : 233	From the ongoing Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON) study, selected *BRCA1/2* mutation carriers with no cancer history when DNA tested.	**Median age at start of observation, years** RRSO: 44 (range 30 to 66) Non-RRSO: 33 (range 30 to 66)
Kotsopoulos et al., 2017[179] Fair	Prospective cohort	Given concerns regarding methods of previous case-control studies, conducted a prospective analysis of oophorectomy and breast cancer risk in BRCA carriers with no history of cancer.	Eligible patients: 3722 *BRCA1* only 2969 *BRCA2* only: 725	Enrollment dates NR BRCA carriers identified at 78 centers in 12 countries	**Mean age at baseline**: 46.2 (range 21 to 88) among 1552 women with oophorectomy 33.4 (range 13 to 85) among 2170 women without oophorectomy

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
Current Review			
Heemskerk-Gerritsen et al., 2015[178] HEBON Study Fair	Inclusion: Female *BRCA1/2* mutation carriers with no history of cancer and both ovaries and both breasts intact at the date of DNA test result, and no cancer diagnosis within the first six months of study observation. Exclusion: Women with breast or ovarian cancer before DNA testing.	BRCA status	Median followup, years: 3.2 for all 822 patients **Mean followup, years** RRSO: 6.8 (range 0.5 to 17.4) Non-RRSO: 3.1 (range 0.1 to 15.9)
Kotsopoulos et al., 2017[179] Fair	Inclusion: BRCA carrier, family history of breast or ovarian cancer Exclusion: personal history of any cancer or of bilateral prophylactic mastectomy	BRCA status	**Mean followup, years**: 5.6 (range 0 to 21.2) All: 20,700 person-years Oophorectomy: 7648 person-years No oophorectomy: 13,052 person-years

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo- oophorectomy			
Current Review			
Heemskerk-Gerritsen et al., 2015[178] HEBON Study Fair	**RRSO (n=346) vs. non-RRSO (n=476)** Breast cancer incidence: 12.1% (42/346) vs. 9.9% (47/476) Incidence rate per 1000 PYO: 25.6 vs. 21.5, HR 1.09 (95% CI 0.67 to 1.77) *BRCA1* : 29.1 vs. 24.2, HR 1.21 (95% CI 0.72 to 2.06*)* *BRCA2* : 14.9 vs. 13.8, HR 0.54 (95% CI 0.17 to 1.66) Age <51 years: rates NR, HR 1.11 (95% CI 0.65 to 1.90) Age ≥51 years: rates NR, HR 1.78 (95% CI 0.52 to 6.15) Note: in addition to requiring no history of cancer, mastectomy, or oophorectomy at baseline, authors' analysis attempted to reduce bias by allocating both person-time before surgery in the RRSO group and a 3- month latency period to the non-RRSO group.	In previous studies, breast cancer risk reduction after RRSO in *BRCA1/2* mutation carriers may have been overestimated because of bias. Using a design that maximally eliminated bias, we found no evidence for a protective effect.	Dutch Cancer Society, the Netherlands Organization of Scientific Research, Pink Ribbon grant, and Biobanking and Biomolecular Resources Research Infrastructure grant
Kotsopoulos et al., 2017[179] Fair	**With oophorectomy (n=1552) vs. without oophorectomy (n=2170)** Annual incidence of new first primary breast cancers, all women: 1.87% vs. 1.59%, HR 0.89 (95% CI 0.69 to 1.14) *BRCA1*: 2.02% vs. 1.57%, HR 0.97 (95% CI 0.73 to 1.29) *BRCA2*: 0.97% vs. 2.32%, HR 0.68 (95% CI 0.38 to 1.21) Breast cancer diagnosed before age 50 years: *BRCA1*: 1.99% vs. 1.46%, HR 0.84 (95% CI 0.58 to 1.21) *BRCA2*: 0.53% vs. 1.70%, HR 0.17 (95% CI 0.05 to 0.61) Note: HRs adjusted for country, age, family history, and reproductive factors	Findings from this large prospective study support a role of oophorectomy for the prevention of premenopausal breast cancer in *BRCA2*, but not *BRCA1* mutation carriers	National Cancer Institute at the National Institutes of Health and the Canadian Cancer Society Research Institute

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
Current Review					
Mavaddat et al., 2013[180] EMBRACE Fair	Prospective cohort	To examine the effect of bilateral prophylactic oophorectomy on cancer risk in *BRCA1/2* mutation carriers.	Eligible patients without breast or ovarian cancer history: 988 *BRCA1:* 501 *BRCA2:* 485	From the ongoing EMBRACE study established in 1998 U.K. and Ireland 28 centers; included *BRCA1/2* carriers with either no breast or ovarian cancer history (reported here), or with history of unilateral breast cancer.	**Age at enrollment of women without cancer history, years** Mean: 41.2 Median: 39.5 Interquartile range: 14.6
Rebbeck et al., 2002[181] Fair	Prospective cohort	To investigate whether bilateral prophylactic oophorectomy reduces the risk of ovarian and breast cancers in women with BRCA mutations	Eligible patients, ovarian cancer study: 551 *BRCA1*: 459 *BRCA2*: 94 Eligible patients, breast cancer subgroup: 241 *BRCA1*: 204 *BRCA2*: 39	Enrollment dates NR Identified from 11 North American and European registries	**Mean age at time of surgical subjects' oophorectomy, years:** Ovarian cancer study: 42.0 (range 21.2 to 74.8) with oophorectomy 40.9 (range 19.6 to 79.1) without oophorectomy Breast cancer study: 40.1 (range 21.3 to 66.4) with oophorectomy 38.9 (range 18.6 to 69.9) without oophorectomy

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
Current Review			
Mavaddat et al., 2013[180] EMBRACE Fair	Inclusion: Women, aged at least 18 years at interview, carriers of a pathogenic *BRCA1* or *BRCA2* mutation, either unaffected at date of baseline questionnaire or diagnosed with unilateral breast cancer. Exclusion: Not reported	BRCA status	**Followup time for women without cancer history, years** Mean: 3.3 Median: 2.6 Interquartile range: 3.7
Rebbeck et al., 2002[181] Fair	Inclusion: women with confirmed BRCA mutations who reported having prophylactic oophorectomy and controls without oophorectomy matched for BRCA mutation, center, and birth year Exclusion: history of unilateral oophorectomy, BRCA variant of unknown significance, or history of ovarian cancer; for study of breast cancer risk, women with history of breast cancer or mastectomy excluded	BRCA status	**Mean followup, years:** In study of ovarian cancer: Oophorectomy: 8.2 No oophorectomy: 8.8 In subgroup followed for breast cancer: Oophorectomy: 10.7 No oophorectomy: 11.9 Subjects who had undergone prophylactic

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
			oophorectomy were followed from date of oophorectomy until occurrence of cancer or until censoring

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo- oophorectomy			
Current Review			
Mavaddat et al., 2013[180] EMBRACE Fair	**Number of women with new breast cancer, with oophorectomy (n=309) vs. without oophorectomy (n=679)** All carriers: 5.8% (18/309) vs. 6.8% (46/679), HR 0.62 (95% CI 0.35 to 1.09) *BRCA1* : 5.6% (9/162) vs. 7.7% (26/339), HR 0.52 (95% CI 0.24 to 1.13) *BRCA2* : 6.2% (9/146) vs. 5.9% (20/339), HR 0.79 (95% CI 0.35 to 1.80) Note: HRs adjusted for reproductive factors were similar and not reported. Stratified by age: All carriers < 45: HR 0.39 (95% CI 0.17 to 0.87) All carriers ≥ 45: HR 1.14 (95% CI 0.50 to 2.61) *BRCA1* < 45: HR 0.38 (95% CI 0.13 to 1.13) *BRCA1* ≥ 45: HR 0.83 (95% CI 0.26 to 2.63) *BRCA2* < 45: HR 0.44 (95% CI 0.14 to 1.38) *BRCA2* ≥ 45: HR 1.74 (95% CI 0.59 to 5.15) Note: patient numbers reported incorrectly in Supplementary Table 4 (compared with Table 4) and not reported here.	Oophorectomy carried out at less than 45 years of age was associated with a greater reduction in cancer risks than oophorectomy carried out at ages 45 years or older.	Cancer Research U.K., National Institute for Health Research, Medical Research Council
Rebbeck et al., 2002[181] Fair	**Ovarian or peritoneal cancer, with oophorectomy (n=259) vs. without oophorectomy (n=292)** All carriers: 0.8% (2/259) vs. 19.9% (58/292), HR 0.04 (95% CI 0.01 to 0.16) Note: 2 peritoneal cancers; excludes 6 occult ovarian cancers found at oophorectomy All carriers, by age at oophorectomy (years): <35 (n=124): No events 35 to 50 (n=348): HR 0.03 (95% CI <0.01 to 0.20) ≥50 (n=79): HR 0.11 (95% CI 0.02 to 0.76) Women without personal history of breast cancer (n=351): HR 0.06 (95% CI 0.01 to 0.25) **Breast cancer, with oophorectomy (n=99) vs. without oophorectomy (n=142)** All carriers: 21.2% (21/99) vs. 42.3% (60/142), HR 0.47 (95% CI 0.29 to 0.77) All carriers, by age at oophorectomy (years):	Bilateral prophylactic oophorectomy reduces the risk of ovarian and peritoneal cancer and breast cancer in women with BRCA mutations	Public Health Service, University of Pennsylvania Cancer Center, Breast Cancer Research Foundation, Dana-Farber Women's Cancers Program, Department of Defense, Utah State Department of Health, and the Nebraska State Cancer and Smoking-Related Diseases Research Program

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
	<35 (n=76): HR 0.39 (95% CI 0.15 to 1.04) 35 to 50 (n=146): HR 0.49 (95% CI 0.26 to 0.90) ≥50 (n=19): HR 0.52 (95% CI 0.10 to 2.70)		

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
Current Review					
Shah et al., 2009[182] Fair	Prospective cohort	To examine the combined effects of oophorectomy and intensive surveillance on breast cancer incidence in a prospective cohort of *BRCA1/2* carriers.	Analyzed: 93 *BRCA1:* 55% (51/93) *BRCA2:* 44% (41/93)	2003 to 2008 U.S. University of Pennsylvania protocol for MRI screening in *BRCA1/2* carriers.	Median age at enrollment, years: 47

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
Current Review			
Shah et al., 20099[182] Fair	Inclusion: Women over 25 years with known *BRCA1/2* mutation, or prior probability of a mutation of >75%. Required to be at least 3 months from any breast biopsies, lactation, radiation treatments, and chemotherapy treatments; women with prior breast cancer otherwise eligible. Exclusion: Patients who were pregnant, had a contraindication to MRI, had bilateral mastectomies, those with unresolved actionable clinical or mammogram findings, or with new or recurrent ovarian cancer within 4 years.	Known deleterious mutation in *BRCA1* or *BRCA2,* or prior probability of a mutation of >75%	Median followup from study entry, years: 3.2

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo- oophorectomy			
Current Review			
Shah et al., 2009[182] Fair	**With oophorectomy (n= 80) vs. no oophorectomy (n=13)** Number of women with breast cancer: 11% (9/80) vs. 15% (2/13), p=NS **With oophorectomy ≤40 years (n=25) vs. no oophorectomy ≤ 40 years (n=68)** Number of women with breast cancer: 12% (3/25) vs. 12% (8/68), p=NS All cancers diagnosed in *BRCA1* carriers	The breast cancer risk reduction from oophorectomy may be greater in *BRCA2* than in *BRCA1* mutation carriers	Cancer Genetics Network, the Marjorie Cohen Foundation, the QVC Network-Fashion Footwear Association of New York, and the National Institutes of Health

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
2013 Review					
Domchek et al., 2010[98] Fair	Prospective cohort	To assess the relationship of RRM or RRSO with cancer outcomes.	Eligible: 2482 Analyzed: 1458 with no prior breast cancer (935 *BRCA1* , 523 *BRCA2*)	1974 to 2008 U.K., Europe and North America Women from 22 centers in the PROSE consortium.	Not reported

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
2013 Review			
Domchek et al., 2010[98] Fair	Inclusion: Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup. Exclusion: Women with cancer diagnosis within first 6 months of followup, women who had undergone RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points.	BRCA status	Patients followed until end of 2009. **Median followup, years** Those who had surgery: 3.65 those who did not have surgery: 4.29 **Oophorectomy & breast cancer outcomes** *BRCA1* followed mean 4.7 years to censoring *BRCA 2* followed mean 4.7 years to censoring **Oophorectomy & ovarian cancer outcomes** *BRCA1* followed mean 5.6 years to censoring *BRCA2* followed mean 5.8 years to censoring

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo-oophorectomy			
2013 Review			
Domchek et al., 2010[98] Fair	**Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery** Risk-reducing salpingo-oophorectomy and ovarian or primary peritoneal cancer risk Total: 1.3% (6/465) vs. 5.8%(63/1092), HR 0.28 (95% CI 0.12 to 0.69) *BRCA1*: 1.8% (6/342) vs. 7.4% (49/661), HR 0.31 (95% CI 0.12 to 0.82) *BRCA2*: 0% (0/123) vs. 3.2% (14/431), HR N/A Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center. Risk-reducing salpingo-oophorectomy and breast cancer risk Total: 12% (39/336) vs. 22% (223/1034), HR 0.54 (95% CI 0.37 to 0.79) *BRCA1* : 14% (32/236) vs. 20% (129/633), HR 0.63 (95% CI 0.41 to 0.96) *BRCA2* : 7% (7/100) vs. 23% (94/401), HR 0.36 (95% CI 18.1 to 82.7) Note: HR adjusted for year of birth and stratified by center. Risk-reducing salpingo-oophorectomy and all-cause mortality Total: 1.8% (8/447) vs. 5.9% (60/1011), HR 0.45 (95% CI 0.21 to 0.95)	Among a cohort of women with BRCA mutations, RRSO was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer specific mortality, and ovarian cancer specific mortality.	Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen Research Fund; SPORE grant from the Dana-Farber/Harvard Cancer Center; the U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade received funding as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Results	Conclusions	Funding source
	BRCA1 : 2.4% (8/327) vs. 7.1% (43/608), HR 0.52 (95% CI 0.24 to 1.14) *BRCA2* : 0%(0/120) vs. 4.2% (17/403), HR N/A Note: HR adjusted for year of birth and stratified by center. Risk-reducing salpingo-oophorectomy and breast cancer specific mortality Total: 0.5% (2/441) vs. 2.3% (22/973), HR 0.27 (95% CI 0.05 to 1.33) *BRCA1*: 1.0% (2/321) vs. 2.8% (16/581), HR 0.30 (95% CI 0.06 to 1.53) *BRCA2*: 0% (0/120) vs. 1.5% (6/392), HR N/A Note: HR adjusted for year of birth and stratified by center. Risk-reducing salpingo-oophorectomy and ovarian cancer specific mortality Total: 0.7% (3/442) vs. 2.5% (24/975), HR 0.39 (95% CI 0.12 to 1.29) *BRCA1*: 0.9% (3/322) vs. 3.4% (20/585), HR 0.46 (95% CI 0.08 to 2.72) *BRCA2*: 0% (0/120) vs. 1.0% (4/390), HR N/A Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center.		received funding from the National Institute for Health Research

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
2013 Review					
Kramer et al., 2005[99] Fair Note: only oophorectomy performed	Prospective cohort	To assess whether population differences in oophorectomy prevalence might significantly influence breast cancer penetrance estimates in *BRCA1* mutation families.	Eligible: 673 (98 *BRCA1* positive, 23 from *BRCA1* families)	Year: NR U.S. Women from self-referred and physician-referred families affected by hereditary breast/ovarian cancer with a *BRCA1* mutation and participating in ongoing studies at the National Cancer Institute.	Not reported Mean 2.7 cases of breast cancer and 3.0 cases of ovarian cancer per family diagnosed before ascertainment.
Olson et al., 2004[100] NA Note: only oophorectomy performed	Retrospective cohort	To estimate the potential risk reduction of breast cancer for women who underwent oophorectomy and had a family history of breast cancer but unknown BRCA status.	Eligible: 851 Analyzed: 634	1970 to 1994 U.S./review of Mayo Clinic Surgical Index Followup survey completed by patient or surrogates (if patient deceased).	**Surrogate respondent vs. self-respondent** Age at surgery, years (n) 21-30: 4% (1/27) vs. 3% (16/607) 31-40: 4% (1/27) vs. 14% (88/607) 41-50: 41% (11/27) vs. 53% (319/607) 51-60: 52% (14/27) vs. 30% (184/607) Age at questionnaire response (followup) of self-respondents, years (n) 31-40: 1% (9/634) 41-50: 8% (48/634) 51-60: 28% (172/634) 61-70: 38% (231/634) 71-80: 20% (124/634) 81-90: 3% (20/634) Deceased: n=30

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
2013 Review			
Kramer et al., 2005[99] Fair Note: only oophorectomy performed	Inclusion: Female, bloodline family member from *BRCA1* positive family, no history of breast cancer before ascertainment, no history of bilateral mastectomy, age ≥20 years by study closing date. Exclusion: Breast cancer diagnosed before family ascertainment and families with variants of uncertain significance.	BRCA status	**Mean followup**: 16.5 years; 11,105 PYO **Mean followup per patient, years** *BRCA1* positive: 14.1 *BRCA1* negative: 17.6 *BRCA1* unknown: 15.8

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Olson et al., 2004[100] NA Note: only oophorectomy performed	Inclusion: Women <60 years old with bilateral oophorectomy during study dates. Exclusion: Women who underwent hysterectomy alone or only had one ovary removed, underwent prophylactic mastectomy at any time, or had any history of cancer prior to surgery, aside from nonmelanoma skin cancer.	High-risk: ≥1 first-degree relative with breast cancer before age 50 or 1 first-degree relative with ovarian cancer at any age and ≥1 other first or second- degree relative with either diagnosis at any age. Moderate-risk: Only 1 first-degree relative with breast cancer at any age. Low- risk: No breast or ovarian cancer family history.	NA

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo- oophorectomy			
2013 Review			
Kramer et al., 2005[99] Fair Note: only oophorectomy performed	**Number of breast cancer cases, oophorectomy vs. no oophorectomy** *BRCA1* positive (n=98): 18% (6/33) vs. 42% (27/65), HR 0.38 (95% CI 0.15 to 0.97), p=0.043 *BRCA1* negative (n=353): 2.9% (1/34) vs. 1.3% (4/319), HR NR *BRCA1* status unknown (n=222): 0% (0/18) vs. 2.5% (5/204), HR NR Absolute risk reduction among women who underwent oophorectomy was most prominent when surgery was done at a younger age (<40 years), figure representation.	Among a cohort of *BRCA1* mutation carriers from multiple case families, oophorectomy was associated with decreased risk of breast cancer; affect was strongest in younger women; oophorectomy status affects breast cancer penetrance.	Intramural Research Program of National Cancer Institute; Funding source not specifically reported
Olson et al., 2004[100] NA Note: only oophorectomy performed	**Expected vs. observed number of cancer cases** Age of surgery <60 years High-risk (n=55): 5.4 vs. 3, RR 0.56 (95% CI 0.11 to 1.33) Moderate-risk (n=193): 10.9 vs. 9, RR 0.83 (95% CI 0.38 to 1.44) Age of surgery <50 years High-risk (n=41): 3.9 vs. 1, RR 0.26 (95% CI 0.001 to 0.99) Moderate-risk (n=130): 7.7 vs. 5, RR 0.65 (95% CI 0.21 to 1.32) Age of surgery <60 years and premenopausal before surgery High-risk (n=52): 5.1 vs. 3, RR 0.59 (95% CI 0.12 to 1.41) Moderate-risk (n=186): 10.4 vs. 7, RR 0.67 (95% CI 0.27 to 1.24) Age of surgery <50 years and premenopausal before surgery High-risk (n=40): 3.8 vs. 1, RR 0.26 (95% CI 0.00 to 1.00) Moderate-risk (n=126): 7.4 vs. 3, RR 0.41 (95% CI 0.08 to 0.98)	The number of observed breast cancers among women in the cohort was lower than expected for nearly all levels of risk, and especially for those <50 years old and premenopausal prior to surgery.	Fraternal Order of the Eagles and the National Cancer Institute

Appendix B Table 10. Evidence Table of Risk-Reducing Surgery Studies

Author, year Quality	Design	Purpose	Sample size	Population/setting	Demographics
Oophorectomy or salpingo- oophorectomy					
2013 Review					
Struewing et al., 1995[184] Poor	Prospective cohort	To determine the incidence of post- oophorectomy carcinomatosis and quantify the effectiveness of risk- reducing surgery.	Eligible: 16 families Analyzed: 12 families (390 first-degree relatives of breast or ovarian cancer cases)	Women with high genetic risk of ovarian cancer and oophorectomies matched to high- risk women who did not undergo surgery from National Cancer Institute, Creighton University, and U.K.	Not reported

Author, year Quality	Inclusion/exclusion criteria	Risk definition	Followup
Oophorectomy or salpingo- oophorectomy			
2013 Review			
Struewing et al., 1995[184] Poor	Inclusion: Families with ≥3 cases of ovarian cancer or ≥2 cases of ovarian cancer and ≥1 case of breast cancer before age 50. Exclusion: Families fitting criteria for Lynch Syndrome II.	Results presented by those with an affected first- degree relative and those with an affected second-degree relative.	**Surgery vs. no surgery** Ovarian cancer incidence 1st degree relative: 460 vs. 1665 person-years 2nd degree relative: 106 vs. 2123 person-years Breast cancer incidence 1st degree relative: 484 vs. 1587 person-years 2nd degree relative: 106 vs. 2131 person-years

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy or salpingo-oophorectomy			
2013 Review			
Struewing et al., 1995[184] Poor	**Surgery vs. no surgery** *Preliminary Analysis from National Cancer Institute only* Ovarian cancer incidence 1st degree relative: 2/44 vs. 8/346 2nd degree relative: 0 vs. 1 Note: incidence includes post-oophorectomy ovarian carcinomatosis Breast cancer incidence 1st degree relative: 3/44 vs. 14/346 2nd degree relative: 0 vs. 3	Findings suggest that there is a finite risk of post- oophorectomy carcinomatosis. Preliminary analysis suggests a statistically nonsignificant protective effect of surgery for ovarian cancer.	Not reported

Abbreviations: BRCA=breast cancer susceptibility gene; BRRM=Bilateral risk-reducing mastectomy; CI=confidence interval; DCIS=ductal carcinoma in situ; DNA=deoxyribonucleic acid; EMBRACE=Epidemiological Study of Familial Breast Cancer; HEBON=Hereditary Breast and Ovarian Cancer in the Netherlands; HR=hazard ratio; MRI=magnetic resonance imaging; NA=not applicable; NR=not reported; NS=not significant; PROSE=Prevention and Observation of Surgical End Points; PYO=person years of observation; RRM=risk-reducing mastectomy; RRSO=risk-reducing salpingo-oophorectomy; U.K.=United Kingdom; U.S.=United States

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and Setting
Current Review						
den Heijer et al., 2013[193] Fair Same population as Rijnsburger et al., 2004[209]	Psychological	To explore long-term psychological distress in women adhering to breast cancer surveillance and compare this with short-term psychological distress.	Prospective cohort	Eligible: Not reported Enrolled: 207 Analyzed: 197	The Netherlands	Family Cancer Clinic of the Erasmus MC-Daniel den Hoed Cancer Center
Portnoy et al., 2015[208] NA	Psychological	To examine: (a) the effect of false- positive breast and ovarian cancer screening test results on perceived cancer risk and cancer worry, and (b) the joint effects of false-positive screening results, risk perceptions, and worry on the choice of risk- reducing surgery among women who are *BRCA1/2* mutation carriers undergoing an intensive cancer screening protocol.	Before and after	Eligible: Not reported Enrolled: 170 Analyzed: 170	U.S.	NCI Clinical Genetics Branch Breast Imaging Study

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
Current Review			
den Heijer et al., 2013[193] Fair Same population as Rijnsburger et al., 2004[209]	Mean age, years: 40.9 (SD 8.4)	Inclusion: No history of breast cancer and having a cumulative lifetime risk of developing breast cancer ≥15%, on the basis of the risk tables by Claus et al., had participated in the MRISC-B study, had not developed breast and/or ovarian cancer during the surveillance program, had remaining breast tissue at risk, and had sufficient understanding of the Dutch language Exclusion: Not reported	Cumulative lifetime risk ≥15%
Portnoy et al., 2015[208] NA	Mean age, years: 39.79 (SD 8.63) White: 95.3% Prior breast cancer: 12.9% (22/170) Prior ovarian cancer: 0.6% (1/170)	Inclusion: Women from the NCI Clinical Genetics Branch Breast Imaging Study, with a *BRCA 1/2* mutation Exclusion: Women who had undergone RRSO prior to study entry	*BRCA 1/2* mutation carriers

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Current Review				
den Heijer et al., 2013[193] Fair Same population as Rijnsburger et al., 2004[209]	13% (25/197) *BRCA 1/2* mutation carriers	Hospital Anxiety and Depression Scale (HADS, both anxiety and depression scales 0 to 21) Impact of Events Scale (IES, intrusion scale 0 to 35 and avoidance scale 0 to 40)	Surveillance (CBE + MRI + mammography)	June 2007 to October 2009 5 to 8 years
Portnoy et al., 2015[208] NA	100% *BRCA 1/2* mutation carriers	Brief Symptom Inventory (BSI, scale 0 to 100) Perceived risk of breast and ovarian cancer (5-	Clinical breast exam, mammogram, breast MRI, and investigational	2001 to 2007 1 year

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
		point Likert scale of 2 questions) Worry about breast and ovarian cancer, adapted from Lerman et al., 1991 breast cancer worry scale (4-point Likert scale of 3 questions)	breast duct lavage to screen for breast cancer, plus serum CA-125 and a transvaginal ultrasound to screen for ovarian cancer	

Author, year Quality	*Results*	*Conclusions*	*Funding source*
Current Review			
den Heijer et al., 2013[193] Fair Same population as Rijnsburger et al., 2004[209]	**Women who lost a first-degree relative to breast cancer, baseline vs. long-term followup** Mean IES-intrusion scale (SD): 6.46 (7.85) vs. 4.77 (6.46), p=0.001 Mean IES-avoidance scale (SD): 4.26 (6.99) vs. 3.47 (6.44), p=0.02 Mean HADS-anxiety scale (SD): 5.22 (3.88) vs. 5.07 (4.16) Mean HADS-depression scale (SD): 2.79 (3.42) vs. 2.71 (3.55) **Women who did not lose a first-degree relative to breast cancer, baseline vs. long-term followup** Mean IES-intrusion scale (SD): 4.58 (6.12) vs. 2.75 (4.58), p=0.001 and p=0.02 vs. those who lost a first-degree relative to breast cancer Mean IES-avoidance scale (SD): 4.07 (6.01) vs. 3.34 (6.41), p=0.02 Mean HADS-anxiety scale (SD): 4.87 (3.36) vs. 4.91 (3.95) Mean HADS-depression scale (SD): 2.47 (3.60) vs. 2.64 (3.38)	Long-term distress does not exceed levels of clinically relevant psychological distress.	Dutch Cancer Society (KWF EMC 2006-3468)
Portnoy et al., 2015[208] NA	**Screening FP (n=27) vs. No FP (n=143)** Mean baseline breast cancer worry: 1.70 vs. 1.75 Mean 3 month breast cancer worry: 1.80 vs. 1.50 Mean 1 year breast cancer worry: 1.45 vs. 1.50	False positive results on MRI were not associated with large increases in cancer worry.	Intramural Research Program of the NIH and the National Cancer Institute

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and Setting
2013 Review						
Rijnsburger et al., 2004[209] Fair Same population as den Heijer et al., 2013[193]	QOL	To describe the short-term effects of screening for breast cancer in high- risk women on health-related quality of life.	Prospective cohort Before and after	Eligible: 529 Enrolled: 329 Analyzed: 288	The Netherlands	MRI Screening Study conducted at 6 family cancer centers.

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Rijnsburger et al., 2004[209] Fair Same population as den Heijer et al., 2013[193]	Mean age, years: 40.9 (SD 8.9)	Inclusion: Women already under intensive surveillance and women who came for the first time to the clinic Exclusion: Women with evident symptoms suspicious for breast cancer or previous breast cancer	Risk category 1: *BRCA 1/2* mutation carriers (50% to 85% cumulative lifetime risk) Risk category 2: 30% to 50% cumulative lifetime risk Risk category 3: 15% to 30% cumulative lifetime risk

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
2013 Review				
Rijnsburger et al., 2004[209] Fair Same population as den Heijer et al., 2013[193]	35 were *BRCA1/2* mutation positive	EuroQoL-5 Dimensions (EQ-5D, scale 0 to 1) Medical Outcomes Study 36-Item Short Form (SF-36, subscales 0 to 100) Symptom Checklist-90 (SCL-90, scale 12 to 60) Visual Analogue Scale (VAS, scale 0 to 100)	A) CBE (n=287) B) CBE + mammography (n=134) C) CBE + MRI (n=109)	2000 to 2002 1 to 4 weeks after screening

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Rijnsburger et al., 2004[209] Fair Same population as den Heijer et al., 2013[193]	**A vs. B vs. C** Experienced no pain after screening: 92.6% vs. 14.3% vs. 88.0%; p=NR Experienced no discomfort after screening: 91.5% vs. 30.8% vs. 54.6%; p=NR Experienced no anxiety after screening: 77.9% vs. 72.4% vs. 63.0%; p=NR **Before screening (T0) vs. day of screening (T1) vs. after screening (T2)** Mean VAS: 81.9 vs. 79.0 vs. 80.7; p<0.01 T0 vs. T1 and p<0.05 T1 vs. T2 **Before screening vs. after screening (A, B, and C groups combined) vs. reference group (Dutch general population)** Mean on SF-36 subscales; p=NS for before and after screening	Women who received MRI experienced less pain and discomfort than those who received mammographies. Women in screening showed better health-related quality of life per the SF-36 than the reference group.	Health Care Insurance Board, The Netherlands

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

Author, year Quality	Results	Conclusions	Funding source
	Physical functioning: 89.9 vs. 89.4 vs. 86.3; p<0.01 for reference group vs. before screening Role-physical: 85.7 vs. 84.1 vs. 77.6; p<0.01 for reference group vs. before screening Bodily pain: 82.4 vs. 83.0 vs. 72.8; p<0.01 for reference group vs. before screening General health perceptions: 76.4 vs. 77.3 vs. 72.2; p<0.01 for reference group vs. before screening Vitality: 67.1 vs. 68.9 vs. 64.8; p=NS Social functioning: 87.7 vs. 87.9 vs. 83.5; p<0.01 for reference group vs. before screening Role-emotional: 85.2 vs. 88.1 vs. 80.1; p<0.05 for reference group vs. before screening Mental health: 76.8 vs. 77.7 vs. 74.4; p<0.05 for reference group vs. before screening Mean SCL-90: 17.5 vs. 17.1 vs. 18.7; p<0.05 for reference group vs. before screening Mean EQ-5D utility score (compared to Swedish reference group): 0.88 vs. 0.88 vs. 0.85; p<0.01 for reference group vs. before screening		

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and Setting
2013 Review						
Spiegel et al., 2011[210] NA	Psychological	To compare women with recall examinations following MRI to those without recall examinations on breast cancer worry and anxiety.	Before and after	Eligible: 221 Enrolled: 134 Analyzed: 55	Canada	Women participating in an MRI screening trial.

Author, year Quality	Demographics	Inclusion and exclusion criteria	Risk level definition
2013 Review			
Spiegel et al., 2011[210] NA	Mean age, years: 45 (range 25 to 60)	Inclusion: Women participating in MRI screening trial who agreed to participate Exclusion: Not reported	All were mutation carriers

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
2013 Review				
Spiegel et al., 2011[210] NA	54.5% (30/55) *BRCA1* 45.5% (25/55) *BRCA2*	Breast Cancer Worry Interference Scale (WIS, scores 7 to 35) Hospital Anxiety and Depression Scale (HAD, subscales 0 to 21)	All received annual mammography, MRI, and ultrasound; and semi-annual CBE A) Women with recall examinations (n=18) B) Women without recall examinations (n=37)	Years: NR 6 months

Author, year Quality	Results	Conclusions	Funding source
2013 Review			
Spiegel et al., 2011[210f] NA	**Before screening vs. 4 to 6 weeks after screening vs. 6 months after screening** Mean HADS-A (SD): 7.15 (4.2) vs. 6.85 (4.5) vs. 6.31 (3.9); NS Mean HADS-D (SD): 2.65 (3.6) vs. 2.60 (3.5) vs. 2.60 (3.5); NS Mean WIS (SD): 10.27 (4.2) vs. 11.07 (4.9) vs. 10.44 (4.7); NS **A vs. B 4 to 6 weeks after screening** Mean HADS-A (SD): 8.8 (5.2) vs. 5.9 (3.9); p=0.03 Mean HADS-D (SD): 3.3 (4.3) vs. 2.2 (3.1); NS Mean WIS (SD): 13.6 (6.4) vs. 9.8 (3.5); NS **A vs. B 6 months after screening** Mean HADS-A (SD): 7.1 (3.8) vs. 5.9 (4.0); NS Mean HADS-D (SD): 3.1 (4.3) vs. 2.3 (3.1); NS Mean WIS (SD): 12.4 (6.3) vs. 9.4 (3.2); NS	Women who were recalled for examinations after screening had increased anxiety 4 to 6 weeks after screening, but by 6 months all scores returned to baseline levels.	Canadian Breast Cancer Research Alliance grant #012345 and private donation from Florence and Maury Rosenblatt

Abbreviations: BRCA=breast cancer susceptibility gene; BSI=Brief Symptom Inventory; CBE=clinical breast exam; EQ-5D=EuroQoL-5 Dimensions; FP=false positive;

Appendix B Table 11. Evidence Table of Psychological and Sexual Functioning Harms of Intensive Screening Interventions

HADS=Hospital Anxiety and Depression Scale; IES=Impact of Events Scale; MRI=magnetic resonance imaging; MRISC-B study=Magnetic Resonance Imaging Screening for Breast Cancer study; NA=not applicable; NCI=National Cancer Institute; NR=not reported; NS=not significant; QOL=quality of life; RRSO=risk-reducing salpingo-oophorectomy; SCL-90=Symptom Checklist-90; SD=standard deviation; SF-36=Short Form 36 Health Survey; U.S.=United States; VAS=Visual Analogue Scale; WIS=Breast Cancer Worry Interference Scale

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Study design	Country/ population/setting	Inclusion/exclusion criteria
Breast cancer screening				
2013 Review				
Kriege et al., 2004[201] NA Dutch MRISC study	Physical harms of increased screening	Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion: Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables; age at entry between 25 to 70 years (could be tested at age younger than 25 if family member diagnosed before age of 30 years) Exclusion: Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation
Kriege et al., 2006[202] NA Dutch MRISC study	Physical harms of increased screening	Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study)	The Netherlands Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites	Inclusion: Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables, age at entry between 25 to 70 years (could be tested at age younger than 25 if family member diagnosed before age of 30 years), no previous breast cancer or symptoms suspicious for breast cancer Exclusion: Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Breast cancer screening				
2013 Review				
Kriege et al., 2004[201] NA Dutch MRISC study	Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables	Enrolled: 1952 Analyzed: 1909 n=358 mutation carriers (276 *BRCA1* , 77 *BRCA2* , 1 both *BRCA1* and *BRCA2* , 2 PTEN and 2 TP53), n=1052 high-risk, n=499 moderate-risk	Mean age at entry, years: 40 (range 19 to 72)	1999 to 2003 Median 2.9 years (mean 2.7, range 0.1 to 3.9 years)
Kriege et al., 2006[202] NA Dutch MRISC study	Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables	Analyzed: 1909 n=358 mutation carriers (276 *BRCA1* , 77 *BRCA2* , 1 both *BRCA1* and *BRCA2* , 2 PTEN and 2 TP53), n=1052 high-risk, n=499 moderate-risk	Mean age at entry, years: 40 (range 19 to 72)	1999 to 2003 Median 2.9 years (mean 2.7, range 0.1 to 3.9 years)

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
Breast cancer screening			
2013 Review			
Kriege et al., 2004[201] NA Dutch MRISC study	A) Bi-annual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When one of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (BI-RADS 3 or 0), further investigation undertaken by ultrasonography +/- fine needle aspiration, or mammography or MRI repeated; When one of the examinations reported as "suspicious abnormality" or "highly suggestive of malignancy" (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; When results of imaging was negative but clinical breast exam was uncertain or suspicious, additional investigations performed.	**Based on 45 cancers, B vs. C** Additional investigations -Ultrasound, 889 times/627 women - Fine needle aspiration, 312 times (267 times plus ultrasound, 45 times plus palpation) -Biopsy, used 85 times/82 women (malignancy in 50 cases, lobular carcinoma in situ in 1 case; rate of positive histologic findings 60.0%) -Benign additional exams*: 207 vs. 420 Benign biopsies: 28% (7/25*) vs. 43% (24/56†)	Grant from Dutch Health Insurance Council
Kriege et al., 2006[202] NA Dutch MRISC study	A) Bi-annual CBE B) Annual mammography C) Annual contrast enhanced MRI Note: When one of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (BI-RADS 3 or 0), further investigation undertaken by ultrasonography +/- fine needle aspiration, or mammography or MRI repeated; When one of the examinations reported as "suspicious abnormality" or "highly suggestive of malignancy" (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; When results of imaging was negative but clinical breast exam was uncertain or suspicious, additional investigations performed.	**Imaging rounds of 39 evaluable invasive breast cancers, B vs. C** First imaging round, with prior mammography False positive rate (%): 5.5 vs. 14.0, P<0.001 False negatives (n): 12 vs. 1 Subsequent imaging rounds False positive rate (%): 4.6 vs. 8.2, p<.001 False negatives (n): 12 vs. 4	Grant from Dutch Health Insurance Council

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Breast cancer screening				
2013 Review				
Leach, 2005[203] NA MARIBS study	Physical harms of increased screening	Prospective cohort, one-arm	U.K. Women attending one of 22 participating centers in the U.K. with increased breast cancer risk	Inclusion: Asymptomatic women aged 35 to 49 years fulfilling one of the following: known carrier of a deleterious *BRCA1* , *BRCA2* , or TP53 mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome Aim was to include women whose affected FDRs had ≥60% chance of being a *BRCA1* or *BRCA2* mutation carrier or women with an annual risk of ≥0.9%. Exclusion: Women with previous breast cancer, those with any cancer such that prognosis was <5 years, participants who underwent predictive genetic testing during study and whose results were negative, women who developed cancer during study period

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Breast cancer screening				
2013 Review				
Leach, 2005[203] NA MARIBS study	Known carrier of a deleterious *BRCA1* , *BRCA2* , or *TP53* mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome	649 13% (82/649) with known *BRCA1* mutation 6% (38/649) with known *BRCA2* mutation	Median age at entry, years: 40 (range 31 to 55; only 1 woman aged >50 years)	Study recruitment 1997 to 2003 Variable screening episodes per individual but screening continued until each women had ≥2 annual scans (in 2004)

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
Breast cancer screening			
2013 Review			
Leach, 2005[203] NA MARIBS study	A) Annual mammography from age 35 years (or younger if FDR developed cancer at age <35 years) B) Annual CE MRI Note: In women with equivocal results, high specificity MRI exam done 2 to 6 weeks later (followed by ultrasound, fine needle aspiration,	**Recall rates, A vs. B (based on 33 screen detected cancers)** 279 exams led to recall (40 based purely on reader's judgment, not score) 3.9% vs. 11% per woman year A plus B: 13% per woman year 245 recalls for benign findings 73% diagnosed cancer-free using non-invasive tests	Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
	localization and tissue sampling by conventional methods as appropriate).	**Additional diagnostic procedures in 245 women without cancer** Ultrasound, n=93 Core biopsy, n=32 Fine needle aspiration, n=47 Surgery, n=7 (3% of recalled women without cancer, 27% of recalled women with cancer) 8.5 recalls per cancer detected 0.21 benign surgical biopsies per cancer detected Number of women per 1000 screening episodes needing diagnostic surgical biopsy was 0.4% (7/1881) for benign lesions, 0.5% (9/1881) for malignant lesions PPV of diagnostic surgical biopsy: 56% 62% (172/279) of suspicious findings on MRI resolved without invasive procedure, n=16 women had diagnostic surgery to complete diagnosis, n=91 had some form of percutaneous biopsy procedure Pre-op diagnosis of cancer made in 73% (24/33) of screen detected cancers	

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Breast cancer screening				
2013 Review				
Le-Petross et al., 2011[204] NA	Physical harms of increased screening	Retrospective analysis of prospective cohort study, one-arm	U.S. Women at increased genetic risk of breast cancer at single-institution	Inclusion: Women aged ≥18 years, having undergone alternating screening mammography and breast MRI every 6 months at study institution, either confirmed *BRCA1/2* carriers or FDR of confirmed *BRCA1/2* carrier Exclusion: Women with history of breast cancer, who had calculated lifetime risk of breast cancer >20%, or who did not undergo a screening MRI, women who used chemoprevention or underwent bilateral prophylactic mastectomy, those with metastatic disease, undergoing treatment, or high BMI preventing MRI, women lost to followup, or died during original trial

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Breast cancer screening				
2013 Review				
Le-Petross et al., 2011[204] NA	Based on BRCA status or FDR of BRCA mutation carrier	Screened: 321 Analyzed: 73 (51% *BRCA1*, 49% *BRCA2*)	Median age at entry, years: 44 (range 23 to 75)	Records from 1997 to 2009 Median followup, years: 2 (range 1 to 6) Mean followup from suspicious finding to diagnosis, years: 1.7 (range 1 to 3)

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
Breast cancer screening			
2013 Review			
Le-Petross et al., 2011[204] NA	All women underwent: A) Mammography every 6 months B) MRI every 6 months Note: imaging was performed on an alternating basis, women had clinical breast exam every 6 months, ultrasound used to evaluate abnormal mammographic or MRI findings, biopsy as required.	13 cancers in 11 women (12 on screen, 1 on prophylactic mastectomy) 20/73 women underwent biopsy, 11 cancers diagnosed by biopsy in 10 women Overall biopsy yield for MRI was 50% (10/20) **False positive, A vs. B** Overall: 15% (11/73) vs. 11% (8/73) Required further imaging: 8 vs. 4 Required biopsy: 3 vs. 2 Required imaging plus biopsy: 0 vs. 2	Not reported

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Ovarian cancer screening				
2013 Review				
Bourne et al., 1993[188] NA	Physical harms of increased screening	Prospective cohort, one-arm	United Kingdom Self-referred asymptomatic women with a close relative diagnosed with ovarian cancer	Inclusion: Women ≥25 of age with ≥1 close relative who had developed ovarian cancer; symptomless
Hermsen et al., 2007[198] NA	Physical harms of increased screening	Prospective cohort, one-arm (Staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies)	The Netherlands Women with BRCA mutation screened at 6 University Family Cancer Clinics	Inclusion: Women with *BRCA1/2* mutation screened at one of participating centers Exclusion: Women with symptoms at first visit, who had only one visit, or who were found to have cancer at first screening visit

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Ovarian cancer screening				
2013 Review				
Bourne et al., 1993[188] NA	Based on pedigree/pattern of inheritance	1601	Mean age, years: 47 (range 17 to 79)	Unclear duration 4 years
Hermsen et al., 2007[198] NA	Based on BRCA status	883 n=683 *BRCA1* , 200 *BRCA2* 459 for analysis of screening/compliance (data available for all screening visits)	**Median age, years** *BRCA1* : 40 (range 21 to 76) *BRCA2* : 44 (range 25 to 77)	1993 to 2005 1473 person-years

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
Ovarian cancer screening			
2013 Review			
Bourne et al., 1993[188] NA	TVUS +/ color flow imaging‡ (screening interval NR)	11 cancers diagnosed (6 screen-detected, 5 interval) 3.8% (61/1601) with positive screening result, referral to surgery False-positive cases: 55/61 referred cases (cancer detected in 6/61 referred cases) False-positive rate: 3.4% (95% CI 2.6 to 4.5%; 55/1595) **Addition of color flow imaging and criterion of morphological score ≥5 or pulsatility index <1** Retrospective addition (applied to positive ultrasound results): 15 false-positive cases Prospective addition (applied at the time of ultrasound exam): 6 false-positive cases Note: 43% of women had only one TVUS (prevalent screen).	Not reported

Appendix B Table 12. Evidence Table of Physical Harms of Intensive Screening Interventions

Author, year Quality	Surgical procedure or screening method and interval	Results	Funding source
Hermsen et al., 2007[198] NA	A) Annual serum CA-125 measurement B) Annual TVUS Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted.	15 cancers diagnosed in cohort 10 cancers diagnosed during followup 5 screen-detected **Based on 459 women with data on each visit** 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) Abnormalities were found by one or both screening modalities in 3% (38/1116) of screening visits. Overall, abnormalities were found in 9% (40/459) of women (some due to physical complaints), resulting in 26 diagnostic operations. **Benign[§] diagnostic surgery, A vs. B** 67% (4/6) vs. 100% (9/9) A+B: 55% (6/11) Note: not all benign diagnostic surgeries were done due to abnormal screen findings; some surgeries were undertaken to followup on abnormal findings from CA-125 measurement +/- TVUS done to assess symptomatic complaints.	NIHR Biomedical Research Centre at Central Manchester Foundation Trust

*Additional investigation included ultrasound +/- fine needle biopsy, or repeat mammography, or repeat MRI
†Women with BIRAD score => 3 on mammography or MRI
‡Color flow imaging applied prospectively to 600 ultrasound exams; retrospectively after a positive ultrasound result to the remainder
§Surgery for final benign diagnosis

Abbreviations: BIRADS=Breast Imaging Reporting and Data System; BMI=body mass index; BRCA=breast cancer susceptibility gene; CA-125=cancer antigen-125; CBE=clinical breast exam; CI=confidence interval; CE=contrast enhanced; FDR=first degree relative; MARIBS=Magnetic Resonance Imaging Breast Screening; MRI=magnetic resonance imaging; MRISC=Magnetic Resonance Imaging Screening Study; NA=not applicable; NIHR= National Institute for Health Research; NR=not reported; PPV=positive predictive value; PTEN=phosphatase and tensin homolog; TP53=tumor protein 53; TVUS=transvaginal ultrasound; U.K.=United Kingdom; U.S.=United States

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Mastectomy						
Current Review						
Borreani et al., 2014[187] Fair	Psychological QOL Body Image	To describe the impact of preventive options on the psychological condition of cancer-unaffected *BRCA1* or *BRCA2* carriers.	Prospective cohort	Eligible: 101* Enrolled: 27 Analzyed: 27	Italy	Cancer centers
den Heijer et al., 2012[192] NA Drawn from same population as Bresser, 2007[191]	Psychological Body image	To explore the course of psychological distress and body image at long-term followup (6 to 9 years) after prophylactic mastectomy and breast reconstruction (PM/BR) in women at risk for hereditary breast cancer, and to identify pre-PM risk factors for poor body image on the long-term.	Before and after	Eligible: Not reported Enrolled: 36 Analyzed: 36	The Netherlands	Family Cancer Clinica of the ErasmusMC-Daniel den Hoed Cancer Center
Gopie et al., 2013[196] NA	Sexual functioning Body image Psychological	To explore the course of body image, and of satisfaction with the sexual and partner relationship, as well as of cancer distress, and health related quality of life in women opting for BPM with immediate breast reconstruction.	Before and after	Eligible: 73 Enrolled: 50 Analyzed: 50	The Netherlands	Academic and regional hospitals
Isern et al., 2008[199] Fair	Psychological	To investigate long-term results of aesthetic outcome, patient satisfaction, health-related quality of life and complication rates among women undergoing prophylactic mastectomy and immediate breast reconstruction in a single institution.	Retrospective cohort	Eligible: Not reported Enrolled: 28 Analyzed: 28	Sweden	Malmo University Hospital

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Mastectomy			
Current Review			
Borreani et al., 2014[187] Fair	Mean age, years: 39.4 (SD 9)	Inclusion: Women who received a positive result of a deleterious mutations in *BRCA1* and/or *BRCA2,* seen at 1 of 3 cancer centers Exclusion: The study included women with cancer, but reported results separately, so we did not include women with cancer.	*BRCA 1/2* mutation carriers
den Heijer et al., 2012[192] NA Drawn from same population as Bresser, 2007[191]	Mean age, years: 40.1 (7.7) Breast cancer history: 33% (12/36) Ovarian cancer history: 3% (1/36) P(B)SO: 47% (17/36)	Inclusion: Women who had participated in PREVOM-B (Bresser, 2007)[227] had not developed a new cancer or recurrent cancer since enrollment in the PREVOM-B study, and still were in followup at the family cancer clinic. Exclusion: Not reported	All women came from families with an apparent autosomal dominant transmission pattern, and therefore had an associated elevated risk of breast/ovarian cancer.

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Gopie et al., 2013[196] NA	Mean age at time of BPM, years: 37.1 (SD 10.2) PBSO: 22.9% (11/50)	Inclusion: Healthy, unaffected women at significantly increased risk of breast cancer due to a BRCA mutation or relevant family history who had opted for BPM with immediate breast reconstruction Exclusion: Suspicion of breast cancer in the planning towards BPM and a detection of breast cancer in the followup, and not being able to understand and speak the Dutch language sufficiently	Unclear, had to either have *BRCA1/2* mutation or relevant family history
Isern et al., 2008[199] Fair	Median age, years: 38 (range: 25 to 51) Median age at followup, years: 40	Inclusion: Otherwise healthy women with an increased risk of developing breast cancer who underwent prophylactic mastectomy and immediate reconstruction. Exclusion: Not reported	Mutation carriers or belonging to families with a dominant inheritance of a greatly increased risk of breast cancer.

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Mastectomy				
Current Review				
Borreani et al., 2014[187] Fair	74.1% (20/27) *BRCAI* 25.9% (7/27) *BRCA2*	Hospital Anxiety and Depression Scale (HADS, both anxiety and depression scales 0 to 21) Breast Cancer Worry Scale (scale 6 to 24) Medical Outcomes Study Short Form Health Survey 12-item (MOS SF-12, scale 0 to 100) Adapted Digital Body Photo Test (scale unclear) Satisfaction measured with three questions not described	A) Surveillance B) Surgery (PBM and/or PBSO)	November 2008 to June 2010 15 months
den Heijer et al., 2012[192] NA Drawn from same population as Bresser, 2007[191]	75% (27/36) *BRCA 1/2* mutation carriers	Body Image Scale (BIS, general body image scale 5 to 25 and breast related body image scale 2 to 10) Hospital Anxiety and Depression Scale (HADS, both anxiety and depression scales 0 to 21) Impact of Events Scale (IES, intrusion scale 0 to 35 and avoidance scale 0 to 40)	RRM with reconstruction	August 1999 to February 2003 Duration: 9 years
Gopie et al., 2013[196] NA	88% (44/50) *BRCA 1/2* mutation carriers	Body Image Scale (BIS, scale 1 to 5) Dutch Relationship Questionnaire, Nederlandse Relatie Vragenlijst (NRV, sexuality subscale 0 to 12) Impact of Events Scale (IES, scale 0 to 75) Dutch version of the 36-item Short-Form Health Survey (SF-36, Physical Component Summary [PCS] and Mental Component Summary [MCS] subscales 0 to 100)	RRM with reconstruction	December 2007 to May 2010 Mean duration 21.7 months (range: 12 to 35 months)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Isern et al., 2008[199] Fair	Not reported for women without cancer only	Hospital Anxiety and Depression Scale (HADS, each subscale 0 to 15) Short Form 36 Health Survey Questionnaire (SF-36, scale 0 to 100)	A) RRM with reconstruction B) Age-matched reference group who did not undergo RRM	1995 to November 2003 Duration: NR

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
Current Review			
Borreani et al., 2014[187] Fair	**Surveillance (n=19) vs. Surgery (n=8)** Mean HADS-anxiety score (difference from baseline): 7.21 (-0.05, 95% CI -1.09 to 0.98) vs. 6.38 (-0.12, 95% CI -2.04 to 1.79) Mean HADS-depression score (difference from baseline): 5.37 (0.37, 95% CI -0.91 to 1.65) vs. 4.5 (0.00, 95% CI -2.75 to 2.75) Mean breast cancer worry scale score (difference from baseline): 5.47 (-0.11, 95% CI -0.70 to 0.49) vs. 4.75 (-2.75, 95% CI -5.15 to -0.35) Mean ovarian cancer worry scale score (difference from baseline): 4.79 (-0.16, 95% CI -0.83 to 0.51) vs. 4.13 (-2.38, 95% CI -5.20 to 0.45) Mean physical QOL score (difference from baseline): 53.66 (-0.69, 95% CI -1.96 to 0.60) vs. 52.43 (-2.80, 95% CI -6.42 to 0.82) Mean psychological QOL score (difference from baseline): 47.17 (0.20, 95% CI -4.41 to 4.81) vs. 6.14 (-0.21, 95% CI -2.28 to 1.85) Mean overall aesthetic satisfaction score (difference from baseline): 6.99 (0.04, 95% CI -0.28 to 0.37) vs. 6.48 (-0.29, 95% CI -1.24 to 0.66) Mean breast aesthetic satisfaction score (difference from baseline): 6.88 (-0.03, 95% CI -1.04 to 0.97) vs. 6.14 (-0.21, 95% CI -2.28 to 1.85) Mean choice satisfaction: 3.84 vs. 4.38	Women who chose surveillance and surgery had average levels of anxiety and depression and neither group was above the 8 point threshold. Breast cancer worry decreased in both groups over time, but was only statistically significant for women who chose surgery. QOL decreased in both groups, but was not statistically significant. Women were satisfied with their overall aesthetic and breast aesthetic.	Italian Cancer League
den Heijer et al., 2012[192] NA Drawn from same population as Bresser, 2007[191]	**2-4 weeks before surgery (T0) vs. 6 months after (T1) vs. 6-9 years after surgery (T2)** Mean general distress: 9.91 vs. 7.45 vs. 6.58, p=0.03 for T0 vs. T1 and p=0.01 for T1 vs. T2 Mean breast cancer specific distress: 22.7 vs. 12.9 vs. 6.1, p=0.01 for both T0 vs. T1 and T1 vs. T2 Mean general body image: 10.7 vs. 12.4 vs. 11.7, p=0.01 for T0 vs. T1 and NS for T1 vs. T2 Mean breast related body image: 5.0 vs. 6.7 vs. 5.9, p=0.01 for T0 vs. T1 and p=0.03 for T1 vs. T2	Psychological distress decreases after RRSO with breast reconstruction.	Grant from the Dutch Cancer Society (KWF EMC 2006-3468)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Results	Conclusions	Funding source
Gopie et al., 2013[196] NA	**Before BPM (T0) vs. 6 months after (T1) vs. 12 months after (T2)** Mean BIS: 3.8 vs. 3.3 vs. 3.5, p<0.001 for T0 vs. T1 and p=0.06 for T0 vs. T2 Mean NRV: 9.0 vs. 8.5 vs. 8.0, p=0.07 for T0 vs. T1 and p=0.06 for T0 vs. T2 Mean IES: 23 vs. 12 vs. 13, p<0.001 for T0 vs. T1 and T0 vs. T2 Mean SF-36 PCS: 55 vs. 48 vs. 53, p<0.001 for T0 vs. T1 and p=0.37 for T0 vs. T2 Mean SF-36 MCS: 48 vs. 51 vs. 50, p=0.02 for T0 vs. T1 and p=0.19 for T0 vs. T2	BPM with immediate breast reconstruction was associated with adverse impact on body image, but satisfaction with sexual relationship did not significantly change over time.	Dutch Cancer Society (UL 2007-3726)
Isern et al., 2008[199] Fair	Women without previous breast cancer scored higher on all aspects of the SF-36 vs. the reference group, but was only statistically significant for physical functioning (p<0.0001), vitality (p=0.042), and social functioning (p=0.007). No significant differences found between *BRCA 1/2* mutation carriers vs. noncarriers or between women with or without previous cancer on HADS, actual data not provided.	SF-36 scores were high in women after surgery, suggesting PM and reconstruction had no negative effect on both physical and psychological issues. Also, anxiety and depression scores were not significant on HADS, suggesting no increase in anxiety or depression among patients.	Not reported

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Mastectomy						
Current Review						
Stefanek et al., 1995[211] Poor	Psychological	To examine the factors related to making a decision about prophylactic mastectomy among women attending a high-risk clinic for breast cancer who chose prophylactic mastectomy compared with women who chose breast surveillance without surgery.	Cohort	Eligible: Not reported Enrolled: 164 Analyzed: 164 (14 cases; 150 controls)	U.S.	Breast Surveillance Services of the Johns Hopkins Oncology Center
2013 Review						
Brandberg et al., 2008[190] Brandberg et al., 2012[189] NA	Sexual functioning Psychological	To prospectively evaluate body image, sexuality, emotional reactions, and quality of life in a sample of women having increased risk for breast cancer before RRM, and 6 months and 1 year after.	Before and after	Eligible: Not reported Enrolled: 90 Analyzed: 65	Sweden	Karolinska University Hospital

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Mastectomy			
Current Review			
Stefanek et al., 1995[211] Poor	Mean age, years: 37.8 (SD 9, range 18 to 70)	Inclusion: Women with ≥1 first-degree relative diagnosed with breast cancer during the period of January 1988 to November 1992 Exclusion: Not reported	Unclear, had ≥1 first-degree relative diagnosed with breast cancer
2013 Review			
Brandberg et al., 2008[190] Brandberg et al., 2012[189] NA	**Age, years** 20-29: 8% (7/90) 30-39: 37% (33/90) 40-49: 39% (35/90) 50-59: 14% (13/90) 60-69: 2% (2/90)	Inclusion: Women how had RRM including reconstruction. Exclusion: Women with a breast cancer diagnosis.	Lifetime risk definition not described 50% lifetime risk: 28.9% (26/90) 25% lifetime risk: 8.9% (8/90)

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Mastectomy				
Current Review				
Stefanek et al., 1995[211] Poor	Not reported	Center for Epidemiologic Studies-Depression (CES-D, scale 0 to 60) Questionnaire assessing satisfaction with PM (5-point Likert type scale, 1=not at all satisfied; 5= very much satisfied) Rating scale of worry (7-items on 7-point Likert type scale; 1=not a problem at all; 7=severe problem)	A) PM B) Surveillance only	January 1988 to November 1992 Mean 9.4 months (SD 6.8, range 6 to 30)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
2013 Review				
Brandberg et al., 2008[190] Brandberg et al., 2012[189] NA	41.1% (37/90) *BRCA* 1 14.4% (13/90) *BRCA* 2 2.2% (2/90) unknown mutation	Body Image Scale (BIS, scale 0 to 30) Hospital Anxiety and Depression Scale (HAD, subscales 0 to 21) Impact on areas of life measures Sexuality Activity Questionnaire (SAQ, pleasure subscale 0 to 18, discomfort subscale 0 to 6, and habit subscale 0 to 3) Swedish Short Term-36 Health Survey (SF-36, subscales 0 to 100)	RRM with reconstruction	October 1997 to December 2005 1 year

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
Current Review			
Stefanek et al., 1995[211] Poor	**A vs. B** Worry of at least moderate problem: 86% (12/14) vs. 60% (90/150), p<0.001 **Satisfaction with PM (n=14)** Very much: 71% (10/14) Little to somewhat: 14% (2/14) Not at all: 14% (2/14) None of the patients had CES-D scores indicative of clinical depression.	Women were satisfied with their decision to undergo surgery, but they did have higher levels of worry than women undergoing suerveillance, which may be why they chose to undergo surgery.	Not reported
2013 Review			
Brandberg et al., 2008[190] Brandberg et al., 2012[189] NA	**Mean scales (SE), before RRM vs. 6 months after RRM vs. 1 year after RRM** HAD-A: 5.59 (0.55) vs. 3.80 (0.55) vs. 3.83 (0.52); p=0.0004 HAD-D: 2.53 (0.39) vs. 1.93 (0.31) vs. 1.98 (0.36); p=NS SAQ, pleasure subscale: 12.82 (0.62) vs. 12.21 (0.66) vs. 11.18 (0.56); p=0.005 SAQ, discomfort subscale: 0.56 (0.15) vs. 0.53 (0.20) vs. 0.81 (0.19); p=NS SAQ, habit subscale: 0.94 (0.06) vs. 0.82 (0.08) vs. 0.82 (0.08); p=NS Bodily pain as reported by SF-36: 81.0 (2.98) vs. 80.7 (2.84) vs. 82.6 (3.29); p=NS NS difference over time on any portion of Impact on areas of life measures, any portion of BIS, and any subscales of SF-36.	Anxiety decreased after surgery, while sexual pleasure increased. All other measures did not change over time.	Swedish Cancer Society, the Swedish Association for Cancer and Traffic Victims, and the Stockholm County Council

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Mastectomy						
2013 Review						
Gahm et al., 2010[195] NA	Sexual functioning QOL Pain	To analyze the physical effects and to report effects on sexual functioning and health-related quality of life at least 2 years after RRM.	Cross-sectional	Eligible: Not reported Enrolled: 1784 (59 with RRM and 1725 included as reference sample)	Sweden	Karolinska University Hospital

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Mastectomy			
2013 Review			
Gahm et al., 2010[195] NA	Mean age, years: 40 (range 25 to 65)	Inclusion: Women with increased risk for breast cancer, who had undergone RRM and immediate breast reconstruction Exclusion: Personal history of breast cancer	Not reported

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Mastectomy				
2013 Review				
Gahm et al., 2010[195] NA	Not reported	Decision Regret Scale (DRS, scale NR) Pain and discomfort questionnaire (subscales 1 to 7) Sexuality questionnaire Swedish Short Term-36 Health Survey (SF-36, subscales 0 to 100)	A) RRM with reconstruction B) Reference comparison group who did not undergo RRM	2004 to 2006 Mean followup, months: 29 (range 24 to 49)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	*Results*	*Conclusions*	*Funding source*
Mastectomy			
2013 Review			
Gahm et al., 2010[195] NA	**Mean SF-36 subscales (estimated from graph), A vs. B** Physical functioning: 94 vs. 89; p=NS Role functioning: 86 vs. 85; p=NS Bodily pain: 87 vs. 72; p=0.002 General health: 79 vs. 77; p=NS Vitality: 68 vs. 68; p=NS Social functioning: 90 vs. 89; p=NS Role emotional: 80 vs. 85; p=NS Mental health: 80 vs. 80; p=NS **Pain and discomfort questionnaire responses after RRM** 69% (38/55) pain in breasts 36% (20/55) pain affected sleep 22% (12/55) pain affected daily activities 71% (39/55) discomfort in breasts 87% (48/55) pain or discomfort in breasts No association between pain and age (OR 0.99, p=0.771); pain and complication (OR 0.60, p=0.538); or pain and re-operation (OR 3.72, p=0.110) Pain or discomfort not related with negative effects in sexual outcomes (p>0.05 for both) **Post operative complications** 18.6% (11/59) had infections 5.1% (3/59) required implant extraction 6.8% (4/59) had hematoma 3.4% (2/59) required acute operative evacuation 3.4% (2/59) had revision of flap necrosis 59% (35/59) had corrective surgical procedures 41% (24/59) had procedure involving implant pockets	Women who underwent RRM had less bodily pain than the reference group, but no other differences on the SF=36. Most women who underwent RRM experienced pain, discomfort, and decrease in sexual enjoyment, attractiveness, and enjoyment. However, almost all women felt the choice was a good one and would make the same decision.	None

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Mastectomy						
2013 Review						
Metcalfe et al., 2004[205] NA	Sexual functioning Psychological	To assess psychosocial functioning in a population-based series of women who have previously undergone RRM in a specified time period.	Case-series	Eligible: 122 Enrolled: 75 Analyzed: 60	Canada	Ontario hospitals in The Central East Health Information Partnership

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Mastectomy			
2013 Review			
Metcalfe et al., 2004[205] NA	Mean age at time of surgery, years: 43.5 (SD 7.8) Mean age at time of questionnaire, years: 47.8 (SD 8.6)	Inclusion: Women who underwent a RRM at an Ontario hospital and returned the questionnaire Exclusion: Prior or current diagnosis of invasive or in situ breast cancer	Strong family history: had either one 1st degree relative or two 2nd degree relatives with any of the following: 1) breast cancer diagnosed <50 years; 2) ovarian cancer; or 3) male breast cancer (55.0% of population, also did not have genetic testing done) Limited family history: none of the above (23.3% of population, also did not have genetic testing done)

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Mastectomy				
2013 Review				
Metcalfe et al., 2004[205] NA	21.7% had *BRCA1/2* mutation	Body Image after Breast Cancer (BIBC, each subscale 1 to 5) Brief Symptom Inventory (BSI, scale 0 to 100) Impact of Events Scale (IES, IES-I subscale 0 to 35 and IES-A subscale 0 to 40) Sexual activity questionnaire (pleasure subscale 0 to 18, discomfort subscale 0 to 6, habit subscale 0 to 3)	RRM 88.3% (53/60) total 11.7% (7/60) subcutaneous	January 1991 to June 2000 Mean time between surgery and questionnaire, months: 52.2 (SD 32.3)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
2013 Review			
Metcalfe et al., 2004[205] NA	97% were satisfied or extremely satisfied with decision to undergo RRM **Mean scales (SD) for whole group after RRM** IES-I: 8.44 (8.11); 7.0% (4/57) scored above clinical cut-off, of these all (100%) had a strong family history of breast cancer and 75% (3/4) had a mother who died from breast cancer IES-A: 8.79 (8.53); 8.8% (5/57) scored above clinical cut-off, 60% (3/5) had a strong family history of breast cancer, 20% (1/5) had a BRCA mutation, and 20% (1/5) had a mother who died of breast cancer Sexual activity, pleasure: 12.25 (4.72) Sexual activity, discomfort: 1.97 (2.13) Sexual activity, habit: 1.22 (0.66) BIBC, vulnerability: 2.43 (0.81) BIBC, body concerns: 3.09 (0.99) BIBC, body stigma: 2.33 (0.89) BIBC, transparency: 2.19 (0.79) **Mean scales (SD), age <50 years vs. ≥50 years** IES-I: 9.07 (8.57) vs. 6.31 (6.10); p=NS IES-A: 8.61 (9.03) vs. 9.38 (6.85); p=NS Sexual activity, pleasure: 12.75 (4.70) vs. 10.25 (4.56); p=NS Sexual activity, discomfort: 1.78 (2.12) vs. 2.88 (2.03); p=NS Sexual activity, habit: 1.18 (0.64) vs. 1.42 (0.79); p=NS BIBC, vulnerability: 2.38 (0.80) vs. 2.60 (0.87); p=NS BIBC, body concerns: 3.12 (1.03) vs. 2.99 (0.86); p=NS BIBC, body stigma: 2.27 (0.91) vs. 2.52 (0.81); p=NS BIBC, transparency: 2.26 (0.86) vs. 1.97 (0.46); p=NS **Post surgical symptoms** 64.4% (38) of women reported post surgical symptoms: Numbness (27), pain (7), tingling (7), infection (7), swelling (2), breast hardness (2), bleeding (1), organizing hematoma (1), failed reconstruction (1), breathing complications (1), thrombosis (1), pulmonary embolism (1) 18 women reported only 1 symptoms, 15 women reported having had 2 symptoms and 5 women reported having 3 symptoms as a result of surgery. No difference in reporting of post- surgical symptoms based on time elapsed since mastectomy.	Most women were happy with their decision to undergo RRM. For most women the surgery did not cause high levels of distress and there was no correlation with age.	Not reported

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Mastectomy						
2013 Review						
Wasteson et al., 2011[212] NA	Risk perception Psychological	To evaluate the long-term physical and psychological consequences of RRM in after 10 years.	Case-series	Eligible: Not reported Enrolled: 15 Analyzed: 13	Sweden	Women at Karolinska University Hospital enrolled in retrospective study.
Mastectomy vs. Oophorectomy						
Current Review						
Bresser et al., 2007[191] Fair	Psychological	To examine whether PM and/or PSO would cause major psychological distress.	Retrospective cohort	Eligible: Not reported Enrolled: 78 Analyzed: 78	The Netherlands	Family Cancer Clinica of the ErasmusMC-Daniel den Hoed Cancer Center *Reference group was from MRISC study*
Michelsen et al., 2009[206] NA	QOL Fatigue	To investigate quality of life (QoL) and fatigue in a sample of women who had RRSO for increase cancer risk and to compare the findings with those of age-matched controls from the general population.	Cross-sectional	Eligible: Not reported Enrolled: 301 Analyzed: 205 (without cancer)	Norway	Stavanger University Hospital, Ulleval University Hospital, or the Norwegian Radium Hospital

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Mastectomy			
2013 Review			
Wasteson et al., 2011[212] NA	Mean age, years: 45 (range 40 to 57)	Inclusion: Women enrolled in previous retrospective study of RRM with reconstruction, agreed to participate 10 years later Exclusion: Not reported	Either BRCA positive or 25% to 40% life-time risk of breast cancer according to Mendelian laws and the estimated penetrance of the *BRCA1* and *BRCA2* mutations, or to Claus tables
Mastectomy vs. Oophorectomy			
Current Review			
Bresser et al., 2007[191] Fair	Mean age, years: 43 (SD 8.6) History of breast cancer: 35% (27/78) History of ovarian cancer: 1% (1/78)	Inclusion: High-risk women who decided to undergo PM and/or PSO as risk reducing procedure, with no signs or suspicion of breast/ovarian cancer should be present in unaffected women at pre-surgical examination (physical and imaging examination, plus CA-125 analysis) performed within 3 months prior to surgery. Women with a history of breast/ovarian cancer were to have no signs of recurrent	All women came from families with an apparent autosomal dominant transmission pattern, and therefore had an associated elevated risk of breast/ovarian cancer.

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
		disease or a new primary breast or ovarian cancer after physical and imaging/dissemination examination consisting of mammography, gynecological ultrasound, chest X-ray, ultrasound liver, bone scan, liver- function tests, and CA-125/CA-153 analysis also performed within 3 months prior to surgery. *Reference group:* Women with comparable increased risks, but opting for regular screening (MRISC study). Exclusion: Not reported	
Michelsen et al., 2009[206] NA	Not reported separately for women without breast cancer	Inclusion: Women who had undergone RRSO for being either carriers of BRCA 1/2 mutations or belonging to hereditary breast-ovarian cancer families without identified mutation based on genetic counseling and/or testing at the Norwegian Radium Hospital Reference group: Women drawn from public address lists, age-representative sample of the Norwegian female population aged 20 to 79 years Exclusion: Not reported	Unclear, had to either have BRCA 1/2 mutation or belonging to hereditary breast-ovarian cancer families without identified mutation

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Mastectomy				
2013 Review				
Wasteson et al., 2011[212] NA	23.1% (3/13) BRCA positive by 10 year followup	Semi-structured interviews focused on experiences related to RRM with reconstruction	RRM with reconstruction	Years: not reported Median 10 years (range 9 to 12)
Mastectomy vs. Oophorectomy				
Current Review				
Bresser et al., 2007[191] Fair	69% (54/78) *BRCA1/2* mutation carriers	Hospital Anxiety and Depression Scale (HADS, both anxiety and depression scales 0 to 21) Impact of Events Scale (IES, intrusion scale 0 to 35 and avoidance scale 0 to 40)	A) PM (n=52) B) PSO (n=26)	August 1999 to February 2003 1 year
Michelsen et al., 2009[206] NA	19% (56/301) BRCA1/2 mutation carriers, of whole population	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30, each subscale 0 to 100) Fatigue Questionnaire (FQ, physical and mental subscales and total score scale) Hospital Anxiety and Depression Scale (HADS, both anxiety and depression scales 0 to 21)	RRSO	1991 to 2006 Mean 5.3 years (SD 3.1)

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Results	Conclusions	Funding source
Mastectomy			
2013 Review			
Wasteson et al., 2011[212] NA	**Affects 10 years after RRM with reconstruction** 61.5% (8/13) stated family life unchanged 30.8% (4/13) stated positive affect on family life 38.5% (5/13) stated negative affect on relationship with spouse (due to decreased sensation and changed body appearance) 76.9% (10/13) considered cosmetic results positive 90.9% (10/11) had discussed breast cancer risk with daughters	Most women stated positive affects 10 years after RRM with reconstruction.	Not reported
Mastectomy vs. Oophorectomy			
Current Review			
Bresser et al., 2007[191] Fair	**A vs. B on HADS anxiety scale (SD)** Mean at 6 months after surgery: 4.6 (3.8) vs. 5.3 (3.7) Mean at 12 months after surgery: 4.5 (3.1) vs. 5.1 (3.5), p=0.003 for time X intervention Scored above cutoff at 6 months: 18% (9/52) vs. 19% (5/26) Scored above cutoff at 12 months: 10% (5/52) vs. 19% (5/26) **A vs. B on HADS depression scale (SD)** Mean at 6 months after surgery: 3.0 (3.1) vs. 3.0 (2.6), NS Mean at 12 months after surgery: 3.3 (2.9) vs. 3.0 (2.3), NS Scored above cutoff at 6 months: 8% (4/52) vs. 4% (1/26) Scored above cutoff at 12 months: 6% (3/52) vs. 4% (1/26) **A vs. B on IES intrusion scale (SD)** Mean at 6 months after surgery: 6.7 (7.1) vs. 6.6 (6.4) Mean at 12 months after surgery: 7.2 (7.2) vs. 7.9 (7.2), NS Scored above cutoff at 6 months: 22% (11/52) vs. 15% (4/26) Scored above cutoff at 12 months: 19% (10/52) vs. 27% (7/26) **A vs. B on IES avoidance scale (SD)** Mean at 6 months after surgery: 7.2 (8.4) vs. 8.0 (8.8) Mean at 12 months after surgery: 5.6 (7.0) vs. 6.7 (7.2), p=0.002 for time X intervention Scored above cutoff at 6 months: 20% (10/52) vs. 41% (11/26) Scored above cutoff at 12 months: 20% (10/52) vs. 22% (6/26)	Most women who undergo PM and/or PSO do not develop major emotional distress.	Grant from the Netherlands' Organization for Health Research and Development (OG98-003)
Michelsen et al., 2009[206] NA	**Mean score (SD) for cancer negative women who underwent RRSO** EORTC QLQ-C30 physical functioning subscale: 90.0 (15.6) EORTC QLQ-C30 role functioning subscale: 86.5 (24.6) EORTC QLQ-C30 emotional functioning subscale: 83.3 (17.6) EORTC QLQ-C30 cognitive functioning subscale: 86.0 (16.7) EORTC QLQ-C30 social functioning subscale: 86.1 (20.9) EORTC QLQ-C30 overall QOL: 75.5 (22.0) FQ-physical fatigue subscale: 7.9 (2.9) FQ-mental fatigue subscale: 4.4 (1.2) FQ-total fatigue: 12.3 (3.7), 13% (27/205) diagnosed with chronic fatigue	Women unaffected by cancer had high levels of QOL and fatigue.	Not reported

Appendix B Table 13. Evidence Table of Psychological and Sexual Functioning Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Purpose	Study type	N	Country	Population and setting
Oophorectomy						
2013 Review						
Finch et al., 2011[194] NA	Sexual functioning	To examine the impact of RRSO on menopausal symptoms and sexual functioning among women who carry a *BRCA 1/2* mutation.	Case-series	Eligible: Not reported Enrolled: 67	Canada	University Health Network

Author, year Quality	Demographics	Inclusion and Exclusion criteria	Risk level definition
Oophorectomy			
2013 Review			
Finch et al., 2011[194] NA	Not reported separately for women without breast cancer	Inclusion: Women aged 30 to 70 years at time of surgery, who underwent RRSO Exclusion: Diagnosed with occult cancer at surgery or with breast cancer during the 1 year followup period	High-risk due to positive genetic mutation

Author, year Quality	Mutation status	Measures	Interventions	Duration of followup
Oophorectomy				
2013 Review				
Finch et al., 2011[194] NA	*BRCA1* or *BRCA2* positive	Menopause-Specific Quality of Life-Intervention (MENQOL, scale NR) Sexual Activity Questionnaire (scale NR)	RRSO	October 2002 to June 2008 1 year

Author, year Quality	Results	Conclusions	Funding source
Oophorectomy			
2013 Review			
Finch et al., 2011[194] NA	Women experienced a significant worsening of vasomotor symptoms ($p<0.01$) and a decrease in sexual function ($p<0.05$)	Women had worse vasomotor symptoms and decrease in sexual functioning.	Toronto Fashion Show, the Kristi Piia Callum Memorial Fellowship in Ovarian Cancer Research, and the University of Toronto Open Fellowship

*The study only reported the overall number enrolled, so this number includes women with cancer and those without cancer

Abbreviations: BIBC=body Image after Breast Cancer; BIS=body Image Scale; BPM=bilateral prophylactic mastectomy; BR=breast reconstruction; BRCA=breast cancer susceptibility gene; BSI=Brief Symptom Inventory; CES-D=Center for Epidemiological Studies Depression scale; DRS=Decision Regret Scale; EORTC QLC-C30=European Organization for Research and
Treatment of Cancer Quality of Life Questionnaire-C30; FQ=Fatigue Questionnaire; HADS=Hospital Anxiety and Depression Scale; IES=Impact of Events Scale; MCS=Mental Component Summary; MENQOL=Menopause-Specific Quality of Life-Intervention; MRISC-B study=Magnetic Resonance Imaging Screening for Breast Cancer study; NA=not

applicable; NR=not reported; NRV=Nederlandse Relatie Vragenlijst; NS=not significant; OR=odds ratio; PBSO=prophylactic bilateral salpingo-oophorectomy; PCS=Physical Component Summary; PM=prophylactic mastectomy; PREVOM-B=study on the psychological impact of prophylactic surgery; PSO=prophylactic salpingo-oophorectomy; QOL=quality of life; RRM=risk-reducing mastectomy; RRSO=risk-reducing salpingo-oophorectomy; SAQ=Sexual Activity Questionnaire; SD=standard deviation; SE=standard error; SF-36=Short Form 36 Health Survey; U.S.=United States

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Mastectomy				
Current Review				
Alamouti et al., 2015[185] Poor	Surgical complications	Retrospective cohort, one-arm	U.K. All patients undergoing RRM with immediate reconstruction from 2007 to 2012 by a single surgeon	Inclusion: women with BRCA mutations Exclusion: known diagnosis of metastatic breast and/or ovarian cancer or significant comorbidities
Arver et al., 2011[186] Fair	Surgical complications	Retrospective cohort, one-arm	Sweden All Swedish women with BPM performed between 1995 and 2005, with increased risk but no personal history of breast cancer	Inclusion: Women with increased hereditary risk of breast cancer undergoing BPM between 1995 and 2005; previous ovarian cancer allowed Exclusion: Previous breast malignancy
Gopie et al., 2013[196] NA	Surgical complications	Before and after	The Netherlands Academic and regional hospitals	Inclusion: Healthy, unaffected women at significantly increased risk of breast cancer due to a BRCA mutation or relevant family history who had opted for BPM with immediate breast reconstruction Exclusion: Suspicion of breast cancer in the planning towards BPM and a detection of breast cancer in the followup, and not being able to understand and speak the Dutch language sufficiently

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Mastectomy				
Current Review				
Alamouti et al., 2015[185] Poor	BRCA mutation	Enrolled: 91 RRM: 66 Therapeutic: 25	Mean age, years: 42.9	Surgery from July 2007 to July 2012, retrospective study (patients invited to participate after surgery)
Arver et al., 2011[186] Fair	Included women divided into 6 risk categories: *BRCA1* carriers; *BRCA2* carriers; women with ≥ 3 relatives with breast or ovarian cancer, unknown mutation; women from an HBOC family without a proven *BRCA* mutation ("50% risk carriers"); women with < 3 affected relatives and Claus ≥ 30% risk; and women with <3 affected relatives and Claus < 30% risk.	Enrolled: 223 Analyzed for complications: 223 *BRCA1:* 43.9% (98/223) *BRCA2:* 13.9% (31/223)	Median age at BPM, years: 40.0 (range 25 to 67)	Surgery 1995 to 2005, followup through 2008 Mean 6.6 years (range 2.1 to 14.0) 1468 person-years
Gopie et al., 2013[196] NA	Unclear, had to either have *BRCA 1/2* mutation or relevant family history	Eligible: 73 Enrolled: 50 Analyzed: 50	Mean age at time of BPM, years: 37.1 (SD 10.2) PBSO: 22.9% (11/50)	Surgery December 2007 to May 2010 Mean followup, months: 21.7 (range 12 to 35)

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Surgical procedure	Results	Funding source
Mastectomy			
Current Review			
Alamouti et al., 2015[185] Poor	Risk-reducing mastectomy with immediate reconstruction performed in one operative episode	Complications of autologous reconstruction: 7.7% (4/52) complete or partial flap failure Complications of implant-based reconstruction: 5.1% (2/39) red breast syndrome (erythema along inferior pole of breast)	NR
Arver et al., 2011[186] Fair	A) Bilateral prophylactic mastectomy (all) B) BPM with implant reconstruction: 93.3% (208/223) C) BPM with flap (autologous tissue) reconstruction: 5.4% (12/223) D) BPM with no reconstruction: 1.3% (3/223)	A) Early complications (≤ 30 days): 51.6% (115/223) Partial skin necrosis or epidermolysis: 29.9% (63/211), patients with flap reconstruction excluded Wound infection: 17.0% (38/223) Other complications, occurring in < 10% of patients: hematoma, seroma, wound rupture, blood loss with transfusion, deep venous thrombosis, pneumothorax, pneumonia, fall trauma, and urinary tract infection Late wound infection (>30 days): 9.9% (22/223) B) Implant complications: 29.8% (62/208) Capsular contracture requiring surgery: 13.9% (29/208) Implant loss due to infection/necrosis: 10.1% (21/208) Other complications, occurring in <10% of patients: implant rupture, expander port leakage C) Flap-related complications: 58.3% (7/12) Partial or complete flap failure: 41.7% (5/12) Reoperation due to anastomotic failure: 33.3% (4/12) Donor site infection/necrosis: 25.0% (3/12)	Stockholm County Council, Karolinska Institutet *[sic]* , Cancer Society in Stockholm, and the Johan & Jakob Söderberg Foundation
Gopie et al., 2013[196] NA	RRM with reconstruction	24% (12/50) reported severe postoperative complications leading to an unfinished result or removal of the primary breast mound reconstruction.	Dutch Cancer Society (UL 2007- 3726)

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Mastectomy				
Current Review				
Heemskerk-Gerritsen et al., 2007[197] Fair	Surgical complications	Retrospective and prospective cohort, one- arm	The Netherlands Women with increased familial or genetic predisposition to breast cancer undergoing prophylactic mastectomy between 1994 and 2004 and/or followup at one site	Inclusion: All women at increased risk of hereditary BC who underwent prophylactic bilateral or contralateral mastectomy ± PBSO between January 1, 1994 and December 31, 2004 Exclusion: Women from families with specific BRCA mutations who did not carry those mutations
Nurudeen et al., 2017[207] Fair	Surgical complications	Retrospective cohort	U.S. BRCA carriers undergoing mastectomy from 1997 to 2013 in a single healthcare system in Boston	Inclusion: BRCA mutation undergoing mastectomy with reconstruction (risk-reducing or therapeutic, reported separately), Exclusion: patients receiving postmastectomy radiation, or reconstruction not considered implant and/or autologous

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Mastectomy				
Current Review				
Heemskerk- Gerritsen et al., 2007[197] Fair	Women with either a proven *BRCA1/2* mutation or a genetic susceptibility (50% risk carriers from an HBOC family).	Enrolled with no history of breast cancer: 177 *BRCA1/2* : 145 HBOC: 32	Median age at PM, years *BRCA1/2:* 36.0 (range 22 to 65) HBOC: 38.5 (range 28 to 55)	Surgery 1994 to 2004 Median followup, years *BRCA1/2:* 4.4 HBOC: 4.7
Nurudeen et al., 2017[207] Fair	BRCA mutation	RRM: 104 *BRCA1*: 59 *BRCA2*: 45	Median age at RRM, years: 41.1 (range 21 to 64.6)	Surgery 1997 to 2013 (retrospective)

Author, year Quality	Surgical procedure	Results	Funding source
Mastectomy			
Current Review			
Heemskerk- Gerritsen et al., 2007[197] Fair	Prophylactic bilateral mastectomy: 177 unaffected women PM with breast reconstruction: 166 With PBSO before, at, or after PM: 83 Without PBSO: 62	Women with complications after breast reconstruction: 49% (82/166) Total number of complications: 127 Early complications (<6 weeks after reconstruction): 33% (42/127) Surgery due to early complications: 36% (15/42) Infection: 19% (8/42) Necrosis: 26% (11/42) Bleeding: 48% (20/42) Other complications, occurring in < 10% of patients: prosthesis luxation, poor arterial inflow, pneumothorax Late complications (>6 weeks after reconstruction): 67% (85/127)	Not reported

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Surgical procedure	Results	Funding source
		Surgery due to late complications: 87% (74/85) Capsular formation: 36% (31/85) Poor cosmetic result: 36% (31/85) Dog ear: 19% (16/85) Other complications, occurring in <10% of patients: infection, necrosis, prosthesis luxation	
Nurudeen et al., 2017[207] Fair	Bilateral prophylactic mastectomy, or contralateral prophylactic mastectomy in patients with previous unilateral therapeutic mastectomy	Any complication: 69.3% (n's NR) Complications requiring surgery (some patients may have had more than one complication): 26.0% (27/104) Skin necrosis: 10.6% (11/104) Other complications, rate <10% of patients: infection, seroma, hematoma, implant removal Unexpected revisions: 56.7% (59/104); 59 patients had one or more unplanned surgical procedures to complete reconstruction beyond expected stages of reconstruction	Reported as none

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Mastectomy				
2013 Review				
Brandberg, et al., 2008[190] Brandberg, et al., 2012[189] NA	Sexual functioning Psychological	Before and after	Sweden Karolinska University Hospital	Inclusion: Women how had RRM including reconstruction. Exclusion: Women with a breast cancer diagnosis.
Gahm et al., 2010[195] NA	Pain	Cross-sectional	Sweden Karolinska University Hospital	Inclusion: Women with increased risk for breast cancer, who had undergone RRM and immediate breast reconstruction Exclusion: Personal history of breast cancer

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Mastectomy				
2013 Review				
Brandberg, et al., 2008[190] Brandberg, et al., 2012[189] NA	Lifetime risk definition not described 50% lifetime risk: 28.9% (26/90) 25% lifetime risk:8.9% (8/90)	Eligible: Not reported Enrolled: 90 Analyzed: 65	**Age, years** 20 to 29: 8% (7/90) 30 to 39: 37% (33/90) 40 to 49: 39% (35/90) 50 to 59: 14% (13/90) 60 to 69: 2% (2/90)	October 1997 to December 2005 1 year
Gahm et al., 2010[195] NA	Not reported	Eligible: Not reported Enrolled: 1784 (59 with RRM and 1725 included as reference sample)	Mean age, years: 40 (range 25 to 65)	2004 to 2006 Mean followup, months: 29 (range 24 to 49)

Author, year Quality	Surgical procedure	Results	Funding source
Mastectomy			
2013 Review			
Brandberg, et al., 2008[190] Brandberg, et al., 2012[189] NA	RRM with reconstruction	**Mean scales (SE), before RRM vs. 6 months after RRM vs. 1 year after RRM** SAQ, discomfort subscale: 0.56 (0.15) vs. 0.53 (0.20) vs. 0.81 (0.19); p=NS Bodily pain as reported by SF-36: 81.0 (2.98) vs. 80.7 (2.84) vs. 82.6 (3.29); p=NS	Swedish Cancer Society, the Swedish Association for Cancer and Traffic Victims, and the Stockholm County Council
Gahm et al., 2010[195] NA	A) RRM with reconstruction B) Reference comparison group who did not undergo RRM	**Pain and discomfort questionnaire responses after RRM, A vs. B** 69% (38/55) pain in breasts 36% (20/55) pain affected sleep 22% (12/55) pain affected daily activities 71% (39/55) discomfort in breasts 87% (48/55) pain or discomfort in breasts	None

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Surgical procedure	Results	Funding source
		No association between pain and age (OR 0.99, p=0.771); pain and complication (OR 0.60, p=0.538); or pain and re-operation (OR 3.72, p=0.110) Pain or discomfort not related with negative effects in sexual outcomes (p>0.05 for both) **Post operative complications** 18.6% (11/59) had infections 5.1% (3/59) required implant extraction 6.8% (4/59) had hematoma 3.4% (2/59) required acute operative evacuation 3.4% (2/59) had revision of flap necrosis 59% (35/59) had corrective surgical procedures 41% (24/59) had procedure involving implant pockets	

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Sub-category	Study design	Country/ population/ setting	Inclusion/exclusion criteria
Mastectomy				
2013 Review				
Metcalfe et al., 2004[205] NA	Sexual functioning Psychological	Case-series	Canada Ontario hospitals in The Central East Health Information Partnership	Inclusion: Women who underwent a RRM at an Ontario hospital and returned the questionnaire Exclusion: Prior or current diagnosis of invasive or in situ breast cancer
Oophorectomy or salpingo-oophorectomy				
Current Review				
Kenkhuis et al., 2010[200] Good	Surgical complications	Retrospective cohort, one-arm (data from medical record)	The Netherlands Women with increased familial or genetic predisposition to breast and/or ovarian cancer undergoing RRSO between 1995 and 2006 at one site	Inclusion: Women at increased risk of developing breast and/or ovarian cancer, either with a *BRCA1/2* mutation or from an HBOC family, who elected RRSO Exclusion: Previous ovarian cancer diagnosis

Author, year Quality	Risk level definition	N	Demographics	Duration/followup
Mastectomy				
2013 Review				
Metcalfe et al., 2004[205] NA	Strong family history: had either one 1st degree relative or two 2nd degree relatives with any of the following: 1) breast cancer diagnosed <50 years; 2) ovarian cancer; or 3) male breast cancer (55.0% of population, also did not have genetic testing done) Limited family history: none of the above (23.3% of population, also did not have genetic testing done)	Eligible: 122 Enrolled: 75 Analyzed: 60	Mean age at time of surgery, years: 43.5 (SD 7.8) Mean age at time of questionnaire , years: 47.8 (SD 8.6)	January 1991 to June 2000 Mean time between surgery and questionnaire, months: 52.2 (SD 32.3)
Oophorectomy or salpingo-oophorectomy				
Current Review				
Kenkhuis et al., 2010[200] Good	*BRCA1* or *BRCA2* mutation or at high risk from an HBOC family without detectable mutation	Enrolled: 179 Analyzed: 159 *BRCA1:* 61% (97/159) *BRCA2:* 20.1% (32/159) HBOC: 18.9% (30/159)	Median age at RRSO, years: 43.8 (range 30.3 to 68.7)	Enrolled 1995 to 2006 Followup visit 6 weeks after surgery

Appendix B Table 14. Evidence Table of Harms of Risk-Reducing Surgery

Author, year Quality	Surgical procedure	Results	Funding source
Mastectomy			
2013 Review			
Metcalfe et al., 2004[205] NA	RRM Total: 88.3% (53/60) Subcutaneous: 11.7% (7/60)	**Post surgical symptoms** 38 (64.4%) of women reported post surgical symptoms: numbness(27), pain(7), tingling(7), infection (7), swelling(2), breast hardness(2), bleeding(1), organizing hematoma(1), failed reconstruction(1), breathing complications(1), thrombosis(1), pulmonary embolism(1) 18 women reported only 1 symptoms, 15 women reported having had 2 symptoms and 5 women reported having 3 symptoms as a result of surgery. No difference in reporting of post-surgical symptoms based on time elapsed since mastectomy.	Not reported
Oophorectomy or salpingo-oophorectomy			
Current Review			
Kenkhuis et al., 2010[200] Good	Risk-reducing salpingo-oophorectomy: 159 women with surgery at study site and medical records available Primary laparoscopy: 96.9% (154/159) Primary laparotomy: 3.1% (5/159) Laparoscopy converted to laparotomy due to complication: 0.6% (1/159) RRSO combined with breast surgery: 16.4% (26/159)	**Intraoperative complications:** 1.3% (2/159) Broken needle (minor): 0.6% (1/159) Bleeding (<500cm3) (major) 0.6% (1/159) **Post-operative complications (within 6 weeks):** 3.1% (5/159) Excessive pain (minor): 0.6% (1/159) Wound infection (minor): 1.3% (2/159) Hematoma (minor): 1.3% (2/159)	Reported as none Authors at the University of Groningen

Abbreviations: BC=breast cancer; BPM=bilateral prophylactic mastectomy; BRCA=breast cancer susceptibility gene; cm=centimeter; HBOC=hereditary breast and ovarian cancer; NA=not applicable; NR=not reported; NS=not significant; OR=odds ratio; PBSO=prophylactic bilateral salpingo-oophorectomy; PM=prophylactic mastectomy; RRM=risk-reducing mastectomy; RRSO=risk-reducing salpingo-oophorectomy

Appendix C1. Familial Risk Assessment Methods

Ontario Family History Assessment Tool (FHAT)[118, 121-123]

Referral with score ≥10 corresponds to doubling of lifetime risk for breast cancer (22%)

Risk Factor		Points
Breast and ovarian cancer	Mother Sibling 2/3rd degree relative	10 7 5
Breast cancer relatives	Parent Sibling 2/3rd degree Male relative (add to above)	4 3 2 2
Breast cancer characteristics	Onset age 20-29 Onset age 30-39 Onset age 40-49 Pre (peri) menopausal Bilateral/multifocal	6 4 2 2 3
Ovarian cancer relatives	Mother Sibling 2/3rd degree relative	7 4 3
Ovarian cancer onset age	<40 40-60 >60	6 4 2
Prostate cancer onset	Age <50	1
Colon cancer onset	Age <50	1
Family Total	Referral	≥10

Appendix C1. Familial Risk Assessment Methods

Manchester Scoring System (MSS)[111, 113, 116, 121-123]

Risk Factor (age of onset for relative in direct lineage)	*BRCA 1* Score	*BRCA 2* Score
Female breast cancer		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1
Male breast cancer		
<60	5*	8†
≥60	5*	5†
Ovarian cancer		
<60	8	5
≥60	5	5
Pancreatic cancer		
Pancreatic cancer	0	1
Prostate cancer		
<60	0	2
≥60	0	1
Total individual genes	10	10
Total for combined=15		

Probability of ≥10% chance of *BRCA1* or *BRCA2* mutation individually or combined

Abbreviation: BRCA=breast cancer susceptibility gene

*If *BRCA 2* tested.

†If *BRCA 1* tested.

Appendix C1. Familial Risk Assessment Methods

Referral Screening Tool (RST)[114]

History of breast or ovarian cancer in the family? If yes, complete checklist.

Risk Factor	Breast cancer age ≤50	Ovarian cancer at any age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 on the same side of the family		
Male breast cancer at any age in any relative		
Jewish ancestry		

Referral if ≥2 checks in table

Appendix C1. Familial Risk Assessment Methods

Pedigree Assessment Tool (PAT)[119,124]

Risk Factor	Score for every family member with breast or ovarian cancer diagnosis, including 2nd/3rd degree
Breast cancer at age ≥50	3
Breast cancer at age <50	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4
Total	

Score ≥8 is the optimal referral threshold

Seven-question Family History Screening (FHS-7)[112]

Number	Questions
1.	Did any of your 1st degree relatives have breast *or* ovarian cancer?
2.	Did any of your relatives have bilateral breast cancer?
3.	Did any man in your family have breast cancer?
4.	Did any woman in your family have breast *and* ovarian cancer?
5.	Did any woman in your family have breast cancer before the age of 50 years?
6.	Do you have 2 or more relatives with breast *and/or* ovarian cancer?
7.	Do you have 2 or more relatives with breast *and/or* bowel cancer?

One positive response initiates referral

International Breast Cancer Intervention Study Model (IBIS)[117]

Number	Risk Factor
1.	Personal history: current age, age at menopause, menarche, childbirth history, menopausal status, use of menopausal hormone therapy.
2.	Personal breast history, breast density (optional), prior breast biopsy, history of cancer (breast or ovarian), genetic testing.
3.	Ashkenazi inheritance
4.	Family history (genetic risk) – relatives with breast or ovarian cancer, age at diagnosis, genetic testing.