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Abstract

Evaluation of mammographic surveillance services in women aged 40–49 years with a moderate family history of breast cancer: a single-arm cohort study

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Background: Women with a significant family history of breast cancer are often offered more intensive and earlier surveillance than is offered to the general population in the National Breast Screening Programme. Up to now, this strategy has not been fully evaluated.

Objective: To evaluate the benefit of mammographic surveillance for women aged 40–49 years at moderate risk of breast cancer due to family history. The study is referred to as FH01.

Design: This was a single-arm cohort study with recruitment taking place between January 2003 and February 2007. Recruits were women aged <50 years with a family history of breast or ovarian cancer conferring at least a 3% risk of breast cancer between ages 40 and 49 years. The women were offered annual mammography for at least 5 years and observed for the occurrence of breast cancer during the surveillance period. The age group 40–44 years was targeted so that they would still be aged <50 years after 5 years of surveillance.

Setting: Seventy-four surveillance centres in England, Wales, Scotland and Northern Ireland.

Participants: A total of 6710 women, 94% of whom were aged <45 years at recruitment, with a family history of breast cancer estimated to imply at least a 3% risk of the disease between the ages of 40 and 50 years.

Interventions: Annual mammography for at least 5 years.

Main outcome measures: The primary study end point was the predicted risk of death from breast cancer as estimated from the size, lymph node status and grade of the tumours diagnosed. This was compared with the control group from the UK Breast Screening Age Trial (Age Trial), adjusting for the different underlying incidence in the two populations.

Results: As of December 2010, there were 165 breast cancers diagnosed in 37,025 person-years of observation and 30,556 mammographic screening episodes. Of these, 122 (74%) were diagnosed at screening. The cancers included 44 (27%) cases of ductal carcinoma in situ. There were 19 predicted deaths in 37,025 person-years in FH01, with an estimated incidence of 6.3 per 1000 per year. The corresponding figures for the Age Trial control group were 204 predicted deaths in 622,127 person-years and an incidence of 2.4 per 1000 per year. This gave an estimated 40% reduction in breast cancer mortality (relative risk = 0.60; 95% confidence interval 0.37 to 0.98; $p = 0.04$).

Conclusions: Annual mammography in women aged 40–49 years with a significant family history of breast or ovarian cancer is both clinically effective in reducing breast cancer mortality and cost-effective. There is a need to further standardise familial risk assessment, to research the impact of digital mammography and to clarify the role of breast density in this population.

Trial registration: National Research Register N0484114809.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 17, No. 11. See the HTA programme website for further project information.

Contents

List of abbreviations xi

Executive summary xiii

Chapter 1 Background to and evolution of FH01 1
The historical situation 1
Conception of FH01 2
Timelines 3

Chapter 2 Design, planned analysis and study size 5
Basic design and end points 5
Study size 6
Planned statistical analyses 7
Recruitment 9
The comparison populations 10

Chapter 3 Baseline characteristics of the recruited population and the Age Trial comparison population 13
Demographic and risk-factor data 13
Projected breast cancer risk in FH01 and in the Age Trial 16

Chapter 4 Surveillance activity and outcomes 17
Mammography episodes 17
Percutaneous and surgical biopsies 18
Radiation exposure 18
Comparison with the National Health Service Breast Screening Programme standards 18

Chapter 5 Cancers diagnosed, end points and efficacy 21
Cancers diagnosed 21
Comparison with the Age Trial and Dutch series and estimated efficacy of the surveillance 23
Internal estimation of the mortality effect using Markov modelling 24
Economic evaluation 26
Withdrawals 29
Discussion and implications 30

Chapter 6 Radiology and pathology reviews 35
Introduction 35
Radiology review 35
Pathology review 37

Chapter 7 Follow-up data 41
Follow-up questionnaire 41
Results 41

Chapter 8 Related studies **45**
Psychological impact of mammography screening for women under 50 years with a family history of breast cancer 45
FH01 blood study 45
FH02 46

Chapter 9 Implications of the results **47**
Implications for care policy 47
Implications for research 48
Overall conclusion 49

Acknowledgements **51**

References **55**

Appendix 1 Protocol of FH01 **61**

Appendix 2 FH01 blood study protocol **75**

Appendix 3 Information sheet used in England and Wales for potential FH01 recruits **85**

Appendix 4 Information sheet for primary care staff **89**

Appendix 5 Data proformas **91**

List of abbreviations

Age Trial	UK Breast Screening Age Trial
BASO	British Association of Surgeons in Oncology
BRCA1	breast cancer type 1 gene
BRCA2	breast cancer type 2 gene
CI	confidence interval
DCIS	ductal carcinoma in situ
HRT	hormone replacement therapy
ICER	incremental cost-effectiveness ratio
MGD	mean glandular dose
MRI	magnetic resonance imaging
NHSBSP	National Health Service Breast Screening Programme
NPI	Nottingham Prognostic Index
OR	odds ratio
PIMMS	Psychological Impact of maMMography Screening for women under 50 with a family history of breast cancer
POSH	Prospective study of Outcomes in Sporadic and Hereditary breast cancer
QALY	quality-adjusted life-year
RR	relative risk
SD	standard deviation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

For the last two decades, there has been a perceived need to evaluate the benefit of mammographic surveillance for young women at moderate risk of breast cancer due to family history.

Objectives

We planned to evaluate the policy of annual mammography in women aged 40–49 years with a significant family history of breast or ovarian cancer. The major questions were 'What is the likely effect of the surveillance on future mortality from breast cancer?' and 'At what cost is this effect on mortality achieved?'. The study is referred to as FH01.

Methods

In FH01, we recruited 6710 women between the ages of 40 and 50 years with an estimated personal risk of at least 3%. Women were recruited in 74 surveillance centres from England, Wales, Scotland and Northern Ireland. The women were offered annual mammography for at least 5 years. The age group 40–44 years was targeted so that they would still be aged <50 years after 5 years of surveillance. This was a single-arm cohort study with recruitment taking place between January 2003 and February 2007. The primary study end point was the predicted risk of death from breast cancer as estimated from the size, lymph node status and grade of the tumours diagnosed. The 10-year deaths were estimated using the Nottingham Prognostic Index. The predicted mortality was compared with that of the control group from the UK Breast Screening Age Trial (Age Trial), adjusting for the different underlying incidence in the two populations. In addition, we compared the predicted mortality with a Dutch series of tumours from a similar risk group with ours, and carried out an internal estimation of the predicted mortality over 20 years using Markov process models.

Results

As of December 2010, there were 165 breast cancers diagnosed in 37,025 person-years of observation and 30,556 mammographic screening episodes. Recall rates for assessment were 8% at prevalence screens and 6% at incidence screens. Cancer detection rates were 5 per 1000 at prevalence screens and 4 per 1000 at incidence screens. Of these, 122 (74%) were diagnosed at screening, 39 (24%) were interval cancers and 4 (2%) were diagnosed in non-attenders (symptomatic diagnosis after failure to attend for the most recent screen offered). The cancers included 44 (26%) cases of ductal carcinoma in situ. Cancers in FH01 were significantly smaller ($p = 0.004$), less likely to be node positive ($p = 0.003$) and of a more favourable histological grade ($p = 0.002$) than the Age Trial control patients. There were 24 predicted deaths in 37,025 person-years in FH01, with an estimated incidence of 6.3 per 1000 per year. The corresponding figures for the Age Trial control group were 204 predicted deaths in 622,127 person-years and an incidence of 2.4 per 1000 per year. This gave an estimated 40% reduction in breast cancer mortality [relative risk = 0.60; 95% confidence interval (CI) 0.37 to 0.98; $p = 0.04$]. This was achieved with recall rates, preoperative diagnosis rates and radiation doses, which would be acceptable in the National Health Service Breast Screening Programme. The Markov model results indicated a 31–34% reduction in future breast cancer mortality over 20 years, and 320–357 life-years saved (256–286 years after quality

adjustment). Depending on assumptions, estimated costs ranged from £4435 (95% CI £3426 to £6234) to £5450 (95% CI £4154 to £7878) per quality-adjusted life-year saved.

Conclusions

Annual mammographic surveillance in women aged 40–49 years with an increased familial risk of breast cancer is likely to bring about a substantial reduction in mortality from breast cancer and to be cost-effective. There is a need to further standardise familial risk assessment, to research the impact of digital mammography and to clarify the role of breast density in this population.

Trial registration

This study is registered as National Research Register N0484114809.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background to and evolution of FH01

The historical situation

In the late 1980s, the UK National Health Service Breast Screening Programme (NHSBSP) was instituted.[1] In the first instance it offered mammography every 3 years to women aged 50–64 years. The lower age limit was based on trial results suggesting a greater impact in women aged >50 years. The age range has since expanded to 50–70 years, and is in the process of further expansion to 47–73 years.

In the 1990s, there was considerable controversy about the benefit of breast screening with mammography in women aged 40–49 years.[2,3] There was evidence that the intervention in this age group could confer a reduction in mortality from breast cancer,[4] but with the following qualifications. First, the benefit was more difficult to achieve because of radiologically denser breast tissue and more rapid progression of tumours in younger women. Secondly, owing to the much lower incidence of breast cancer in women aged 40–49 years than in women aged >50 years, the absolute benefit was likely to be markedly lower than that achieved by screening older women.

At the same time, discovery of high-risk gene mutations and the generally increased level of awareness of breast cancer was leading to a growing body of women concerned about their risk of breast cancer because of diagnosis of the disease among their relatives.[5–7]

Risk triage based on family history was already becoming common practice in the late 1990s and early 2000s.[8] There is a large population with a family history which does not increase risk substantially above that of the general female population. For this population, no particular intervention is indicated. There is also a very small population with a high-risk mutation identified in the family or with such a strong family history as to have a serious probability of a mutation. For these women, magnetic resonance imaging (MRI) surveillance was under investigation during the late 1990s and early 2000s.[9,10] Potential surgical interventions were also options, including prophylactic mastectomy and prophylactic oophorectomy.[11,12]

There is a third population of intermediate risk, whose family history is sufficiently strong as to confer a level of individual risk around three times the risk of the general population, but not sufficiently strong as to give rise to suspicion of a high-risk gene mutation. For this population, towards the end of the last century, it was not clear what the appropriate management strategy should be, but one option was to offer mammographic surveillance at an earlier age and a greater frequency (usually annually, but in some centres biennially) than that provided by the NHSBSP.[13,14] This service was already being provided in a non-standardised and sporadic fashion, and in the early 2000s it remained unevaluated.

A survey of British Association of Surgeons in Oncology (BASO) breast units indicated that 96% of units offered regular mammography to women aged <50 years with a family history, but 12% of these had no written inclusion criteria. Practice varied considerably around the country. There was, however, evidence that screening in this group could achieve at least the same detection capability as in the NHSBSP, with detection rates at screening almost double the interval cancer rates.[13]

Contemporaneously, the science and technology of individual risk prediction was progressing rapidly.[15–17] There was now a serious possibility of a standardised surveillance service for family history subjects below the NHSBSP age, with rigorous inclusion criteria based on familial risk.

Conception of FH01

Against this background, there was considerable interest in the early years of the twenty-first century in the evaluation of mammographic surveillance of women aged <50 years with a family history of breast cancer. The ultimate aim of screening asymptomatic women for breast cancer is to prevent deaths from the disease by the mechanism of detection at an early stage when treatment is more likely to be curative.[18] The ideal evaluation design would be a randomised trial in which one group is randomised to the offer of surveillance and the other to usual care, with death from breast cancer as end point.[4,18]

There were a number of circumstances mitigating against this strategy. First, with survival from breast cancer having improved markedly throughout the 1990s, a trial based on mortality would need very large numbers, a very long follow-up or both. Power calculations indicated that such a randomised trial would require approximately 30,000 subjects followed up for 15 years. In the meantime, many centres would continue to provide the mammographic surveillance service, unevaluated, as it was perceived as prudent clinical practice. It was clear that a more rapid and economically viable evaluation was necessary.

Secondly, a feasibility study including a survey of breast units revealed a distinct lack of equipoise on the part of the clinicians providing breast services. The consensus was that randomly allocating a substantial proportion of the population to no surveillance would be clinically imprudent. There was also a prevailing opinion that with the clear mortality reduction in women aged >50 years in the randomised trials,[19] and the evidence for a slightly weaker but still worthwhile benefit in women aged 40–49 years,[2,4] it was no great leap of faith to expect a similar benefit in younger women with a family history.

As a result of the lack of equipoise it was evident that we could not design an evaluation in which part of the population received no surveillance at all. Suggested randomised designs included a comparison of annual with 3-yearly mammography and a trial of mammography compared with clinical breast examination. These were considered, but were not adopted, on the basis that the question of interest at the time was 'Does mammographic surveillance save lives in women aged <50 years at enhanced familial risk, in comparison with no surveillance?'.

This left the study team with a difficult design problem. However, some time previously Professor Howard Cuckle had proposed a single-arm evaluation based on quality measures of screening, a positive result being defined as achieving realisations of these measures similar to those in the intervention arms of the randomised trials. This was taken as a basis for the design of the study, hereafter referred to as FH01, but there was a perceived need for an evaluation which gave an estimate of the intervention's effect on the clinical outcome, breast cancer mortality.

This in turn necessitated resolving two further issues: first, how to estimate the future breast cancer mortality in the cohort since, as mentioned above, it would take many years to accrue large numbers of breast cancer deaths; second, how to estimate the future breast cancer mortality if the surveillance had not taken place. For the first of these, it had already been observed and validated that the pathological characteristics size, node status and grade of breast cancers were excellent predictors of death from the disease.[20,21] Thus, it would be possible to predict the numbers of breast cancer deaths from the tumour data. This has two advantages: first, the end point is observable at the time of diagnosis, long in advance of the time of death; and, second, with the standard error dependent on all cancers, not only fatal ones, the statistical power is greater.

As for the second question, an external comparison group was indicated. After considerable thought, it was decided that the main comparison group would be the control group in the UK Breast Screening Age Trial (Age Trial),[22] as this population was of similar age to the putative FH01 cohort, and was not undergoing surveillance. It was appreciated that the comparison would have to be adjusted for the differing risk profiles of the two populations: the Age Trial recruits would be from the general female

population, whereas the FH01 cohort would be at enhanced familial risk. The development of individual risk prediction models meant that this was a practicable option.[15–17]

This gave rise to one further problem of design and research ethics. In order to make the adjustment for the different risk profiles, we needed risk-factor data on the Age Trial population. Because of the prevailing ethics and governance environment at the time the Age Trial was initiated, the controls had never been contacted and did not necessarily know that they were in a screening trial. Contacting them at the start of FH01 to elicit risk factor information on breast cancer was not considered practical and might not survive ethical scrutiny. However, as part of an epidemiological study under way, the required risk factor information was available from a subset of the Age Trial intervention group. Since randomisation would be expected to render the intervention and control groups comparable with respect to risk factors, this was considered sufficient for purposes of adjusting comparisons for underlying risk.

A final consideration was that the aim was to evaluate rather than change current practice. We did stipulate that annual mammographic surveillance was the target for our evaluation, so that some centres offering 2-yearly surveillance could not participate without changing, but aside from that, the design was non-prescriptive, with the following basic features:

- a single cohort of women at moderately increased risk due to family history of breast cancer
- annual mammography for 5 years
- ideally aged 40–44 years at recruitment, so that they would still be aged <50 years after 5 years
- end points of the size, node status and grade of the tumours diagnosed, plus the expected future breast cancer mortality based on these tumour features; and
- comparison of these end points with the Age Trial control group, adjusted for underlying risk.

Timelines

Detailed design of the study is reported in *Chapter 2*. The study began on 1 January 2003 and was planned to end in 2009. Owing to slower recruitment than expected, the study was extended to 2010, when the predicted mortality results were published,[23] and the cohort will now be followed up for actual mortality.

Chapter 2 Design, planned analysis and study size

Basic design and end points

FH01 was designed as a single-arm cohort study (see *Appendix 1* for protocol and *Appendix 2* for protocol of the accompanying blood study). The intervention to be evaluated was annual mammography (or at any rate, with the interval not slipping beyond 18 months) for 5 years. We targeted women aged 40–44 years at recruitment so that after 5 years of mammography they would still be in the age range 40–49 years. This was to avoid arguments about 'age creep': the theory propounded about randomised trials of screening that the apparent benefits of screening in women aged 40–49 years at randomisation were actually due to screening activity taking place after the recruits had passed their 50th birthdays.[20] It should be noted that there is little empirical evidence for the phenomenon,[21,24] but it was considered prudent to head off the issue by design if possible.

It was specified that, to be eligible, women had to satisfy at least one of the following family history criteria:

- one first-degree female relative with breast cancer diagnosed at ≤40 years of age
- one first-degree female relative with bilateral breast cancer diagnosed at <50 years of age
- two first-degree or one first- and one second-degree female relative, both with breast cancer diagnosed at ≤60 years of age (same side of family)
- one first- or second-degree female relative with breast and ovarian cancer, with the first cancer diagnosed at ≤60 years of age
- three first- or second-degree female relatives with breast or ovarian cancer at any age (same side of family)
- one first-degree male relative with breast cancer at any age
- paternal history of a minimum of two second-degree relatives (father's first-degree relatives) with breast cancer at ≤50 years of age, or one with breast cancer at ≤50 years of age and an ovarian cancer (any age), or paternal uncle/grandfather with breast cancer at <50 years of age.

A first-degree female relative is defined as mother, sister or daughter. A second-degree female relative is defined as granddaughter, grandmother, aunt or niece. Exclusion criteria were:

- inability to give written informed consent
- pregnancy
- age <40 years
- proven breast cancer or ductal carcinoma in situ (DCIS)
- previous bilateral prophylactic mastectomy
- presence of a breast cancer type 1 (*BRCA1*) or breast cancer type 2 (*BRCA2*) mutation in the family in women who have been tested negative for the mutation.

On the basis of the inclusion criteria, the study group was anticipated to have at least a 3% probability of breast cancer between ages 40 and 49 years, inclusive. Although *BRCA1*- and *BRCA2*-positive cases were not explicitly excluded, the moderate-risk criteria implied that relatively few FH01 recruits would be *BRCA* positive.

The information sheet for potential recruits is given as *Appendix 3*. The information for primary care professionals is given in *Appendix 4*.

For reasons noted in *Chapter 1*, the primary end points were the size, node status and histological grade of tumours diagnosed and the projected mortality from these. The primary comparison group was the control group of the Age Trial. We planned to adjust the comparison for differences between the FH01 cohort and the Age Trial population in underlying risk of breast cancer. The adjustment was made by calculating the expected 10-year absolute incidence of breast cancer[17] for each population (FH01 and Age Trial controls), and dividing the projected rate of breast cancer for each group by its expected incidence. We also planned to compare the FH01 results with those from other, historical family history cohorts undergoing little or no surveillance.[25] Further details are given in *Planned statistical analyses*.

Collaborating units were expected to offer annual (or at least 18-monthly) two-view mammography and to:

(a) operate a breast cancer unit in line with the recommendations of the British Breast Group and the BASO guidelines for surgeons in the treatment of symptomatic breast disease[26]
(b) have experience in mammography in symptomatic women aged < 50 years
(c) either participate in the NHSBSP or offer mammographic services at a level consistent with the quality standards set out by the NHSBSP
(d) have a clearly defined referral line for high-risk women to a regional clinical genetics service
(e) have at least one member of the multidisciplinary team trained in pedigree construction and interpretation, and risk analysis.

Study size

We had originally designed FH01 to have the power for the same comparison of tumour attributes and the consequent expected mortality in two risk-stratified subgroups. As a result, the planned sample size at the initiation of the study was 10,000. A monitoring visit by the funding body noted that recruitment had been poor in the early years, and recommended changing the target to a more modest study size designed to have adequate power for the cohort as a whole, with no regard for subgroup analyses. For this target, assuming use of the controls in the Age Trial as a comparison group, an important planned comparison was the incidence of node-positive tumours in the FH01 cohort with that expected from the comparison group, taking into account the different underlying incidences in the two groups. From the Swedish Two-County Study controls, we would expect an unscreened tumour series in the age group 40–49 years to be node-positive in 42% of cases.[27] In the Age Trial control group, with 7 years of cancer incidence in 106,000 women,[22] we conservatively expected around 742 cancers, and therefore 311 (42%) node-positive tumours.

Results from the Two-County Study suggest a screening sensitivity of 83% and a mean sojourn time (average duration of the preclinical screen-detectable period) of 2.44 years in women aged 40–49 years.[24] This suggests that with a 1-year interval there would be 77% screen-detected cancers, of which 11% would be node positive. We assume that the interval cancers would have the same 42% node-positive cancer rate as an unscreened group, giving an overall 18% node-positive cancer rate. Thus, the comparison anticipated is between a group with 42% node-positive cancers and one with 18% node-positive cancers. This would correspond, on the basis of the relative fatality of node-positive and node-negative cancers, to long-term survival of 64% compared with 74%, with a relative risk (RR) in the FH01 cohort of 0.72. A 5-year incidence rate at around 4 per 1000 per year (due to high familial risk) would mean a total incidence of node-positive disease of 3.6 per 1000 ($0.18 \times 0.004 \times 5$). For 90% power to detect a difference in incidence of node-positive cancers of 3.6 per 1000 and 8.4 per 1000 ($0.0036 \times 0.42/0.18$) as significant, and allowing a 5% increase in standard errors as a result of adjustment for different underlying risk in the two populations, we would require 6000 women and 120 cancers. Thus, we aimed to recruit 6000 women and expected to be in a position to analyse the data and report after an average of 5 years' observation.

Planned statistical analyses

The data proforma is given in *Appendix 5*. As noted above, the primary analyses planned were the comparison of the prognostic variables tumour size, lymph node status and histological grade, and the consequent predicted breast cancer mortality, between the FH01 cohort and the Age Trial controls. Secondary comparisons with other historical data sets were anticipated. Categorical variables were compared between the FH01 tumours and comparison groups using the chi-squared test. Continuous variables were compared using the *t*-test. We calculated the Nottingham Prognostic Index (NPI) score for invasive cases as $a + b + c$, where

$a = 0.2 \times$ size in cm

$b = 1$ if node-negative, 2 if 1–3 positive nodes, 3 if ≥4 positive nodes; and

$c =$ histological grade (1, 2 or 3).

From this, we estimated the 10-year survival as shown by Blamey *et al.*,[28] who regressed 10-year survival on NPI, splitting their data set in two for cross-validation purposes. They obtained two quadratic equations for the prediction of survival from NPI, which gave very similar predictions. Here we use the average of their two equations, giving an estimate S of average 10-year per cent survival as a function of NPI, denoted N in equation (1).

$$S = -2.59N^2 + 8.74N + 90.07 \quad (1)$$

For the FH01 cohort and the Age Trial control group, we then calculated the absolute expected rate of tumours proving fatal over 10 years, and divided this in each case by the underlying risk in the two populations, calculated from family history and other risk-factor data using the absolute risk model of Tyrer *et al.*[17] The Tyrer *et al*.[17] model has been independently validated and shown to predict risk with accuracy.[29] The absolute risk was calculated directly on all of the FH01 recruits. For the Age Trial comparison group, for the ethics and governance reasons outlined in *Chapter 1*, a more indirect process had to be used. There were no risk-factor data on the Age Trial control group, and there were ethical problems with contacting members of this group to ascertain risk factors. However, in another, unrelated study, a subset of the Age Trial intervention group had undergone risk factor ascertainment. We therefore used this study population to estimate the underlying risk in the Age Trial control group, on the basis that, owing to the randomisation, the risk profiles of members of the study group would be the same as those of the control group.

Thus, we were able to calculate the RR of absolute mortality, corrected for the different risk profiles of the two populations. This was done by dividing the expected death rates by Tyrer *et al*.'s[17] independent estimates of the underlying incidence. The corrected RR was:

$$RR = \frac{\frac{d_1}{P_1 r_1}}{\frac{d_2}{P_2 r_2}} \quad (2)$$

where d_1, P_1 and r_1 are the expected deaths, person-years of observation and underlying 10-year average risk in the FH01 cohort, and d_2, P_2 and r_2 the corresponding quantities in the Age Trial control group. The numerator and denominator of the RR are simply the ratios of expected death rates from the NPI to the expected incidences based on Tyrer *et al*.'s[17] model, to adjust for the fact that the FH01 cohort has higher underlying risk than the Age Trial population. Again, note that r_1 was calculated directly from the FH01 subjects, whereas r_2 was calculated from a subgroup of 3001 members of the study group of the Age Trial. Note that the division by the expected incidence figures, r_1 and r_2, calculated from an independently

derived algorithm, is a safeguard against lead time, length bias and overdiagnosis. *Actual* incidence in the FH01 cohort would have been potentially susceptible to these biasing factors, but independently estimated incidence is not.

The variance of the logarithm of RR is:

$$\begin{aligned} V\left[\ln(RR)\right] &= V\left[\ln(d_1)-\ln(d_2)+\ln(P_2)-\ln(P_1)+\ln(r_2)-\ln(r_1)\right] \\ &= \frac{V(d_1)}{d_1^2}+\frac{1}{d_2}+\frac{V(r_1)}{r_1^2}+\frac{V(r_2)}{r_2^2} \\ &= \frac{n^2V(f)}{d_1^2}+\frac{1}{d_2}+\frac{V(r_1)}{r_1^2}+\frac{V(r_2)}{r_2^2} \end{aligned} \quad (3)$$

where f is the predicted case fatality rate from the NPI, that is, the complement of the predicted survival, and n is the number of invasive cancer cases in FH01.

The standard error of the logarithm of RR was then calculated as s, the square root of the variance and the 95% confidence interval (CI) on ln(RR) calculated as:

$$\ln(RR)\pm 1.96s \quad (4)$$

The end points of the interval were then transformed exponentially to give the 95% CI on RR.

In addition to the Age Trial controls, we also compared the FH01 results with those from a Dutch series of 238 breast cancers (all invasive) in women largely not subject to surveillance, with a family history of breast cancer and not *BRCA1* or *BRCA2* positive.[25] However, for the Dutch series, we had only published tabular results. We did not have risk-factor data on which to calculate the absolute risks and correct the comparison for these.

From the published tabular data on tumour size, node status and grade in the Dutch study, we calculated average NPI and, to be conservative, the maximum possible standard error on this consistent with the tabular data. The predicted average 10-year survival and its standard error in the Dutch study were calculated from the average NPI, using the second-order Taylor approximation.[30]

It had originally been planned to compare our results with those of a French series of tumours in women with a family history who had not been subject to mammographic surveillance. However, preliminary results suggested that geographical and temporal confounding factors were rendering the comparison unreliable, in that our results would have seemed too good to be true. For example, 62% of the tumours in the French series were of size >20 mm. We therefore abandoned this planned analysis.

One further analysis of clinical outcome was performed. From the rates of screen-detected and interval cancers by node status, we estimated the parameters of progression by node status in a Markov process. From these we estimated the cancers by node status which would have been expected to occur if the surveillance had not taken place. These were then combined with 20-year fatality rates of cancer by node status in the Swedish Two-County Trial of breast screening[27] to estimate long-term mortality from breast cancer with and without mammographic surveillance. These results were used in the health economic analysis.

Other analyses planned included summaries of screening activity and negative outcomes of the surveillance, including false-positives, benign surgery cases and radiation dose. The study was accompanied by a psychosocial evaluation, which was funded separately and has already been published in detail.[31–34] FH01 also incorporated radiology and pathology reviews, and an economic evaluation. These are also briefly reported on in the following chapters.

Recruitment

Recruitment took place between 16 January 2003 and 28 February 2007, with a total of 6710 women in the study. *Figure 1* shows recruitment over time. A number of centres remained ineligible for the study because of an ongoing policy of 2-yearly surveillance. Recruitment began slowly, but accelerated steadily. In the first year, around 600 women were recruited, in the second year, around 1200, and in each of the third and fourth years >2000. A number of measures were taken to improve recruitment during the course of the study, including expansion of the eligible centres to include Scotland and Northern Ireland, personal visits and other contacts to potentially high-recruitment centres and the institution of regional co-ordinators to take local responsibility for recruitment and data capture. Although these measures did bear fruit in terms of improved accrual, it is not clear which particular measures were the most effective. It is likely that if we had taken these measures from the study's inception, recruitment would have been considerably faster. However, the pattern of slow recruitment in the early months, gradually accelerating, is common in large population studies.

Table 1 shows recruitment by individual centre. Interestingly, Scotland, Wales and Northern Ireland contributed around 30% of recruits. Within England, major recruiting centres were the Withington Community Hospital Manchester, Nottingham City Hospital and the Jarvis Breast Screening and Diagnostic Centre, Guildford. In Wales, women were recruited in a single genetics service covering the entire country and within a single research network, although surveillance took place at three sites.

It should be noted that the slow recruitment in the first 2 years was not because of unwillingness of eligible women to participate in the study. In five centres polled, four reported that participation rates in excess of 90%, and one of 65%. The phenomenon derived from a combination of the delay in centres joining the study, largely because of ethics and governance formalities, and the fact that many centres had relatively few eligible women.

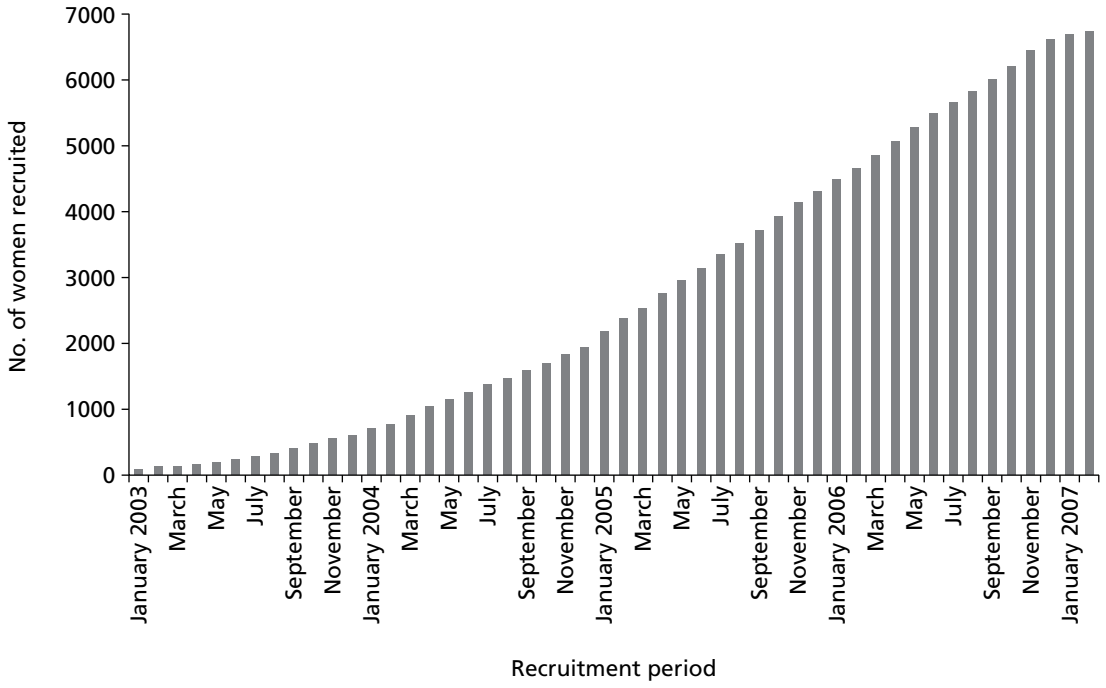


FIGURE 1 FH01 cumulative recruitment over time.

The comparison populations

The Age Trial randomised 53,890 (study group) women aged 40–42 in the general population years to invitation to annual mammography for 7 years, and 106,971 (control group) women of the same age to usual care.[22] Recruitment took place between 1991 and 1999. As noted above, our aim was to compare the pathological characteristics and the corresponding predicted 10-year mortality between the cancers diagnosed in FH01 and those diagnosed in the control group of the Age Trial, during 622,127 person-years of follow-up. Thus, our comparison group would be of similar ages to the FH01 population and would not have been offered mammographic surveillance. The group would, however, have general population risk, whereas the FH01 population would be at enhanced risk of breast cancer owing to family history. To adjust for this, we used risk-factor data on 3001 subjects within the Age Trial study group, assuming equal underlying risk between the study and the control group due to the randomisation. We estimated the 10-year probabilities of breast cancer in the Age Trial and FH01 recruits, and corrected our estimate of relative mortality for these.

The Dutch comparison series comprised 238 breast cancers in women with a family history of the disease but without a known *BRCA* mutation, during the period 1980–2004. Ages at diagnosis ranged from 25 to 77 years. The cases were from a population largely not undergoing surveillance. Thus, the Dutch series was comparable with FH01 with respect to family history, and was mostly not subject to mammography. However, the age range was much wider in the Dutch series.

TABLE 1 Final recruitment figures from each screening centre

Hospital name	Total no. of patients recruited
Aberdeen Royal Infirmary	116
Addenbrooke's Hospital	113
Airedale General Hospital	31
Ardmillan Breast Screening Centre	308
Ayr Hospital	3
Barnsley District General Hospital	40
Basildon Hospital	83
Brighton General Hospital	47
Burnley General Hospital	3
Charing Cross Hospital, London	2
City Hospital, Birmingham	62
Countess of Chester Hospital	68
Coventry and Warwickshire Hospital	71
Craigavon Area Hospital	33
Crosshouse Hospital, Kilmarnock	9
Cumberland Infirmary	3
Darlington Memorial Hospital	12
Derby City General Hospital	145
Derriford Hospital	26

TABLE 1 Final recruitment figures from each screening centre (*continued*)

Hospital name	Total no. of patients recruited
Elizabeth Garrett Anderson and Obstetrics Hospital, London	43
Frenchay Hospital	149
Glasgow Royal Infirmary	16
Guy's Hospital, London	36
Hairmyres Hospital/RAH	6
Hinchingbrooke Hospital	69
Hope Hospital	37
Ipswich Hospital	41
James Paget Hospital	7
Jarvis Screening Centre, Guildford	231
Kettering General Hospital	59
Leighton Hospital, Crewe	50
Macclesfield District General	80
Mayday Hospital, London	9
Medway Hospital	29
Milton Keynes General Hospital	7
New Cross Hospital, Wolverhampton	43
Newcastle General Hospital	103
Ninewells Hospital, Dundee	49
North Hampshire Hospital	9
Northampton General Hospital	45
Northwick Park Hospital, London	34
Nottingham City Hospital	270
Parapet Breast Screening Centre, Windsor	145
Princess Royal Hospital, Telford	73
Queen Alexandras Hospital, Portsmouth	190
Queen Elizabeth Hospital, Gateshead	6
Queen Mary Hospital, Roehampton	2
Queen Mary's Hospital, Sidcup	31
Queen's Hospital Burton	16
Royal Cornwall Hospital (Treliske)	107
Royal Devon and Exeter Hospital	94
Royal Free Hospital, London	25
Royal Liverpool Hospital	76

continued

TABLE 1 Final recruitment figures from each screening centre (*continued*)

Hospital name	Total no. of patients recruited
Royal Marsden Hospital, London	229
Royal United Hospital, Bath	181
Sandwell Hospital, Birmingham	9
Scarborough General Hospital	41
Southend Hospital	110
Southport and Formby District General Hospital	52
St Bartholomew's Hospital, London	44
St George's Hospital, London	109
St James Hospital, Leeds	100
St Mary's Hospital, London	23
Stobhill Hospital, Glasgow	30
University Hospital Aintree	31
University Hospital of North Tees	4
Victoria Infirmary, Glasgow	80
Wales	1116
West Suffolk Hospital	12
Western Infirmary, Glasgow	263
Weston-super-Mare Hospital	20
Whiston Hospital	26
Wishaw General Hospital	73
Withington Hospital	755
Worthing Hospital	40
Total	**6710**

Chapter 3 Baseline characteristics of the recruited population and the Age Trial comparison population

Demographic and risk-factor data

When considering the baseline status of the populations under study, it is as well to be reminded of the basic analysis plan. The projected analysis was as follows:

1. Obtain the pathological tumour size, lymph node status and histological grade of tumours diagnosed in FH01.
2. Obtain the same data from the Age Trial control group.
3. From each, calculate the NPI score and the consequent estimated numbers of deaths within 10 years.[28]
4. In each group, divide the expected numbers of breast cancer deaths by the corresponding person-years.
5. Calculate the average absolute predicted 10-year breast cancer incidence in each group:[17] for FH01 directly using the risk-factor data on the FH01 recruits, for the Age Trial controls using the data on 3001 Age Trial study group members.
6. Divide the rates calculated in point 4 (above) by their corresponding breast cancer incidence figures. The ratio of the resulting figures is an estimate of the relative breast cancer mortality in the two populations, corrected for their different underlying breast cancer risks.

The necessity of points 5 and 6 lends considerable importance to the risk factor status in both the FH01 and the comparison populations.

Table 2 shows the recruited FH01 population by baseline epidemiological characteristics. Of the 6710 recruits, 91% were aged between 40 and 44 years at recruitment. Owing to the eligibility criteria, there are considerably higher proportions with relatives affected with breast cancer than in the general population in this age group.

As expected, there were very few *BRCA1*- or *BRCA2*-positive recruits. For 374 subjects, there had been a test for a *BRCA1* mutation in the family, of whom 82 (1% of recruits) had a positive test. For 3546 recruits, there had been no testing in the family. For the remaining 2790 recruits, *BRCA1*-testing status in the family was unknown. For the vast majority of these subjects the mutation would not have been tested for in the family. Of the 82 recruits with a positive test in the family, 14 recruits had themselves tested positive. Similar figures apply for *BRCA2*. For 3539 recruits, there had been no testing in the family. For 284 recruits, there had been a test in the family, of which 65 cases (1%) had a positive test. Of those recruits with a positive *BRCA2* test in the family, 21 had themselves tested positive. Eight subjects were excluded on the basis of a positive mutation in the family, but a negative personal test.

Table 3 shows selected comparisons with the 3001 Age Trial recruits used for determining the baseline risk in the Age Trial control group. It should be noted that although the cancers in the Age Trial occurred in the same broad age group as in FH01, the Age Trial subjects in the subsample of 3001 were interviewed for risk factors some years after recruitment to the age trial, so that 30% of them were aged ≥50 years at the time of interview. As a result, reported menopausal status, age at menopause and hormone replacement therapy (HRT) use, were all substantially different for the Age Trial recruits (data not shown). Although the Age Trial recruits had slightly but significantly higher parity than the FH01 subjects, the most striking differences, as expected, were for family history. Almost 10 times as many FH01 subjects had an affected mother and 15 times as many an affected sister. These differences emphasise the need to adjust the mortality comparison for the different underlying risks in the two populations.

TABLE 2 Attributes of the FH01 cohort at recruitment

Factor	Category	No. (%)
Age (years)	<40	185 (3)
	40	1578 (24)
	41	1180 (17)
	42	1144 (17)
	43	1160 (17)
	44	1070 (16)
	45+	393 (6)
	Total	6710 (100)
Parity	0	1071 (17)
	1	1068 (17)
	2	2623 (41)
	3+	1586 (25)
	Not known	362
Age at first pregnancy (years)	<20	564 (11)
	20–24	1413 (28)
	25–29	1767 (34)
	30–34	981 (19)
	35+	396 (8)
	Not known/nulliparous	1589
Age at menarche (years)	<13	2592 (44)
	13+	3362 (56)
	Not known	756
Menopausal status	Premenopausal	4650 (90)
	Post/perimenopausal	492 (10)
	Not known	1568
Age at menopause (years) (if applicable)	<40	202 (63)
	40+	119 (37)
	Not known	171
HRT use	Never	4508 (93)
	Yes, now	228 (5)
	Yes, previously	119 (2)
	Not known	1855
Mother have breast cancer	No	2178 (34)
	Yes	4300 (66)
Sister have breast cancer	No	4486 (69)
	Yes	1992 (31)

TABLE 2 Attributes of the FH01 cohort at recruitment (*continued*)

Factor	Category	No. (%)
Relative with breast cancer before age 40 years?	No	3660 (57)
	Yes	2781 (43)
	Affected relative data missing	232[a]
Previous mammography?	No	1761 (28)
	Yes	4605 (72)
	Not known	344
Previous breast biopsy?	No	4320 (88)
	Yes	616 (12)
	Not known	1774

a An additional 37 individuals had age of affected relative missing.

TABLE 3 Comparison of risk factors between FH01 cohort and Age Trial recruits

Factor	Category	FH01, no. (%)	Age Trial, no. (%)	Significance
Age at menarche (years)	<13	2592 (44)	1239 (43)	$p = 0.5$
	13+	3362 (56)	1652 (57)	
Parity	0	1071 (17)	411 (14)	$p < 0.001$
	1	1068 (17)	422 (14)	
	2	2623 (41)	1475 (49)	
	3+	1586 (25)	693 (23)	
Mother have breast cancer	No	2178 (34)	2786 (93)	$p < 0.001$
	Yes	4300 (66)	215 (7)	
Sister have breast cancer	No	4486 (69)	2617 (98)	$p < 0.001$
	Yes	1992 (31)	67 (2)	

Apart from family history, we had limited risk-factor data within FH01 and, in particular, did not have weight and height data. However, since 90% of the subjects were premenopausal, this did not seriously affect the risk prediction.

Projected breast cancer risk in FH01 and in the Age Trial

As estimated from the Tyrer–Cuzick programme,[17] the average 10-year risk of the FH01 recruits was 6.3% (95% CI 6.2% to 6.4%). This is estimated to be 2.61 times the population risk for this age group. Of the 6710 recruits, 6251 (93%) were estimated to have a 10-year risk of at least 3%, as targeted by the eligibility criteria. It should be borne in mind that this 10-year risk is not for the 10 years aged 40–49 years inclusive, but for the 10 years from age at recruitment, hence the rather high cumulative risk.

The average 10-year risk of the 3001 Age Trial subjects estimated using the Tyrer–Cuzick programme[17] was 2.4% (95% CI 2.3% to 2.5%); this is estimated to be 0.96 times the population risk. As the Age Trial subjects were from the general population, this was to be anticipated.

Chapter 4 Surveillance activity and outcomes

Mammography episodes

Table 4 shows the number of prevalence and incidence surveillance episodes. For our purposes, a prevalence episode is defined as the individual's first ever screen (not necessarily the first screen within FH01), and an incidence episode any subsequent screen. There were 2068 prevalence episodes and 28,488 incidence episodes, giving a total of 30,556 screens in the study. Recall rates were 8% at prevalence episodes and 6% at incidence, with corresponding cancer detection rates of 5 per 1000 and 4 per 1000, respectively. False-positive rates were 7% and 5% at prevalence and incidence episodes, respectively.

Of the 30,556 mammographic surveillance episodes, 11,503 (38%) were accompanied by clinical breast examination and 2598 (9%) by ultrasound. Taking only those episodes where the clinical examination or ultrasound were done before knowledge of the mammogram result, to exclude those cases where the additional examination might have been prompted by the mammogram result, there was no indication of an increased detection rate from the clinical examination, but there was a result suggestive of increased detection due to ultrasound. For the 8002 episodes in which clinical examination took place before knowledge of the mammogram result, there were 33 cancers detected, almost exactly equal to the overall average of 4 per 1000. For the 400 episodes in which ultrasound examination took place before knowledge of the mammogram result, seven cancers were detected, 18 per 1000: a highly significant difference from the remaining episodes ($p = 0.001$). Being based on only seven cancers, however, this result requires confirmation in a larger data set.

One centre had to suspend surveillance for 2 years because of funding difficulties, but rejoined the study when these were resolved. All cancers from all centres are included in the analyses in later chapters on the intention-to-treat principle. Average time since last mammogram for screen-detected cases was 13 months [standard deviation (SD) 5 months]. Average time for interval cancers was also 13 months (SD 8 months). For cancers diagnosed after failure to attend most recent screen, the average time since last mammogram was 19 months (SD 5 months). Ninety-two per cent of incidence screen-detected cancers were detected at a screen within 18 months of the previous screen.

Numbers of screens attended are shown in *Table 5*. There was an average of 4.6 screens per person. Sixty per cent of subjects had five screens or more. It is likely that the 97 women (1%) for whom we have no record of mammography are a result of missing data, as it is likely that they would have had at least one mammography episode around the time of recruitment. Of the 23,943 second or subsequent screens within FH01, we had data on dates of screen and previous FH01 screen on 23,913 (99.9%) of episodes. The average interval for these was 13 months (SD 5 months). Five per cent (1263 subjects) had a longer interval than 18 months, the maximum specified in the protocol.

TABLE 4 Prevalence and incidence screens, numbers recalled for assessment and cancers detected at screening in FH01

Episode type	No. of episodes	Recall for assessment (%)	Cancers detected (no. per thousand)
Prevalence	2068	165 (8)	10 (5)
Incidence	28,488	1639 (6)	112 (4)
Total	30,556	1804 (6)	122 (4)

TABLE 5 Number of screens attended in FH01

No. of screens attended	No. of subjects (%)
0	97 (1)
1	356 (5)
2	421 (6)
3	582 (9)
4	1292 (19)
5	2153 (32)
6	1146 (17)
7	507 (8)
8	150 (2)
9	6 (<1)

Percutaneous and surgical biopsies

Of those recalled for assessment, 21% (387 out of 1804) had percutaneous biopsy (for the most part core biopsies). Of the 122 screen-detected cancers, 113 (93%) had a percutaneous biopsy and therefore a preoperative cancer diagnosis. There were 93 women who had surgery or open biopsy for what transpired to be normal or benign disease: six at prevalence screen and 87 at incidence screens. This gave a ratio of 4:3 of screen-detected cancers to benign surgery cases, and a ratio of just under 2:1 for all cancers to benign surgery cases.

Radiation exposure

We had radiation dose data from two centres on 190 women screened at least once between January 2004 and December 2010, with a total of 666 screening episodes. *Table 6* shows radiation doses experienced by these women. At the first episode, 38 (14%) women had single-view mammography. All had two-view mammography in subsequent episodes. Average doses ranged from 1.7 to 2.0 mGy for mediolateral oblique views, and from 1.5 to 1.8 mGy for craniocaudal views. The doses declined at successive episodes. Mean breast thickness was 54 mm (range 18–95 mm) for mediolateral oblique views and 50 mm (range 16–88 mm) for craniocaudal. At the first episode, 12% of women had a mean glandular dose (MGD) >2.5 mGy, declining to 5% at the fourth episode. Doses from mediolateral oblique views were more likely to exceed the standard than from craniocaudal.

Comparison with the National Health Service Breast Screening Programme standards

The standard for recall rate at prevalence screen in the NHSBSP is a rate of <10%. The achieved rate in the national programme is 8.7%[35] and in FH01 it was 8%. For incidence screens, the NHSBSP standard is a maximum of 7%, with 3.4% achieved in the NHSBSP and 6% achieved in FH01. In terms of cancer detection rates, a direct comparison is not possible, as the underlying incidence of FH01 differs from that of the general population in the target age range of the NHSBSP (although invasive and in situ cancer detection rates in FH01 do exceed the minimum NHSBSP standards for both prevalence and incidence screens). The benign biopsy rate was 2.7 per 1000, exceeding the NHSBSP standard of 2.0 per 1000. On the other hand, the preoperative diagnosis rate of screen-detected cancers was 93%, well above the national minimum standard of 80%.

TABLE 6 Mean glandular dose by screening episode in two centres in FH01

Screening episode	Mediolateral oblique views		Craniocaudal views	
	No.	MGD (mGy), mean (range)	No.	MGD (mGy), mean (range)
1	277	1.9 (0.6–6.5)	239	1.8 (0.6–5.0)
2	229	2.0 (0.8–4.8)	229	1.8 (0.9–4.4)
3	110	2.0 (0.8–4.8)	110	1.8 (0.9–5.5)
4	37	1.7 (1.1–3.2)	37	1.5 (1.0–2.8)
5	10	1.8 (1.3–2.6)	10	1.6 (1.3–2.1)
6	3	1.6 (1.3–1.8)	3	1.5 (1.3–2.0)
Overall	666	1.9 (0.8–4.4)	628	1.7 (0.6–5.0)

In our radiation dose substudy on 277 participants and 666 mammographic episodes, the vast majority of radiation doses were within the national standard of 2.5 mGy as MGD per film.[36] Possibly because of the higher breast density in this age group, a small number did exceed the national standard. Exposures were slightly lower than observed in the Age Trial.[37]

Chapter 5 Cancers diagnosed, end points and efficacy

Cancers diagnosed

In total, there were 165 cancers diagnosed in 37,025 person-years of observation, a rate of 4.45 per 1000 person-years. *Table 7* shows the cancers diagnosed in FH01 by age and mode of detection, notified to the data centre before 16 December 2010. The dates of diagnosis ranged from 19 June 2003 to 8 December 2010. The average age at diagnosis was 45 years (SD 2.2 years).

Although >90% of subjects were aged <45 years at recruitment, the majority of tumours were diagnosed after age 45 years. Overall, 122 out of 165 (74%) of the cancers were diagnosed at screening, 122 out of 161 in those actually attending, giving a programme sensitivity of 76%. In those women aged <45 years, the programme sensitivity was 78% and in those women aged ≥45 years it was 70%.

Table 8 shows the cancers by invasive status and detection mode. There were 120 (73%) invasive cancers, 44 (26%) in situ and one with invasive status unknown. The one woman with unknown invasive status was detected at an incidence screen. Almost exactly 33% of screen-detected cancers and 9% of symptomatic tumours were DCIS. Correspondingly, 81 of 120 (68%) invasive tumours and 40 out of 44 (91%) DCIS cases were screen detected.

Table 9 shows the pathological characteristics of the 120 invasive cancers, cross-classified by detection mode (screening or symptomatic). Relatively high proportions were small (42% were <15 mm in maximum diameter) and node-negative (68%). The screen-detected cancers were smaller and more likely to be node-negative than the symptomatic tumours. They were also slightly more likely to be oestrogen receptor- and progesterone receptor-positive, suggesting an element of length bias. However, the distributions of histological grade and type were very similar for screen-detected and symptomatic tumours.

TABLE 7 Cancers diagnosed in FH01 by age and detection mode

	Age group, no. (%)		
Detection mode	<45 years	45+ years	Total
Prevalence screen	9 (90)	1 (10)	10 (100)
Incidence screen	53 (47)	59 (53)	112 (100)
Interval cancer	16 (41)	23 (59)	39 (100)
Non-attender[a]	1 (25)	3 (75)	4 (100)
Total	79 (48)	86 (52)	165 (100)

a Cancer in a non-attender is defined as a cancer diagnosed symptomatically in a woman who did not attend her last scheduled surveillance episode.

TABLE 8 Cancers diagnosed in FH01 by invasive status and detection mode

Detection mode	Invasive status (%)		
	Invasive	DCIS	Total
Prevalence screen	7 (70)	3 (30)	10 (100)
Incidence screen	74 (67)	37 (33)	111 (100)
Interval cancer	36 (92)	3 (8)	39 (100)
Non-attender	3 (75)	1 (25)	4 (100)
Total	120 (73)	44 (27)	164 (100)

TABLE 9 Pathological attributes of the 120 invasive cancers

Factor	Category	Screen detected (%)	Symptomatic (%)	Total (%)
Tumour size (mm)	<15	37 (48)	12 (31)	49 (42)
	15–20	18 (23)	14 (37)	32 (28)
	21–30	17 (22)	9 (24)	26 (22)
	31–50	5 (6)	1 (3)	6 (5)
	51+	1 (1)	2 (5)	3 (3)
	NK	3	1	4
Lymph node status	Negative	55 (73)	22 (58)	77 (68)
	1–3 positive nodes	14 (19)	12 (32)	26 (23)
	4+ positive nodes	6 (8)	4 (10)	10 (9)
	NK	6	1	7
Histological grade	1	15 (19)	8 (22)	23 (20)
	2	29 (36)	13 (35)	42 (36)
	3	36 (45)	16 (43)	52 (44)
	NK	1	2	3
Histological type	Ductal	71 (90)	31 (88)	102 (90)
	Lobular	4 (5)	2 (6)	6 (5)
	Other	4 (5)	2 (6)	6 (5)
	NK	2	4	6
Oestrogen receptor status	Negative	13 (18)	10 (29)	23 (21)
	Positive	61 (82)	24 (71)	85 (79)
	NK	7	5	12
Progesterone receptor status	Negative	12 (21)	10 (34)	22 (25)
	Positive	46 (79)	19 (66)	65 (75)
	NK	23	10	33

NK, not known.

Comparison with the Age Trial and Dutch series and estimated efficacy of the surveillance

Table 10 gives the pathological attributes of the tumours diagnosed in FH01, in the Age Trial control group and in the non-*BRCA* family history cases from the Dutch study.[22,25] Invasive cancers in FH01 were significantly smaller ($p = 0.004$), less likely to be node-positive ($p = 0.003$) and of more favourable histological grade ($p = 0.002$) than the Age Trial controls. They were also significantly less likely to be node-positive than the Dutch cancers ($p = 0.005$), but did not differ significantly from the Dutch tumours in terms of size ($p = 0.2$). The grade distribution of the FH01 cancers was more favourable than that of the Dutch tumours, with borderline significance ($p = 0.05$).

Average NPI[28] score in the FH01 tumours was 3.98 (95% CI 3.76 to 4.20). This differed significantly ($p < 0.001$) from the average NPI score of 4.53 (95% CI 4.44 to 4.62) in the Age Trial controls, and from the average NPI score of 4.62 (95% CI 4.43 to 4.81) in the Dutch series ($p < 0.001$).

The predicted average 10-year survival rates from the NPI score were 84% (95% CI 81% to 87%), 73% (95% CI 71% to 75%) and 71% (95% CI 68% to 74%) for the FH01 tumours, the Age Trial control group tumours and the Dutch series, respectively.

For the absolute mortality comparison, the fatality rates (complement of the survival rates) were applied to the 120 invasive tumours in FH01 and the 755 in the Age Trial control group,[22] to give 19 and 204 expected deaths, respectively. With person-years for FH01 and the Age Trial controls of 37,025 and 622,127, respectively, and underlying 10-year average breast cancer risks from Tyrer *et al.*'s method[17] of 6.3% [standard error (SE) 0.02%] and 2.4% (SE 0.03%), we have:

$$RR = \frac{19}{37{,}025 \times 0.063} \Big/ \frac{204}{622{,}127 \times 0.024} = 0.60 \qquad (5)$$

TABLE 10 Size, node status and grade of invasive breast cancers diagnosed in FH01 and in the two comparison groups

Factor	Category	No. (%) in FH01	No. (%) in Age Trial controls[22]	No. (%) in non-*BRCA* Dutch cases[25]
Tumour size	≤20 mm	81 (70)	397 (55)	145 (63)
	>20 mm	35 (30)	321 (45)	87 (37)
	NK	4	37	6
Node status	Negative	77 (68)	306 (53)	121 (52)
	Positive	36 (32)	276 (47)	111 (48)
	NK	7	173	6
Grade	1	23 (20)	53 (8)	20 (8)
	2	42 (36)	285 (43)	56 (31)
	3	52 (44)	324 (49)	101 (61)
	NK	3	93	61
Average NPI score (95% CI)		3.98 (3.76 to 4.20)	4.53 (4.44 to 4.62)	4.62 (4.43 to 4.81)

NK, not known.

The 95% CI on RR is 0.37 to 0.98. Thus, there was a significant ($p = 0.04$) reduction in predicted mortality as a result of the surveillance in FH01. The expected number of breast cancer deaths in the absence of the surveillance is 19/0.60 = 32. Thus, we estimated that 13 breast cancer deaths were prevented as a result of 30,556 surveillance episodes and 4.3 deaths avoided per 10,000 screening episodes. Note that this figure pertains only to deaths avoided within 10 years of diagnosis, and so is conservative.

The comparison with the Dutch series would give a rather larger reduction in mortality, 45%.

Internal estimation of the mortality effect using Markov modelling

The broad strategy in internal estimation of the effect of the surveillance on mortality was to:

1. Estimate the parameters of a Markov model of disease progression by lymph node status.
2. From this, estimate the numbers of node-positive and node-negative cancers which would have been diagnosed during the surveillance period in the absence of the mammographic surveillance (comparison group).
3. Combine these with 20-year survival data by node status to estimate the year by year expected numbers of deaths in the cohort if the surveillance had not taken place.
4. Combine the observed cancers in the cohort by node status with the same survival data, to obtain the expected numbers of deaths in each year in the cancers actually observed.
5. Accumulate the differences between points 3 and 4 (above) to estimate the reduction in mortality and life-years saved as a result of the surveillance over 20 years of follow-up from diagnosis.

A number of issues arise in this activity. Firstly, we obtained conservative estimates of life-years saved by only including in the comparison group those cancers which would have arisen in the period of surveillance in our cohort in the absence of screening. Thus, we will be working with a larger number of cancers in the real FH01 cohort than in the notional comparison group because of lead time.

Our Markov model was estimated from the data on prevalence screen, incidence screen and interval cancers, as in Day and Walter.[38] We performed the estimation twice, first using only the invasive tumours with known node status, and second including DCIS and cases with nodes unknown as node-negative.

Table 11 shows the data used to estimate the parameters of the Markov model. *Table 12* shows the resulting progression parameters estimated by the two strategies. The latter can then be applied to estimate the probability of node-positive and node-negative disease in the absence of surveillance. Because the time of 'birth' of tumours into the presymptomatic phase is unknown and could predate entry to the study by several years, we follow Day and Walter[38] in approximating the inception of tumours as a uniform annual rate, but use the traditional Markov assumption of exponential rates for all other transitions. If parameters are named as in *Table 12*, the probability of breast cancer during the average 5.52 years of observation is:

$$\lambda_1 \times 5.52 \qquad (6)$$

This would equal 0.0215 in the first estimation strategy and 0.0232 in the second, giving total numbers of cancers as 144 and 156, respectively. The numbers are smaller than the 165 observed in our cohort as a result of the detection of additional cancers in FH01 because of lead time, as noted above. To be conservative, we base our estimates on these numbers of cancers, potentially inflating the estimated numbers of breast cancer deaths in our cohort.

TABLE 11 Cancers by detection mode and node status (with numbers screened), used for estimation of Markov model parameters

Detection mode	No. screened	Cancers by node status			
		Node-negative	Node-positive	DCIS	Node status unknown
Prevalence screen	2068	4	2	3	1
Incidence screen	28,488	51	18	37	6
Interval	–	20	15	3	1
Non-attender	–	2	1	1	0

TABLE 12 Estimates of transition rates from no disease to asymptomatic cancer, from node-negative to node-positive and from asymptomatic to symptomatic disease

Transition	Parameter symbol	Estimate (95% CI)	
		Strategy 1	Strategy 2
No disease to asymptomatic N–	λ_1	0.0039 (0.0037 to 0.0042)	0.0042 (0.0034 to 0.0051)
Asymptomatic N– to symptomatic N–	λ_2	0.6047 (0.4314 to 0.8477)	0.3535 (0.1026 to 1.2180)
Asymptomatic N– to asymptomatic N+	λ_3	1.0660 (0.8182 to 1.3889)	0.4015 (0.1013 to 1.5905)
Asymptomatic N+ to symptomatic N+	λ_4	1.7598 (1.0694 to 2.8959)	2.0634 (0.1084 to 39.2740)

N–, node-negative; N+, node-positive.

The expected number of node-negative cancers is:

$$\int_0^{5.52} \lambda_1 e^{-\lambda_3(5.52-x)} \int_0^{5.52-x} \lambda_2 e^{-\lambda_{2y}}\, dy\, dx \tag{7}$$

This simplifies to:

$$\frac{\lambda_1\lambda_2}{\lambda_2+\lambda_3}\left\{5.52-\frac{1-e^{-5.52(\lambda_2+\lambda_3)}}{\lambda_2+\lambda_3}\right\} \tag{8}$$

This is equal to 0.0069 under the first estimation strategy and 0.0083 under the second, yielding estimated numbers of node-negative cancers of 46 and 56, respectively. The corresponding expected numbers of node-positive cancers are calculated by subtraction as 144 – 46 = 98 and 156 – 56 = 100.

Table 13 shows the survival of 642 node-positive and 1557 node-negative tumours in the Swedish Two-County Trial,[27] by year since diagnosis, up to 20 years' follow-up. If we apply these to the numbers of node-positive and node-negative tumours in our FH01 cohort, we have 46 deaths from breast cancer expected. For the comparison group with no surveillance, we expect 67 deaths under estimation strategy 1 and 70 deaths under strategy 2. These correspond to a reduction in breast cancer mortality of between 31% and 34% and an absolute benefit of between 6.9 and 7.8 deaths prevented over 20 years of follow-up per 10,000 screening episodes. The corresponding year-on-year differences give 387 life-years saved by the surveillance under strategy 1 and 427 under strategy 2. Lagging the comparison group figures by a year's lead time would give 320 and 357 life-years saved. The combined effect of this lag, the estimated additional cancers in the FH01 cohort and the stratification by node status together give a complete and likely conservative adjustment for lead time. In terms of quality adjustment, these additional life-years saved would be spent with a diagnosis of breast cancer.

TABLE 13 Survival of node-negative and node-positive cancers in the Swedish Two-County Trial, by year since diagnosis

Time since diagnosis (years)	Survival (%)	
	Node negative	Node positive
0	100.0	100.0
1	99.8	89.7
2	99.0	79.6
3	97.5	73.7
4	96.1	69.5
5	94.8	63.7
6	93.5	60.0
7	92.7	56.6
8	91.5	54.0
9	90.1	52.1
10	89.0	50.3
11	88.1	49.0
12	87.2	47.7
13	86.5	46.1
14	85.8	45.8
15	84.7	44.2
16	83.3	43.4
17	82.4	41.9
18	81.8	41.2
19	81.3	40.3
20	81.3	40.3

Economic evaluation

Having derived the life-years saved in *Internal estimation of the mortality effect using Markov modelling*, we now:

1. tabulate the screening and diagnostic activity undergone in the study as a result of the surveillance
2. tabulate the treatment activity
3. tabulate the treatment activity by node status and apply this to the expected cancers by node status in the absence of surveillance, in point 2 above
4. cost the activities; and
5. calculate difference in costs corresponding to the life-years saved, after quality adjustment.

Table 14 shows the screening and diagnostic activity in the FH01 cohort. There were 30,554 screening episodes, generating 1803 assessment clinic visits, with the consequent investigations shown in *Table 14*. Note that we do not include primary care costs in either the FH01 cohort or the notional comparison groups. The procedures associated with screen detection were directly observed in the cohort. Since we did not have information on negative symptomatic consultations, we used data from 16,603 symptomatic

TABLE 14 Diagnostic procedures in the FH01cohort (observed for screening, estimated for symptomatic)

Detection mode	Procedure/investigation	Quantity
Screening	Screening mammography episodes	30,554
	Ultrasound at clinic	1390
	Mammography at clinic	1803
	Clinical examination at clinic	1372
	Percutaneous biopsies	411
	Open biopsies	162
Symptomatic	Ultrasound at clinic	377
	Mammography at clinic	383
	Clinical examination at clinic	577
	Percutaneous biopsies	98
	Open biopsies	5

breast clinic visits reported by Britton *et al.*[39] to estimate these. In the 16,603 symptomatic clinic visits, 1235 (7.4%) breast cancers were diagnosed, suggesting 13.44 visits for each cancer diagnosed. This would imply 578 symptomatic clinic visits in the FH01 cohort, with the numbers of procedures incurred estimated from the proportions observed by Britton *et al.*[39]

We also used the Britton *et al.*[39] data to estimate the diagnostic activity taking place in the notional comparison groups. With estimation strategy 1, we would expect 1935 clinic visits (13.44×144) and with strategy 2, 2097 (13.44×156). Corresponding expected numbers of procedures also calculated from the proportions in Britton *et al.*[39] are shown in *Table 15*. Since the diagnostic activity took place in the twenty-first century, the majority of percutaneous biopsies are likely to be core biopsies.

Table 16 shows the treatments used in the 165 cancers in FH01. Four women had no surgery recorded, possibly because diagnostic open biopsy was judged to have removed the tumour. *Table 17* shows the percentage of women by surgical and adjuvant treatment for node-negative and node-positive tumours separately. These were used to estimate the numbers receiving the various treatments in the comparison group, for the two estimation strategies (*Table 18*).

The ranges of estimated benefits in terms of life-years saved were 320–387 for estimation strategy 1 and 357–427 for estimation strategy 2. To be conservative, we used the lower points of these ranges, 320 and 357. The total cost-incurring items are shown in *Table 19*, as observed in FH01 and for the two estimation strategies for the comparison group not subject to surveillance. Note that the estimated life-years saved are all spent with breast cancer.

The costs were derived from the Department of Health's national schedule of costs for trusts and primary care trusts augmented with costs estimated from research studies where necessary.[40–45] The life-years saved were quality adjusted by a factor of 0.8 since all would be spent with a diagnosis of and with the consequences of treatment for breast cancer. Results are shown in *Table 20*. We also calculated 95% CIs on the incremental cost-effectiveness ratios (ICERs) by Monte Carlo simulation, using the dispersion data for the cost variables and assuming a normal distribution assumption. The estimated ICERs for the two estimation strategies were, respectively, £5450 (95% CI £4154 to £7878) and £4435 (95% CI £3426 to £6234) per quality-adjusted life-year (QALY) saved.[46] If we discount the future benefits achieved by 2% per annum, this would increase the ICERs by approximately 20%, giving ICERs of £6540 and £5322, respectively.

TABLE 15 Diagnostic procedures estimated in the notional comparison group

Estimation strategy	Procedure/investigation	Quantity
1 (144 cancers)	Ultrasound at clinic	1264
	Mammography at clinic	1283
	Clinical examination at clinic	1933
	Percutaneous biopsies	329
	Open biopsies	15
2 (156 cancers)	Ultrasound at clinic	1369
	Mammography at clinic	1390
	Clinical examination at clinic	2095
	Percutaneous biopsies	356
	Open biopsies	17

TABLE 16 Treatment of cancers in FH01

Treatment	Quantity
Mastectomy	65
Local excision (sometimes referred to as lumpectomy)	96
No surgery recorded	4
Radiotherapy	68
Hormone therapy (almost invariably tamoxifen)	64
Chemotherapy	57

TABLE 17 Observed percentages receiving various treatments by node status

	Per cent treated	
Treatment	Node-negative cases (includes DCIS)	Node-positive cases
Mastectomy	34	41
Local excision	63	59
No surgery	3	0
Radiotherapy	36	59
Hormone therapy	34	54
Chemotherapy	25	68

TABLE 18 Treatment of cancers in comparison group (absolute expected numbers of treatments administered)

Treatment	Strategy 1 (144 cancers)	Strategy 2 (156 cancers)
Mastectomy	56	60
Local excision	87	94
No surgery	1	2
Radiotherapy	74	79
Hormone therapy	69	73
Chemotherapy	78	82

TABLE 19 Cost incurring items observed in FH01 and estimated for the comparison group not subject to surveillance, under the two estimation strategies

Item	FH01 cohort	Comparison group estimation 1	Comparison group estimation 2
Mammograms	30554	1283	1390
Ultrasound exams	1767	1264	1369
Clinical exams	1949	1933	2095
Core biopsy	509	329	356
Open biopsy	167	15	17
Mastectomy	65	56	60
Lumpectomy	96	87	94
Radiotherapy	68	74	79
Tamoxifen	64	69	73
Chemotherapy	57	78	82

Withdrawals

Table 21 shows withdrawals or women censored from the study with reasons for withdrawal. There was a total of 165 women censored because of confirmed breast cancer and 534 (8%) withdrawals. The most common reason for withdrawal was removal from the local programme because of non-attendance (47% of withdrawals). Only 35 women withdrew because of change of genetic status (including eight with *BRCA* mutations in the family but a negative personal test) and 24 because of risk-reducing surgery.

There were six deaths from breast cancer. One woman did not receive surgery and so had no pathology data. Of the remaining five women, four were node positive at diagnosis, two were of grade 3, two were of grade 2 and one was of grade 1. Average size was 21 mm.

TABLE 20 Estimated costs in FH01 and in comparison groups in pounds sterling, and cost-effectiveness summary

Item	Unit cost/QA coefficient	Sources	Costs for groups (£)		
			FH01 cohort	Comparison group estimation 1	Comparison group estimation 2
Mammogram	47	43–45	1,436,038	60,301	65,330
Ultrasound examination	76	41, 43	134,292	96,064	104,044
Clinical examination	161	41	313,789	311,213	337,295
Core biopsy	149	42, 43, 45	75,841	49,021	53,044
Open biopsy	216	41	36,072	3240	3672
Mastectomy	7,342	41	477,230	411,152	440,520
Lumpectomy	2,023	41	194,208	176,001	190,162
Radiotherapy	2,479	45	168,572	183,446	195,841
Tamoxifen	155	45	9920	10,695	11,315
Chemotherapy	7,127	40	406,239	555,906	584,414
Total cost			3,252,201	1,857,039	1,985,637
Net cost over comparators				1,395,162	1,266,564
Minimum life-year gains over comparators				320	357
QALYs	0.80	46		256	286
ICER, cost per QALY				5450	4435

QA, quality adjustment.

Discussion and implications

The results here indicate a significant 31–45% reduction in predicted breast cancer mortality due to the annual (or approximately annual) mammographic surveillance in women at moderately increased risk due to family history. This translates to 4.3 breast cancer deaths prevented within 10 years of diagnosis per 10,000 screening episodes and to 6.9–7.8 deaths prevented over 20 years for the same number of screening episodes. Our economic analysis suggests that the intervention is cost-effective in UK terms and is unlikely to exceed £7878 per QALY.

The results differ slightly from those published in 2010.[23] This is because of increased follow-up and further tumours diagnosed, pursuit and checking of baseline data and more accurate estimation of the person-years at risk.

The major limitations of this study are the absence of a control group (a consequence of insufficient equipoise) and the use of predicted rather than actual mortality. Mortality was predicted using the NPI, which is a combination of the pathological size, node status and grade of the tumours, and also from the Markov model for node status. We did originally approach breast centres offering family services, proposing a randomised trial, but met with negative responses. The clinicians in the breast units felt that there was insufficient equipoise. The consensus was that it was ethically dubious to randomise intermediate-risk subjects to no surveillance. Alternative designs were considered, such as randomised trials of mammography against clinical breast examination and different mammographic frequencies, but it was felt that these did not answer the question of interest: is mammographic surveillance saving

TABLE 21 Women withdrawing or censored from FH01

Reason for withdrawal	Number of withdrawals or censored
Change of genetic status	35
Removed from local programme because of non-attendance	252
Diagnosed with breast cancer	159
Breast cancer – unconfirmed	1
Died of breast cancer	6
Died of other cause	27
Moved out of area	90
Refused further surveillance	35
Risk-reducing surgery	24
Other	70
Total	699

lives in comparison with no surveillance? These designs, with a mortality end point in subjects all of whom were receiving some surveillance, would also have entailed recruiting very large numbers and follow-up for 10–20 years to observe the breast cancer deaths. However, it was also felt that evaluation results were needed in the next few years, and not several decades hence; it was therefore necessary to identify a design and analysis that allowed surveillance to continue in all subjects and that delivered a timely end point. It has to be acknowledged that these considerations did dictate a less definitive and less straightforwardly interpretable study than a randomised trial.

We corrected our comparison with the Age Trial control group for the independently calculated 10-year risk of breast cancer rather than the observed incidence, to avoid length bias and overdiagnosis bias. The estimated incidences are higher than those observed, owing to the former being based on a 10-year period rather than the observed periods of 5–6 years on average. This means that the estimated risks necessarily pertain to a higher average age and, therefore, a higher average incidence. The proportional difference is greater for the Age Trial controls (2.4 per 1000 per year vs 1.3 per 1000 per year) than for the FH01 cohort (6.3 per 1000 per year vs 4.5 per 1000 per year), so the reduction in mortality is underestimated rather than overestimated. Also, given the fact that the observed incidence is if anything lower than expected, there is no evidence of serious overdiagnosis.

Although the age ranges of the comparison groups differ from that in FH01, the main comparison group, the Age Trial control group, is similar to that of FH01, with ages at diagnosis of 40–49 years compared with 40–50 years in FH01. The faster growth rates of tumours in younger women[47] might mean that our comparison with the Dutch series is indeed conservative.

Also, although the epoch of diagnosis is earlier in both comparison groups, there was no indication of a change in prognostic attributes with time in the Age Trial controls. No significant trends in node-positive rates ($p = 0.89$), tumour size ($p = 0.54$) or histological grade ($p = 0.56$) were observed. Prior to 1996, 48% of cases were node positive. Thereafter, the proportion was 47%. The corresponding proportions of invasive tumours of size ≥20 mm were 56% and 53%, and of grade 3 tumours 48% and 49%. With improvements in treatment over time, a comparison of actual mortality would be confounded with treatment effects. However, use of the projected mortality from the tumour attributes is unaffected by treatment. It might be expected that the actual breast cancer mortality in the FH01 cohort will be lower than projected mortality, owing to improved treatment. It should also be noted that the predicted mortality for both comparison groups was close to but slightly lower than the observed. For the Age Trial

controls the actual survival was approximately 71% and for the Dutch series 70%, suggesting that our results may in fact be conservative.[25,48]

We specifically targeted the age range 40–44 years at recruitment so that the subjects would contribute 5 years of observation before reaching age 50 years, thus avoiding arguments about 'age creep'.[20] This also rendered our group comparable with the Age Trial controls who were recruited at ages 40–42 years and followed up for 10 years (in our case, the recruits were mainly aged 40–44 years and followed up for an average of 5.52 years). The age range of the Dutch cases varies widely and the comparison with the latter must be interpreted much more cautiously.

The basic principles of our estimates of the effect on breast cancer mortality are (1) that the effects of screening on tumour size, node status and grade are predictive of its effect on future mortality, and (2) that node status alone or in combination with other factors as in the NPI gives accurate prediction of survival from breast cancer. These have both been subject to empirical validation. Blamey *et al.*[28] estimated the effect of NPI on 10-year survival in two mutually exclusive tumour sets and found that the two graphs of dependence were virtually overlapping. *Table 22* shows the RR of node-positive disease together with the RR of mortality (study vs control group) in the results from the randomised trials of breast screening.[48–54] Clearly, the effect of screening on node-positive disease is closely reflected in its effect on breast cancer mortality.

It could be argued that the comparisons are confounded by other tumour attributes than size, node status and grade. However, biological variables such as hormone receptor status are strongly correlated with size, node status and grade.[55] Also, Dawson *et al.*[56] investigated the effects of 11 biological variables on survival in breast cancer and found that they added little to NPI in explaining the survival advantage of screen-detected cancers.

It is also of interest to compare the attributes of the FH01 cancers with those diagnosed in the NHSBSP. In those attending for surveillance in FH01, 24% of cancers were interval cancers and the remainder were screen detected. In the West Midlands Screening Histories project in 2002, around 41% of cancers in attenders to the national programme were interval cancers.[57] *Table 23* shows the proportions of

TABLE 22 Relative risk (study compared with control group) of incidence of breast cancer mortality and of incidence of node-positive disease in the randomised trials of breast screening

Trial[48–54]	RR mortality	RR node-positive
HIP Greater New York	0.77	0.85
Malmö[a]	0.78	0.83
Two-County	0.68	0.73
Edinburgh	0.71	0.81
Stockholm	0.90	0.82
NBSS1	1.06	1.20
NBSS2	1.02	1.09
Gothenburg	0.76	0.80
Age Trial	0.83	0.89

a Stage II or worse was used for the Malmö trial since node status data were unavailable.

node-positive, size >20 mm, and grade 3 invasive cancers in FH01 and in 14,672 invasive tumours in the West Midlands project,[58] for interval cancers and screen-detected cancers separately.

Results for node status were similar for the two series, each showing a substantially lower rate of node-positive disease in the screen-detected tumours. There was a smaller difference in the FH01 series for tumours of size >20 mm. Reflecting the younger age at diagnosis, the FH01 tumours, including the screen-detected tumours, were much more likely to be grade 3. This may explain the smaller effect on tumour size in FH01.

A relatively high proportion of cancers diagnosed in FH01 were DCIS, 26% overall and 33% of screen-detected cancers, compared with approximately 20% in the NHSBSP. *Table 24* shows the size and grade of DCIS cases detected at surveillance compared with 700 cases detected in the NHSBSP in the West Midlands.[59] A higher proportion of large and high-grade tumours was observed in FH01, again possibly because of the younger age at presentation. The high grade of the FH01 tumours suggests that the high rate of DCIS is unlikely to be because of overdiagnosis.

In conclusion, our most conservative estimate of the cost per QALY saved was £6450, which is less expensive than combined mammography and MRI in *BRCA1* mutation carriers.[60] The conclusion of this work is that annual mammography surveillance for women at moderate familial risk is both clinically effective and cost-effective.

TABLE 23 Attributes of invasive breast cancers in FH01 and in the NHSBSP in the West Midlands, by detection mode

	Per cent with attribute in screen-detected cancers		Per cent with attribute in interval cancers	
Attribute	FH01	NHSBSP West Midlands	FH01	NHSBSP West Midlands
Node positive	27	22	43	39
Tumour size >20 mm	29	21	34	44
Grade 3	45	17	47	37

TABLE 24 Attributes of DCIS cases detected at surveillance in FH01 and screen-detected cancers in the NHSBSP

		Per cent (screen-detected cancers only)	
Attribute	Category	FH01	NHSBSP West Midlands
Size	≤20 mm	57	88
	>20 mm	43	12
Grade	Low	8	12
	Intermediate	25	30
	High	67	58

Chapter 6 Radiology and pathology reviews

Introduction

The intention to carry out radiology and pathology reviews was noted in the original FH01 protocol, although their design and conduct was not specified. In this chapter, we summarise the protocols of the reviews, report progress on the reviews and give some preliminary results. The reviews are substantial pieces of work, involving the collation from multiple centres of radiological images and biological material. Consequently, they are still ongoing, but there are already some interesting observations, notably for the radiology review.

Radiology review

Radiology review is standard practice in major screening studies.[61,62] This radiology review has two components: a rereading of mammograms of cancers and selected non-cancer cases for radiological features and their correlation with pathological and biological features; and a case–control study of mammographic density. The first component of the review includes:

- Determination of the observed radiological features of the cancers on mammography, to identify diagnostic features with verified poor outlook either on histology, biological features or outcome (in the long term, survival and disease-free survival).
- Radiological audit to identify those tumours which could have been detected at a screen previous to the diagnosis, (i.e. potential false-negatives), with a review of the reasons for failure of mammographic diagnosis. This is particularly relevant to the 26% interval cancers.
- Comparison with other age groups or risk profiles, including:
  - the NHSBSP for women aged 50–70 years – essentially postmenopausal women
  - women in the UK study comparing MRI with mammography. These women have a high probability of carrying *BRCA1* or *BRCA2* mutations because of intensity of family history. These are women aged < 50 years, similar to FH01, but with a considerably higher level of risk[63]
  - the ongoing FH02 study – women aged 35–39 years at elevated risk due to family history.

The review includes the films of the cancers including their previous mammograms, as in the radiology reviews of the previous breast screening studies such as the Age Trial and the Breast Screening Frequency Trial.[61,62] The review differs from that of previous studies in three important respects. First, it includes mammograms from subjects who never developed cancer during the study, two per cancer matched for age, centre and date of screening. Second, the X-rays are digitised (where not already digital) so that reviewers can view the mammograms without either readers or films having to travel. Third, the review includes the density study mentioned above.

Digitisation of the analogue mammograms was by Array Corporation's 2905 X-ray film digitiser (Array Corporation USA, Hampton, NH, USA), which gives a pixel size of 3600 by 4800 and DICOM resolution of 1 mm = 20 pixels, equivalent to 12 bit. The DICOM images were converted to bitmap images as this format is the most suitable for uploading to the web. This conversion reduces the resolution to 8 bit. Digital mammograms were anonymised, assigned a unique study number, then converted to bitmap (8 bit) format and uploaded to the web.

The formatted and anonymised images were uploaded into Image-box, version 1 (University of Southampton, Southampton, UK), where there is further compression of the images to 550 by 900 pixels. We used the image database developed for the Prospective study of Outcomes in Sporadic and

Hereditary breast cancer (POSH) radiological review.[64] This is web based and was developed by Kevin Wheeler of Southampton University, who is employed by Professor James Batchelor, in the Department of Computer Science.

Features of the POSH database include:

- It is web based and password controlled.
- It incorporates anonymised scanned mammographic and ultrasound images.
- Recording sheets appear online to match images and screening events under examination.
- It enables a greater number of radiologists to participate and can therefore be opened up to volunteers from the centres.
- It allows for two readers per study.
- A third reader arbitrates on any differences (we have a limited list of final decision arbitrators). For each field the final observation is adopted if both initial readers agree or two out of three after arbitration agree. If all three differ, we take as the final observation the decision of the third reader.
- The database uses Breast Imaging-Reporting and Data System (BI-RADS) terms so that it is suitable for publication in American journals.
- Studies are reviewed starting with the latest screening episode and progressing backwards through the series so that any information on the site of the cancers can be used to look for subtle earlier signs (in the same way as interval cancer audit is generally done).

A major outcome of the first component of the radiology review is radiological audit of cancers arising in FH01 – could these have been picked up at previous screens, and what are the key radiological signs of this? The inclusion of the non-cancers will give us information about specificity of earlier signs of malignancy, yielding an estimate of the likely effect on false-positives of a change in practice or training. Other outcomes include a quality assessment of both radiology and radiography in FH01. It should be noted, however, that with the advent of digital mammography, accuracy will improve in any case for this young population with relatively dense breast tissue.

The second component of the radiology review is a case–control study of breast density, again using at least two age-matched controls per cancer case. The major aim is to determine whether or not breast density is a risk factor in this population at enhanced familial risk, as it is in the general population.[65] Secondary outcomes will be the determination of whether per cent density or absolute dense area is the better predictor of breast cancer risk in this population, and how far in advance of diagnosis does density predict risk. Density was measured by the Cumulus interactive threshold computer program version 4 (University of Toronto, Toronto, Canada),[66] operated by a single radiologist (Ruth Warren) with extensive experience in reading mammograms for density, both visually and using Cumulus. The program yields measures of dense area and total breast area. From these, the per cent dense area and the non-dense area can be calculated.

Density was read on digitised mammograms as described above. We have digitised mammograms for 103 cancer cases and 231 disease-free controls. The multiple readings for earlier mammographic signs of malignancy, quality assessment and radiology/pathology/biology correlation is ongoing. Density readings were available for 101 cases and 228 controls. Some results of the density study are already available. *Table 25* shows the dense area, total breast area and per cent density for cases and controls. The cases have slightly higher values than the controls for all three measures, but especially so for absolute dense area. As expected, per cent density was negatively correlated with age, although this was of borderline significance (correlation coefficient –0.10; $p = 0.06$).

Formal analysis was by conditional logistic regression, taking into account the individual matching of cases and controls.

TABLE 25 Mean and SD of dense area, total area and per cent density on mammograms of 101 cases and 228 controls

Group	Mean (SD) dense area in cm^2	Mean (SD) total breast area in cm^2	Mean (SD) per cent density
Controls	47 (32)	152 (66)	34 (19)
Cases	59 (41)	162 (74)	37 (19)

There was a significant increase in risk of cancer with absolute breast density after adjustment for menopausal status ($p = 0.03$), with an 8% increase per 10 cm^2 of dense tissue [odds ratio (OR) = 1.08, 95% CI 1.01 to 1.19]. The difference was more marked in premenopausal women ($p = 0.008$), defined as having had a menstrual period within the last 6 months. There was a 12% increase in risk per 10 cm^2 of dense tissue (OR = 1.12, 95% CI 1.02 to 1.22). This remained significant after adjusting for HRT, age at menarche, parity and age at first birth (OR = 1.15, 95% CI 1.02 to 1.29; $p = 0.01$). A non-significant decrease in risk was observed in postmenopausal women; however, only 25 (8%) women were postmenopausal.

Per cent breast density did not have a significant effect on risk, regardless of menopausal status, unless adjusted for total breast area. In terms of both significance ($p = 0.008$ vs $p = 0.03$) and the magnitude of the standardised regression coefficient (0.41 vs 0.34), absolute dense area was a stronger predictor of risk than total area-adjusted per cent density.

Further analysis will focus on time between the mammographic examination from which density was estimated and diagnosis of cancer, on association of density with other breast cancer risk factors, and on the combined effects of density and other factors on breast cancer risk. In the meantime, the conclusions from the density component of the radiology review are that absolute density is a stronger predictor of breast cancer risk than per cent density in this population, and that absolute density increases risk in addition to the effect of other breast cancer risk factors. There is suggestive evidence that the effect is stronger in premenopausal women.

Pathology review

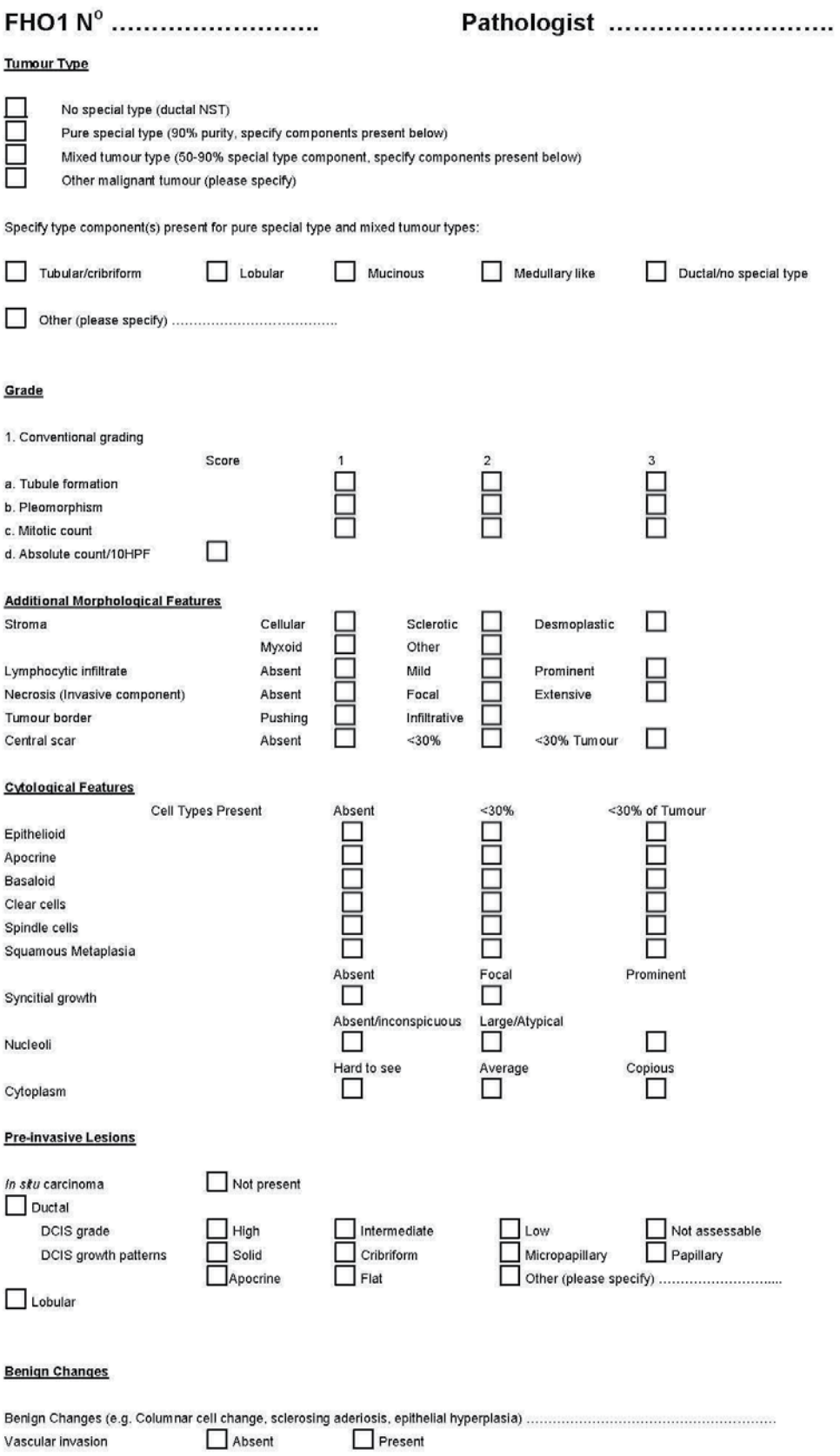
This will be a standardised review of conventional histopathological features (grade, type, size, etc.), which will be compared with the original pathology laboratory determination. In addition, this gives an opportunity to record other morphological features that are increasingly recognised as important characteristics of specific tumour subtypes, such as central scar formation, lymphocytic response, pushing or infiltrative tumour margin and degree of stromal response.[67] In addition, features of 'background' non-involved breast tissue will be documented, which will be of relevance to the linked radiology review (see *Radiology review* above). It is suggested, therefore, that all haematoxylin- and eosin-stained slides for each case are requested for review. The pathology review form is shown in *Figure 2*.

This is similar to the pathology reviews carried out in the various UK breast screening trials. However, in addition to the standard pathological variables, we also propose to stain the tumour samples for the recently discovered molecular subtypes of tumour, to determine the underlying aggressiveness of cancers occurring in the FH01 risk group. An 'intrinsic gene set' identified by Perou *et al.*[68] and validated by Sortie *et al.*[69] has led to the recognition of five 'molecular' subgroups: luminal (Lum) A, Lum B + C, human epidermal growth factor receptor-2 (HER-2) positive, basal and 'normal-like'. These molecular subgroups of breast cancers have been shown to differ in their clinical behaviour, with HER-2-positive and basal groups exhibiting the poorest prognosis. *BRCA1*-associated breast cancers frequently exhibit a basal phenotype,[70] but basal tumours are also more common in non-*BRCA*-associated cancers arising in young women,[71] and may be associated with loss of *BRCA* function through other mechanisms such as gene methylation.[72] There is, however, growing evidence that the basal subtype of breast cancer may not be a single entity,[73,74]

and different subsets may differ in their clinical behaviour and in potential therapeutic targets. Recent research identifying molecules that are highly effective at targeting *BRCA*-null tumours (and therefore potentially all or a subgroup of basal tumours) underlines the importance of accurately establishing the molecular phenotype of breast cancers.[75] This study will employ a wide panel of markers that should better identify biologically important tumour subsets. In addition, whole sections will be analysed for *BRCA1*-methylation status (methodology already optimised).

As a comparison group, we will interrogate the POSH database[64] to identify a cohort of age-matched non-family history cases on which the same analysis will be performed as part of the POSH study.

The tumour samples are still being collated, which is proving a demanding job in terms of administration and governance, with material transfer agreements being required for >70 sites. For one centre with seven cancers, the tumour material has been transferred to Barts Health and the rereading of invasive status and grade is 100% in agreement with that in the original pathology laboratory, and correlation of tumour size with that of the original laboratory is 0.9997.



FHO1 N° ..... Pathologist .....

Tumour Type

- ☐ No special type (ductal NST)
- ☐ Pure special type (90% purity, specify components present below)
- ☐ Mixed tumour type (50-90% special type component, specify components present below)
- ☐ Other malignant tumour (please specify)

Specify type component(s) present for pure special type and mixed tumour types:

☐ Tubular/cribriform ☐ Lobular ☐ Mucinous ☐ Medullary like ☐ Ductal/no special type

☐ Other (please specify) .....

Grade

1. Conventional grading

	Score	1	2	3
a. Tubule formation		☐	☐	☐
b. Pleomorphism		☐	☐	☐
c. Mitotic count		☐	☐	☐
d. Absolute count/10HPF	☐			

Additional Morphological Features

Stroma	Cellular	☐	Sclerotic	☐	Desmoplastic	☐
	Myxoid	☐	Other	☐		
Lymphocytic infiltrate	Absent	☐	Mild	☐	Prominent	☐
Necrosis (Invasive component)	Absent	☐	Focal	☐	Extensive	☐
Tumour border	Pushing	☐	Infiltrative	☐		
Central scar	Absent	☐	<30%	☐	<30% Tumour	☐

Cytological Features

Cell Types Present	Absent	<30%	<30% of Tumour
Epithelioid	☐	☐	☐
Apocrine	☐	☐	☐
Basaloid	☐	☐	☐
Clear cells	☐	☐	☐
Spindle cells	☐	☐	☐
Squamous Metaplasia	☐	☐	☐

	Absent	Focal	Prominent
Syncitial growth	☐	☐	

	Absent/inconspicuous	Large/Atypical	
Nucleoli	☐	☐	☐

	Hard to see	Average	Copious
Cytoplasm	☐	☐	☐

Pre-invasive Lesions

In situ carcinoma ☐ Not present

☐ Ductal

DCIS grade ☐ High ☐ Intermediate ☐ Low ☐ Not assessable

DCIS growth patterns ☐ Solid ☐ Cribriform ☐ Micropapillary ☐ Papillary

☐ Apocrine ☐ Flat ☐ Other (please specify) .....

☐ Lobular

Benign Changes

Benign Changes (e.g. Columnar cell change, sclerosing aderiosis, epithelial hyperplasia) .....

Vascular invasion ☐ Absent ☐ Present

FIGURE 2 Pathology review form.

Chapter 7 Follow-up data

Follow-up questionnaire

We planned to send a follow-up questionnaire to all subjects who had completed 5 years in the study. The purpose of this was to update risk factor information, in particular family history, and to check on the reliability of the data by estimating agreement/disagreement rates between the first and second enquiry. For example, although parity and number of affected relatives might both increase over the period of the study, they cannot decrease. The approval of clinical staff managing the subject's surveillance was sought before sending the questionnaire. The items of information in the questionnaire were as follows:

- ever in employment (yes/no)
- educational level attained
- weight and height
- parity
- breastfeeding
- menopausal status/age at menopause
- HRT use
- tamoxifen use
- update to family history (relatives diagnosed with breast cancer since recruitment).

Results

So far, 5462 follow-up questionnaires have been sent out and 2760 (51%) returned. Data have been entered and successfully linked with FH01 baseline data for 2705 (98%) of these. *Table 26* shows the distributions of risk factors reported in the follow-up questionnaire. Understandably, the proportion of postmenopausal subjects is higher in the follow-up survey than at baseline, and the parity distributions are similar (see *Chapter 3*, *Table 2*). Substantial numbers reported a relative diagnosed with cancer since their initial family history was taken at recruitment, 13% reporting a diagnosis in their mothers and 9% in their sisters.

Table 27 shows the individual baseline responses tabulated against the follow-up responses for the binary variables menopausal status and HRT use. *Table 28* gives the baseline responses for parity cross-tabulated with the corresponding follow-up responses. For menopausal status, the agreement rate was 80%. It is plausible that the 402 subjects whose status was premenopausal at baseline and postmenopausal at follow-up did indeed change their status during the study. The eight subjects (<1%) who reported being postmenopausal at baseline but premenopausal at follow-up suggest a small element of response error at one or both occasions. Results for HRT use suggest a similarly small error rate.

For parity, there was 89% agreement and the small numbers with lower parity reported at follow-up than at baseline (115 subjects, 5%) suggest a small degree of response error for this factor.

The family history factors are rather more difficult to interpret. For maternal breast cancer, 13% report a diagnosis since their original family history was taken at recruitment. For sisters, the figure is 9%. *Table 29* shows the original baseline response tabulated against the report of new diagnoses in the follow-up questionnaire. The vast majority of those reporting a new diagnosis in mother or sister already had such a report at baseline, on average 5–6 years before. Although some of the reports may pertain to recurrences or new primaries in the same relative, or to cancer in different sisters, it is likely that the reports refer to the original cancer in the affected relative. The subjects were posted the questionnaire and did not have

TABLE 26 Risk factor distributions from the follow-up questionnaire

Factor	Category	No. of subjects (%)
Body mass index (kg/m^2)	<20	103 (4)
	20–24.9	951 (41)
	25–29.9	779 (33)
	30+	511 (22)
	Not known	361
Parity	0	366 (14)
	1	444 (17)
	2	1191 (46)
	3+	569 (23)
	Not known	135
Ever breastfed?	No	1705 (75)
	Yes	578 (25)
	Not known	422
Menopausal status	Premenopausal	1932 (72)
	Postmenopausal	737 (28)
	Not known	36
HRT use?	No	2430 (90)
	Yes	256 (10)
	Not known	19
Tamoxifen use?	No	2581 (99)
	Yes	27 (1)
	Not known	97
Mother diagnosed with breast cancer since recruitment?	No	2347 (87)
	Yes	358 (13)
Sister diagnosed with breast cancer since recruitment?	No	2455 (91)
	Yes	250 (9)

TABLE 27 Baseline responses vs follow-up responses for binary factors[a]

		Follow-up response (cell %)	
Factor	Baseline response	No	Yes
Postmenopausal?	No	1491 (74)	402 (20)
	Yes	8 (<1)	123 (6)
HRT use (ever)?	No	1653 (89)	80 (4)
	Yes	23 (1)	104 (6)

a Total numbers vary by factor because of variable numbers with missing data.

TABLE 28 Parity reported at baseline vs parity reported at follow-up

Parity reported at baseline	Parity reported at follow-up (cell %)			
	0	1	2	3+
0	325 (13)	21 (1)	17 (1)	9 (<1)
1	6 (<1)	368 (15)	51 (2)	9 (<1)
2	9 (<1)	29 (1)	1012 (41)	34 (1)
3+	3 (<1)	10 (<1)	58 (2)	489 (20)

TABLE 29 Baseline status of mother or sister with breast cancer tabulated against follow-up reporting

Factor	Baseline response	Report of new diagnosis at follow-up (cell %)	
		No	Yes
Mother have breast cancer?	No	727 (28)	16 (<1)
	Yes	1548 (59)	334 (13)
Sister have breast cancer?	No	1811 (69)	40 (1)
	Yes	574 (22)	200 (8)

their baseline responses to hand when completing it. There has been at least one study where a postal questionnaire was considered adequate for taking a family history of colorectal cancer.[76] However, another study investigating personal history of all cancers found rather poor sensitivity of a postal questionnaire.[77] The results here suggest that if a family history is to be updated without a face-to-face interview, then it would be reasonable simply to request the entire family history again, rather than ask the individual to qualify the reported history with respect to previous responses.

Chapter 8 Related studies

Psychological impact of mammography screening for women under 50 years with a family history of breast cancer

The study of the Psychological Impact of maMMography Screening for women under 50 with a family history of breast cancer (PIMMS) was carried out independently of FH01, but was considered a companion study, with several members of management committees in common. PIMMS was completed before FH01, and has been published extensively.[31–34,78] The major findings of PIMMS were:

- Gaps in knowledge on the part of screened women were noted, with respect to their own level of lifetime risk and the sensitivity of the screening test.
- Women who received an immediate all-clear result after mammography experienced a decrease in cancer worry and negative psychological consequences immediately after their screening result, whereas those women recalled for further tests did not. However, recalled women experienced a significant increase in cancer worry which was present at 1-month follow-up. This was not significant for women who only received a non-invasive procedure at recall.
- By 6 months' follow-up, cancer-specific distress had reduced significantly in both groups. Recalled women did not have higher levels of worry than non-recalled women at 6 months.
- Worry was significantly stronger at the woman's first screen in the programme.
- Changes in levels of distress pre and postscreening between women with an immediate all-clear and those who received an all-clear after further tests were significantly different, but in absolute terms the difference was not large.
- By far, the strongest predictor of worry at an individual level following a screening test was the level of worry experienced before the test. Prescreening worry explained 55–60% of the variability in postscreening worry.
- Recalled women reported significantly greater positive psychological consequences of screening immediately after their final result and were also more positive about the benefits of screening compared with women who received an immediate all-clear result.
- Women diagnosed with breast cancer in the programme reported a sense of reassurance from screening prior to diagnosis.

From this it was concluded that women who are recalled for further tests do not appear to be harmed by screening and the study findings suggest that they view any distress caused by recall as an acceptable part of screening.

FH01 blood study

For many years, there has been interest in identifying a blood test indicative of either presence of or very high risk of breast cancer. Although the breast screening programme in the UK serves the population well,[79] there is scope for improvement in sensitivity of screening for those subjects with radiologically dense breast tissue. High breast density both increases risk of breast cancer and impairs the sensitivity of mammography.[80] A population such as FH01 is potentially fertile ground for discovery or validation of such markers, as it is relatively young and so has a substantial proportion of subjects with dense breasts, but it has higher incidence than the general population of the same age.

Two blood-testing strategies which show considerable promise are a gene expression test carried out on extracted ribonucleic acid (RNA) from peripheral blood,[81] and a serum test for a panel of oncoantibodies.[82]

In addition, there is considerable interest in epigenetic markers.[83] Accordingly, we have set up a prospective study taking blood samples from FH01 recruits, and follow-up for subsequent occurrence of breast cancer.

The objectives can be summarised as:

1. Prospective estimation of sensitivity of the gene expression and antibody tests in subjects with a significant family history of breast cancer.
2. Prospective estimation of specificity of the tests in subjects with a significant family history of breast cancer.
3. If the test proves sensitive to breast cancer in this setting, estimation of how far in advance of diagnosis a positive test is observed.
4. Do the answers to questions 1–3 (above) differ between those subjects with dense breasts and those with fatty-replaced breasts?
5. What is the typical profile of this moderate familial risk group with respect to the epigenetic markers?
6. Do any of the epigenetic markers act as early markers of the development of breast cancer in this population?

From the highest recruiting breast cancer clinics for FH01 we propose to recruit 4000 subjects so far free of cancer. These subjects will be asked to provide a blood sample every 12 months for 2 years (at baseline, 12 months and 24 months). In addition to mammographic surveillance within FH01, the subjects are flagged with the Medical Research Information Service, so that all breast cancers, whether detected at surveillance or outwith the study, will be ascertained. A dedicated member of staff at each centre will be trained and responsible for taking all samples.

Blood samples will be collected into three tubes. RNA for the gene expression test will be extracted from two of the tubes in an external laboratory. The extracted RNA will be analysed only for those who are subsequently diagnosed with breast cancer and for 10 control subjects for each breast cancer case. Results will then be analysed for questions 1–4 in the objectives summary above.

Serum from the third tube of each blood sample will be separated and stored for epigenetic testing, and for the onco-antibody assays. Storage will be at <–70 °C. So far we have recruited 132 subjects in four centres and taken 480 blood samples. The pace of progress of the study depends on funding applications currently under way. Further details are given in the blood study protocol (see *Appendix 2*).

FH02

FH02 is a study of mammographic surveillance in women aged 35–39 years at increased familial risk of breast cancer. The National Institute for Health and Clinical Excellence recommended that such surveillance in this age group only take place in a research context. The aim is to recruit 2800 women satisfying similar family history criteria to FH01. The study end points are detection and interval cancer rates. FH02 is funded by the Breast Cancer Campaign. The funding decision was strongly influenced by the positive results from FH01. To date, 1911 women have been recruited in 32 centres and 17 cancers have been diagnosed.

Chapter 9 Implications of the results

Implications for care policy

The first question to consider is whether or not the study results are sufficiently robust to give indications for policy. FH01 was a volunteer-based, single-arm cohort study. The issue of the volunteer population gives rise to the issue of selection bias. However, in the five centres polled, four reported participation rates in excess of 90%. The early delay in recruitment was due to centre difficulties rather than refusal of women approached to join the study. In addition, the volunteer population reflects practice in the management of women at increased familial risk. There is no unsolicited invitation to surveillance, as there is in the NHSBSP. Women managed by the genetics and family history services have sought advice of their own volition. In terms of the study design, the analytical strategy has dealt with this by adjusting external comparisons for underlying risk using independent estimates, by supplementing this with internal estimation of the future effect and by use of well-validated predictors of breast cancer mortality. It is therefore likely that the results with respect to the effect of the surveillance on future breast cancer mortality are reliable and can inform policy.

The primary implication of the results of FH01 is that the provision of annual mammographic surveillance services from age 40 years to women at moderately increased familial risk of breast cancer is both clinically effective and cost-effective. The policy can be expected to confer at least a 25% reduction in ultimate mortality from the disease in the population offered the service. We estimate that the policy will cost between £4435 and £5450 per QALY saved.

A number of centres practised clinical breast examination and/or ultrasound in addition to mammography. Our results did not indicate any substantially marginal additional benefit of clinical examination, but did suggest that use of ultrasound boosted the detection rates. This is consistent with the age of this population and the associated high prevalence of dense breast tissue.

It should also be noted that at the stage of recruitment, we encountered a wide variation across the country in policies for managing this risk group. It may be that a standardisation of policy, with nationwide co-ordination, would not only enhance the surveillance service for this population, but also bring economies of scale.

The human costs in terms of false-positives and radiation exposure are within the standards of the NHSBSP, as are detection rates. Although the proportion of cancers with preoperative diagnosis is well within the national standard, there is still a rather high rate of benign open biopsies. This needs future monitoring and improvement. Also, although the recall rates for assessment conform to national standards, they are somewhat high. The figures are 8% at prevalence screen and 6% at incidence, corresponding to positive predictive values of 6% and 7%, respectively. To minimise anxiety for this population, the issue might be addressed by immediate interpretation of mammograms with additional imaging, including ultrasound, at the same visit, to eliminate a proportion of the false-positives. This would imply the surveillance taking place at static units, which is generally the case in this risk group. Also, digital mammography was not universally used in FH01, but it is reasonable to assume that it will be in the near future. This may improve the accuracy of the examination. In addition, the advent of digital mammography is likely to improve sensitivity and reduce interval cancer rates.

A reasonable model for management of women aged 40–49 years (or 40–47 years bearing in mind the age expansion of the national programme) would be to have a risk assessment performed by a genetics service or at a specialist breast centre. If there is no or only mild family history, the subject may be reassured and recommended to have no additional surveillance but to be breast aware until she qualifies

for the NHSBSP. For those women at high risk, that is, those women with a strong probability of a *BRCA1* or *BRCA2* mutation, there are management strategies including MRI surveillance and possible surgical interventions. Those women at moderate risk might be referred to the screening programme for an earlier starting age for screening, and an annual interval until age 50 years.

The results of the density component indicate that at least in premenopausal women, breast density adds to information on risk within this moderate-risk population, independently of other risk factors. Although measurement of density is currently labour intensive, with the advent of digital mammography, the scope for development and exploitation of fully automatic computerised density measurement will increase.[84]

This begs the question: how to define the moderate-risk group? Resources are limited and the call on these resources will depend on the minimum-risk criterion to qualify for surveillance. From the risk estimates in our data on the FH01 moderate-risk cohort and in the general population sample from the Age Trial, we have estimated the proportion of the population aged 40–49 years who would qualify for the surveillance, for various eligibility criteria based on risk relative to the general population. These are shown in *Table 30*, along with minimum approximate absolute risks at age 40–49 years and total number of subjects eligible in the UK. The last is based on an approximate estimated female population of 4.5 million women aged 40–49 years in the UK.[85] *Table 30* also shows the percentage of FH01 subjects who would qualify by each cut-off.

A cut-off of three to four times the population risk would seem reasonable. Given that only a proportion of the eligible population is likely to come forward, a reasonable cut-off, such as a risk of three times the population risk, would involve an increase of <10% in the mammography activity in the NHSBSP.[36] A cut-off of four times the population risk would involve only a marginal increase in activity, but this would exclude a large number of women with a substantially higher risk than the population. Surveys in the USA find 7–12% prevalence of moderate familial risk,[86,87] but their definition of moderate is likely to include what would be considered mild risk in a UK context.

The results of the follow-up study suggest that in using a self-administered postal questionnaire to update family history, it would be prudent to request the full family history again. In many centres, this is the policy even when family history is reascertained and risk assessment updated by direct interview with a health professional.

Implications for research

First, it should be noted that much of the mammographic activity in FH01 used traditional film mammography and this is steadily changing to digital. There is a need for research to assess the impact that this will have on mammographic accuracy in this population. Indeed, there is a need for research on the optimal way of delivering surveillance, minimising both false-negatives and false-positives, and dealing with the latter in a way which minimises anxiety and other human costs.

TABLE 30 Implications of different relative risk criteria for surveillance at ages 40–49 years

RR cut-off	Approximate cumulative 10-year risk, age 40–49 years	Per cent of population qualifying	Number of UK women aged 40–49 years qualifying	Per cent of FH01 subjects qualifying
2	3%	10	450,000	70
2.5	3.75%	7	315,000	45
3	4.5%	4	180,000	25
4	6%	1	45,000	9

Second, there will always be pressure to streamline any risk-based surveillance system. In view of the unsatisfactory family history information in the follow-up study, there is need for research to further improve self-administered family history questionnaires. There will also be room for improvement in delineating individual risk. When standardised risk assessment and referral to the programme are under way, there will be an opportunity to validate and, if necessary, amend the individual risk prediction algorithm.

Third, the results of the breast density part of the radiology review suggest that density adds to risk prediction in this group already at enhanced familial risk, and are consistent with a stronger effect on risk of absolute dense area on the mammogram than of per cent dense area. This issue remains unresolved.[88,89] The increased risk with density appeared to be confined to premenopausal women but we had too few postmenopausal women to conclude this with any certainty. These results indicate that density probably has a role in risk management in the medium term, but in the meantime the following issues should be targets of future research:

- The effect of density in larger postmenopausal populations at increased familial risk of breast cancer, taking account of other risk factors.
- Investigation of whether or not automatic methods of breast density can reliably replace traditional methods.
- Confirmation of the better risk prediction using absolute dense area rather than per cent density.
- Detailed quantification of the marginal addition to risk information conferred by density.

Overall conclusion

Annual mammographic surveillance in women aged 40–49 years at moderate familial risk of breast cancer results in a significant reduction in future deaths from breast cancer, at reasonable financial and human cost.

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Contribution of authors

Stephen W Duffy was joint principal investigator (PI), supervised the statistical analysis and drafted the report.

James Mackay was joint PI, took responsibility of clinical aspects of the study and contributed to editing the report.

Sue Thomas co-ordinated the study, participated in data-analysis and contributed to editing the report.

Elaine Anderson took a leading role in study conduct in Scotland, participated in study management nationally and contributed to editing the report.

Tony HH Chen carried out the Markov modelling and contributed to editing the report.

Ian Ellis led on pathological aspects and contributed to editing the report.

Gareth Evans led on clinical genetics aspects, participated in study management nationally and contributed to editing the report.

Hilary Fielder was a co-applicant, took a leading role in study conduct in Wales and guardianship of the study data, participated in study management nationally and contributed to editing the report.

Rosemary Fox took a leading role in study conduct in Wales and guardianship of the study data, participated in study management nationally and contributed to editing the report.

Gerald Gui took a leading role in study conduct in London, participated in study management nationally and contributed to editing the report.

Douglas Macmillan was one of the team initiating the study, participated in study management nationally and contributed to editing the report.

Sue Moss participated in study management nationally, took a leading role in comparison with the Age Trial data and contributed to editing the report.

Cerilan Rogers was a co-applicant, was one of the team initiating the study, took the lead in the first 2 years on study conduct in Wales and guardianship of the study data, participated in management of the study nationally and contributed to editing the report.

Mark Sibbering contributed to management of the study nationally, led on surgical aspects and contributed to editing the report.

Matthew Wallis took a leading role in radiological aspects and contributed to editing the report.

Ruth Warren led the radiology review, participated in study management nationally and contributed to editing the report.

Eila Watson took a leading role in psychosocial aspects of the study and contributed to editing the report.

David Whynes carried out the health economic evaluation and contributed to editing the report.

Prue Allgood took a leading role in study co-ordination in London, in the blood and radiation dose substudies and contributed to editing the report.

Jack Caunt was responsible for informatics aspects, data management and processing, and contributed to editing the report.

Publications

Mackay J, Rogers C, Fielder H, Blamey R, Macmillan D, Boggis C, *et al*. Development of a protocol for evaluation of mammographic surveillance services in women under 50 with a family history of breast cancer. *J Epidemiol Biostat* 2001;**6**:365–9.

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Appendix 1 Protocol of FH01

EVALUATION OF MAMMOGRAPHIC SURVEILLANCE SERVICES IN WOMEN UNDER 50 WITH A FAMILY HISTORY OF BREAST CANCER

Background, design and protocol of study

Based on an original idea by Howard Cuckle.

Aims

1. To estimate the difference in breast cancer mortality in women under the age of 50 with a significant family history of breast cancer having regular mammography compared to those not being screened.
2. To estimate the cost-effectiveness of regular mammography in this group of women, compared to no screening.

Summary

The identification of two highly penetrative breast cancer susceptibility genes attracted intense media interest. Unrealistic expectations of genetic testing and understanding about the relevance of family history have raised public and professional anxiety. Many women presenting with a family history of breast cancer under the age of 50 are offered mammograms as preliminary retrospective data suggest it is possible to identify impalpable breast cancer in this group with regular mammography. The effectiveness of this service, however, has not been formally evaluated.

We propose to perform such an evaluation in a cohort of 6,000 women under the age of 50 with a significant family history of breast cancer, given regular mammographic surveillance over five years. Comparison of surgical and pathological data with completed and on-going population screening trials using analysis techniques of varying complexity will be performed to obtain an accurate estimate of breast cancer mortality reduction.

The change in health service resource use attributable to mammography will be compared with no screening and costed. Incremental cost effectiveness ratios of implementing the standardised mammography strategy compared with no screening will be presented in terms of the additional cost per cancer detected, per life saved and per life year saved.

Background

In the past five years, the identification of two breast and ovarian cancer susceptibility genes – BRCA1 and BRCA2 – has received a lot of publicity. Public and professional expectations of the availability and utility of genetic testing have been raised and the importance of a family history of breast cancer overemphasised. This has resulted in an increase in the number of women presenting to their general practitioner because they are worried about a family history of breast cancer, many of whom are then referred on for specialist advice. However, the most appropriate way to manage these women is not known.

Familial breast cancer risk

All women with a family history of breast cancer are at increased risk of breast cancer themselves. However the extent of that risk will vary according to the nature of the family history, specifically which relative was affected, their age at diagnosis, the number of relatives affected, as well as the age of the woman concerned. The relative risks associated with different family histories have been summarised in a recent systematic review and meta-analysis.[1] The relative risks associated with various family history categories are: any relative, RR = 1.9; any first degree relative, RR = 2.1; mother, RR = 2.0; sister, RR = 2.3; daughter,

RR = 1.8; mother and sister, RR = 3.6; a second degree relative, RR = 1.5. Risks are increased in subjects under the age of 50 and when the relative had been diagnosed before the age of 50. For example the relative risk to a woman under the age of 50 who has a first degree relative affected before the age of 50 is 3.3.

The risk categories described in most studies are however simple, being usually based on single factors. The risks associated with more complex histories are difficult to establish. For example, it is difficult to estimate with any precision the risk of breast cancer in a 40 year old woman with three sisters, whose mother and oldest sister developed breast cancer at the age of 65 and 51 years respectively.

Management of familial and genetic risk

Although a high proportion of large breast cancer families are due to the inheritance of dominant predisposing genes, the number of such families is small, and there are well established guidelines for the management of unaffected women in these families.[2] In addition, the cost implications of implementing the guideline recommendations are limited.

Of greater concern are those women with a moderate family history, who are unlikely to inherit a mutation in a predisposing gene, but who are at moderately increased risk of breast cancer. Little evidence is available to inform risk management in these women.

There are several potential methods for primary prevention – i.e. reducing the likelihood of developing breast cancer – including chemoprevention, prophylactic mastectomy and lifestyle modification. Possible methods for early detection (secondary prevention) include breast self-examination, clinical breast examination and regular mammography.

Good evidence for the effectiveness of breast self-examination is lacking. The results of observational studies have been conflicting,[3–6] and preliminary results from two randomised controlled trials failed to show benefit.[7,8] Approximately 10% of breast cancers may be detected by clinical examination alone.

The mainstay of early detection of breast cancer is regular screening of the breasts by mammography. Before considering the merits of mammography in those at high risk, the arguments for and against mammographic screening in women of average (or population) risk need to be rehearsed and interpreted with respect to women at increased risk.

The UK National Breast Screening Programme offers three-yearly mammography to women between the ages of 50 and 64. It is planned to extend this to 50–69 by 2004. The effectiveness of mammography for women aged 50–69 of general population risk has been confirmed by several randomised controlled trials. Meta-analyses of these trials have shown that mammography will produce a relative reduction in breast cancer mortality of around 30% in these women.[9] The absolute reduction in risk is however small and it has been argued that the high financial costs of a screening programme outweigh the marginal clinical benefit.[10,11] The effectiveness of mammographic screening in younger women remains controversial. A US National Cancer Institute workshop concluded that there was no proof of benefit for women under the age of 50,[12] though evidence of benefit in women aged 40–49 is mounting[13,24] and some groups, including the American Cancer Society, recommend screening for women aged 40 to 49 years. Even if the relative risk reduction were the same as in older women, the absolute benefit would be considerably reduced because breast cancer is less common in this age group.

The potential harm caused by mammographic screening includes the false reassurance of women with a false negative mammogram, the adverse effects of unnecessary investigation of false positives and a potential increased cancer risk associated with early and repeated radiation exposure.[14]

Perhaps the most serious concern is the generation of false positive results. About 5% of women screened will have a mammographic abnormality, of whom only 10–20% will subsequently be found to have

cancer.[15] A positive or suspicious mammogram inevitably leads to further studies or interventions including fine needle aspiration, core biopsy or open biopsy, all of which have an associated morbidity. Considerable anxiety can be generated by false positive results.[16,17]

The issues discussed above relate to women of population risk, but the benefit harm ratio may be quite different in women at increased risk because of family history. Various authors have argued that because women with a family history are at greater risk it is likely that the absolute benefit will be greater.[2,10,18,19] This is likely to be true if the performance of the screening test is the same in high risk and average risk women. There is, in addition, the possibility of greater harm from mammography in some groups. For example, some genetic alterations may increase susceptibility to ionising radiation, though many experts believe the benefit of early detection will outweigh the risk.[2] It has also been assumed that because the prevalence of cancer will be higher in a high risk group, the problem of false positives will be lessened, but no research data are available to confirm this.

Basic Design

Over the last ten years there has been debate over the method of evaluation of mammographic surveillance in women at moderate familial risk. Despite repeated calls for a randomised study, the majority opinion in those who manage women with a family history of breast cancer is that a randomised study is not feasible. However a recent survey of BASO breast units indicated that 96 of 100 responding units offered regular mammography to women with a family history, although only 84 had written inclusion criteria.[20] Extrapolating anecdotal evidence from several units to the whole population gives an estimate of 30,000 mammograms being performed annually within the symptomatic breast service in the United Kingdom in women under 50. In this area there is a high volume of ongoing activity without adequate evaluation.

In our proposed evaluation, we plan to gather complete family history, screening, intervention and pathological data on a cohort of women between 40 and 49, and compare screening performance with ongoing and completed randomised studies.

The basic design is to follow up for five years 6,000 women offered annual mammography. It is possible that some centres may experience slippage of the interscreening interval, as this has been observed in the NHS Breast Screening Programme. To remain eligible for inclusion, centres must not allow slippage to an average interscreening interval of more than 18 months.

All breast cancers diagnosed in this period of observation will be followed up for breast cancer death, but our primary endpoint will be the tumour incidence rates by size, node status and histological grade of the tumours diagnosed. Rates by these factors, which are well established as predictors of breast cancer death, will be compared with those expected if screening had not taken place. These will be calculated from a contemporaneous comparison group (controls in the UK age trial) and a historical comparison group. Such comparisons will need careful interpretation and will be adjusted for the difference in underlying risk of breast cancer between our cohort and the comparison groups.

Eligibility Criteria

Data will be collected on women between the age of 40 and 49 offered annual mammography (recruited at ages 40–44 to ensure that each subject contributes five years of observation below age 50), who fulfil at least one of the following criteria:[21,22]

Inclusion criteria

- 1 first degree female – breast cancer at age 40 or under
- 1 first degree female – bilateral breast cancer first cancer diagnosed at age 50 or under
- 2 first or 1 first and 1 second degree female – both with breast cancer at age 60 or under (same side of family)
- 1 first or second degree female – breast and ovarian cancer first cancer diagnosed at age 60 or under

- 3 first or second degree female – breast or ovarian cancer at any age (same side of family)
- 1 first degree male – breast cancer at any age
- Paternal history of a minimum of 2 second degree relatives (NB. father's first degree relatives) with breast cancer at or less than age 50, or one with breast cancer at or less than age 50 and an ovarian cancer (any age), or paternal uncle/grandfather with breast cancer <50 years.

A first degree female relative is mother/sister/daughter
A second degree female relative is granddaughter/grandmother/aunt/niece
A paternal relative is on father's side

Exclusion criteria

- Inability to give written informed consent.
- Pregnant women.
- Women below the age of 40.
- Women with proven breast cancer or ductal carcinoma in situ.
- Women who have had bilateral prophylactic mastectomy.
- Women in whom a BRCA1 or BRCA2 mutation is present in the family, but who have been tested negative for the mutation.

Surveillance Strategy

Agreement on an appropriate regime depends on balancing two opposing considerations; a screening interval which is likely to be effective in view of the disease's natural history, and a screening frequency considered radiologically safe. There is considerable evidence that the disease has a shorter preclinical detectable period in women aged under 50,[23] and that mammographic parenchymal patterns in premenopausal women make for poorer sensitivity[24] of mammography in younger women. This suggests that screening every two years or more cannot be expected to make a substantial impact.[1,3,23,26] Two views at first screen will be necessary, and in this age group two views at subsequent screen are desirable. We therefore plan to offer annual two-view (craniocaudal and mediolateral oblique) mammography.

Study Centres And Units

All units offering regular mammography to women with a family history of breast cancer in the United Kingdom subject to certain quality control standards as outlined in this protocol will be invited to contribute data. The units forming the familial breast cancer group will form the core.

Collaborating units are expected to:

(a) operate a breast cancer unit in line with the recommendations of the British Breast Group and the BASO guidelines for surgeons in the treatment of symptomatic breast disease[27]
(b) have experience in mammography in symptomatic women under the age of 50
(c) either participate in the NHS Breast Screening Programme or offer mammographic services at a level consistent with the quality standards set out by the NHS BSP
(d) have a clearly defined referral line for high risk women to a regional clinical genetics service
(e) have at least one member of the multidisciplinary team trained in pedigree construction and interpretation, and risk analysis.

Power Calculation

Assuming it is possible to use the controls in the UK age trial as a comparison group, an important comparison would be the incidence of node positive tumours in our cohort with that expected from the comparison group, taking into account the different incidences in the two groups. From the Swedish Two-County Study controls, we would expect an unscreened tumour series in the age group 40–49 to be node positive in 42% of cases.[28] In the UK age trial control group, with seven years of cancer incidence in 106,000 women, we conservatively expect around 742 cancers, and therefore 311 (42%) node positive tumours.

Results from the Two-County Study suggest a screening sensitivity of 83% and a mean sojourn time (average duration of the preclinical screen-detectable period) of 2.44 years in women aged 40–49.[23] This suggests that with a one-year interval there would be 77% screen-detected, of which 11% would be node positive. We assume that the interval cancers would have the same 42% node positive as an unscreened group, giving an overall 18% node positive.

A study size of 6,000 will confer approximately 90% power to attain significance of the comparison of incidence rates of node positives, allowing for a 5% increase in standard deviation as a result of adjustment for different underlying risk in the two populations. Five years incidence in 6,000 women at around 4 per 1000 per year (due to high familial risk) would yield 120 cancers.

Data Capture

The evaluation requires three types of data. First, basic attributes recorded at baseline for all subjects. This includes family history, demographic and risk-factor data. The second is the screening information for each screening episode for each subject. The third is the cancer data collected for those who develop breast cancer during the five-year study period. Subjects will be flagged with ONS, but in view of the potential delays in cancer registration, centres will be asked to notify the co-ordinator of all breast cancers among recruits as they arise.

The details of the data required are given in the tables below. It is understood that not all the data items specified (notably updates of menopausal factors at each screen) will be available for all subjects, but there should at least be willingness to aim at recording these.

It is also planned to develop a final 'exit' questionnaire for all subjects at the end of their five years in the study. This will be the subject of a separate application for resources and will undergo ethical scrutiny before implementation.

Data will be accepted and processed by the audit co-ordinator in whatever format is most convenient for each centre. For subjects who have been screened before recruitment, screeening histories, again in whatever form is most convenient for each centre, would be welcome. For the most part, it is anticipated that centres will supply baseline and screening data in digital rather than paper format. In terms of the cancers diagnosed, some centres may prefer to supply cancer details in confidence on paper, as the number of cancers per centre is likely to be small. Some centres newly instigating the surveillance programme for purposes of this evaluation or who have previously not kept computerised records may need extra assistance in terms of data retrieval. In such cases, compact database can be supplied by the audit co-ordinator. This will be a simple database set up solely for the purpose of gathering the data listed below, and will not have complex relational links or provide automated prompts for call, recall etc.

1. Baseline data not pertaining to family history recorded at recruitment	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number – for flagging and a double check on identification
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Date of recruitment	__/__/____ Date of recording these data
BRCA1 identified?	BRCA1 mutation identified in family?
BRCA2 identified?	BRCA2 mutation identified in family?
Personal search	If yes to either of above, has subject been tested for relevant mutation?
Personal BRCA status	If yes, to above, was subject positive for relevant mutation?
Menopausal status	Pre- (regular periods), peri- (7–12 months since last period) or post (>12 months since last period)
Age at menopause (years)	0 if pre- or perimenopausal
Age at hysterectomy (years)	0 if no hysterectomy
HRT use	Never/previously/currently
Parity	Number of pregnancies to at least 30 weeks
Age at first pregnancy	Age at first pregnancy of at least 30 weeks duration
Age at menarche	Age in years at first period
Previous mammography	Screening mammography prior to recruitment (yes/no)?
Time since last mammo	If so, how long since last mammogram (months)?
Breast biopsy	Previous benign breast biopsy? No, ADH, LCIS, Benign NOS
Previous breast surgery?	Yes/no

1a. Family history of breast and ovarian cancer taken at baseline – list only relatives with a diagnosis						
Relative (first or second degree only)	Maternal/ paternal	Breast cancer (Y/N)	Bilateral (Y/N)	If Y, age first diagnosed	Ovarian cancer (Y/N)	If Y, age first diagnosed
How many sisters has the participant?						
How many sisters has the participant's mother?						
How many sisters has the participant's father?						
Has the family history data been verified from medical records?					Yes/no	

2. Screening and assessment data recorded for each screening episode	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Menopausal status	As in 1
Age at menopause	As in 1
Age at hysterectomy	As in 1
HRT use	As in 1
Date of mammogram	__/__/____
Screening round	Prevalence, second, third…
Suspicion left breast	Five-point score
Suspicion right breast	Five-point score
Mammographic pattern	Fatty/mixed/dense
Recall for assessment	Yes/No
Percutaneous biopsy	Yes/No
Physical examination	Not done/done after mammography result/done before mammography result/ mammography and physical examination results each assessed with knowledge of the other
Palpable lump	Yes/no
Other tests	Specify-use text field for name of test, text field for result. Up to 4 tests
Surgery/open biopsy	Yes/No
Final diagnosis	Breast cancer, BBD, normal- if cancer, form below required

3. Cancer data- all cancers, whether detected by screening or clinically	
Data item	Content
Name	Full name
Address	Address, excluding postcode
Postcode	Postcode of residence
NHS number	NHS number
Centre	Screening centre
Study number	Identification number. This together with centre uniquely specifies each subject
Date of birth	__/__/____
Date of diagnosis	__/__/____ Date of surgery if performed, date of most definitive test otherwise
Mode of detection	Prevalence screen, incidence screen, interval cancer, clinically diagnosed after non-attendance at last scheduled screen
Date of mammogram	__/__/____ Date of mammogram prompting diagnosis if screen detected
Date of last scheduled mammogram	__/__/____ Date of last scheduled mammogram if clinically detected
Date of last actual mammogram	__/__/____ Date of last actual mammogram if clinically detected
Tumour palpable	Is tumour palpable on physical examination?
Symptoms	Does the subject report any symptoms (yes/no)
Invasive status	Invasive/In situ
Neoadjuvant chemotherapy	Preoperative chemotherapy (yes/no)
Tumour size	Pathological size of invasive component (mm)
Lymph nodes examined	Number of lymph nodes examined pathologically
Lymph nodes positive	Number of pathologically examined nodes with tumour
Axillary surgery	None, sentinel only, sampling, clearance (either immediately or after positive sentinel finding)
Histological grade	1, 2 or 3
Histological type	DCIS, invasive ductal, lobular, medullary, tubular, mucinous…
Ultrasound size	Ultrasonically assessed size, if pathology not available (mm)
Mammographic size	Mammographic size if pathology and ultrasound size both unavailable (mm)
Surgery	None, local excision, mastectomy.
Radiotherapy	Yes/no
Hormone therapy	Yes/no
Chemotherapy	Yes/no
Oestrogen receptor status	Positive/negative
Progesterone receptor status	Positive/negative

Data Analysis

The major objective of the analysis will be to estimate the likelihood of death from breast cancer, on the basis of the features of the tumours diagnosed in our cohort, and compare this to that which would be expected if the mammographic surveillance had not taken place. To do this we take two comparison groups, one approximately contemporaneous and of comparable age, the UK Age Trial controls. The second is a historical group breast cancer cases with a family history of breast cancer, from France. The first group has the advantage that it is more comparable in temporal and demographic terms, but it involves adjustment for the fact that it does not have the same familial risk status as our cohort. The second does have at least a similar familial risk status, but is confounded by temporal, geographic and other factors.

Our cohort will consist of 6,000 women aged 40–44 at recruitment, with a significant family history of breast cancer, offered annual mammography and followed up for 5 years. The principal comparison group will be the control group of the UK Breast Screening Age Trial, which comprises 106,000 women aged 40–41 at recruitment, not offered screening, and followed up for seven years. These women are from the general population, so analysis of the data must be adjusted for the higher incidence in our cohort with a family history, and the potentially different distribution of histological type of breast cancer between the two groups.

The difference in underlying risk status between our study population and the comparison group needs careful evaluation in order to be correctly adjusted for. We therefore need an independent measure of average risk on the basis of family history and other risk factors, impartially applied to both groups. We therefore need to data on the family history and a minimal set of other breast cancer risk factors in our cohort and the comparison groups. It might be considered unethical to raise concerns about risk among the Age Trial controls, since this group is being offered no intervention. We therefore propose to estimate their average risk indirectly, by taking the family history and other risk factor information from a random sample of 3,000 members of the Age Trial Study Group, who are invited to annual mammography. The average risk of the control group can be estimated as that of the study group due to randomisation. The same average risk estimation will be performed on our cohort, so that incidence of advanced tumours and projected mortality from this can be compared with the expected incidence and projected mortality in the absence of screening on the basis of the age trial controls' incidence. The comparison will be adjusted for the difference between the two groups in the underlying average risk of breast cancer.

In addition, we have negotiated the use of a historical comparison group from France of 800 breast cancer patients aged 40–49 with a family history of breast cancer but no prior regular mammography. This will have to be adjusted for differences in stage distribution due to temporal and cultural effects. We shall use both published sources and the Age Trial control group to estimate such trends and adjust the comparisons.

The basic analytic strategy is therefore as follows.

1. Direct indicators-primary outcomes

(a) Projection of anticipated incidence of advanced breast cancer if screening had not been introduced, compared with actual incidence of advanced breast cancer since inception of screening by internal estimation.
(b) Projection of anticipated mortality from breast cancer if screening had not been introduced, compared to projected mortality since inception of screening, again using internal estimation.[30]
(c) Direct comparison with a contemporaneous (the controls from the UK Age Trial) unscreened group of rates of cancer by size, node status and malignancy grade, and comparison of the expected mortality from breast cancer as calculated from the size, node status and malignancy grade. These have been shown to be good predictors both of absolute survival of cases, and of the mortality reduction conferred by screening.[32,33] This will be adjusted for the greater incidence in our familial risk group and for the potentially different distribution of histological type in tumours in women with a family history of breast cancer. Centres will be invited to participate in a pathology review where cancers

which develop in either the family history cohort or the UK Age Trial controls will have their pathology reviewed on a research basis by the same team of pathologists organized by the Cancer Screening Evaluation Unit. In addition, the radiologist applicant will convene a radiology quality review.

2. Indirect indicators- secondary outcomes

(a) Sojourn time, lead time achieved, test sensitivity and program sensitivity.
(b) Estimates of over-diagnosis (if any), by comparison with expected incidence in the absence of screening and by reference to the balance of in situ and invasive cancers diagnosed at screening, by type of screen (prevalence or incidence).

3. Basic description- secondary outcomes

(a) Attendance, assessment, percutaneous biopsy and surgical biopsy rates.
(b) Cancer detection rates by age, size, node status and malignancy grade.
(c) Interval cancer incidence by age and time since last negative screen.
(d) Comparison of these with rates observed in the control and intervention groups of randomised screening trials (adjusted for a different incidence rate in this population).
(e) Cancers arising clinically in those not attending for screening (if available), by age and clinico-pathological attributes.

Economic Analysis

The economic evaluation will estimate the costs associated with the change in health service resource use arising as a result of implementing the standard mammographic surveillance strategy as opposed to no screening. The difference in costs will be compared to the estimated change in cancers detected, lives saved and life years gained. It is anticipated that the surveillance strategy will be more effective but also more costly, in which case incremental cost-effectiveness ratios will be presented in terms of the additional cost per cancer detected, per life saved and per life year gained. The findings will be stratified for low to moderate familial risk group and a moderate to high familial risk group using the criteria described above, under statistical analysis.

Psychosocial Study

Several psychological aspects of regular surveillance of at risk women will be examined by the Primary Care Education Research Group under the directorship of Dr Joan Austoker. These proposals, particularly concentrating on the importance of informed consent and the negative psychological consequences of false positive screening results, are outlined in Dr Austoker's application for five yearly programme funding to the CRC Scientific Committee. They are dealt with in a separate protocol.

Radiology And Pathology Reviews

All centres will be invited to take part in radiology and pathology reviews. In the former, all available mammograms from centres participating in the review up to and including the diagnostic mammogram will be reviewed by a panel of expert screening radiologists. In the latter, slides from all malignancies from centres participating in the review will be re-read by an expert panel of breast pathologists.

Basic Work-Plan For Participating Centres

Starting up

1. Obtain LREC approval (with support from the Audit co-ordinator and members of the management group if necessary).
2. Liaise with audit co-ordinator and local cancer research network to establish procedures and responsibilities for data retrieval and transfer.

Recruitment

1. Potential participants should have a risk assessment, including three-generation family history, performed be appropriately experienced member of staff. Subjects already under management at the

centre are eligible, even if they have already been screened (their first study screen should be the one immediately following recruitment, however).
2. First check that inclusion criteria are satisfied (pages 63–64) and that the potential recruit has none of the exclusion criteria (page 64).
3. If eligible, and subject gives consent, recruit.
4. Record baseline data for tables 1 and 1a (pages 66–67).
5. Regularly transfer baseline data to audit co-ordinator.

Screening

1. Invite each subject to annual mammography for five years (six screens in all). Slippage to more than 18 months between scheduled screens should not occur (if a participant fails to attend a screen, invite her again one year later as per protocol).
2. Record the data in table 2 (page 67) for each screening episode. Some of the data (for example the updated menopausal factors) may not be known but the basic screening details and outcomes must be recorded.
3. Regularly transfer screening data to audit co-ordinator.

Cancers

1. Every effort must be made to identify all breast cancers occurring in women recruited, whether detected at screening or not. Regular checks should be made with local pathology laboratories and treatment centres for breast cancers in recruits but diagnosed outwith the screening (e.g. interval cancer and non-attenders).
2. For each centre record data in table 3 (page 68). Some data may not be available, but as a minimum, relevant dates and basic pathology data (invasive status, size, node status, grade) should be recorded.
3. In view of the likely small numbers of cancers per centre, it may be more convenient to transfer cancer data to the audit co-ordinator as each single case arises.

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Appendix 2 FH01 blood study protocol

1. General information

Title
Validating two blood tests for early breast cancer and gathering epigenetic information in the FH01 cohort

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2. Background information

2.1 Investigational product

This is a study of potential markers for early breast cancer. The first is a test based on a gene expression panel (37 genes) in RNA from peripheral blood.[1] The second is of a combination of onco-antibody assays.[2] These two tests have already been fully developed and the purpose of this proposed study is to validate them. The third component of this study is more exploratory. It aims to describe the epigenetic profile of subjects at increased familial risk of breast cancer, in terms of a number of markers, notably methylation markers which have been shown to be influential in related malignancies such as prostate cancer.[3,4]

2.2 Summary of findings to date

In internal k–fold cross-validation, the gene expression test was found to have 87% sensitivity and 86% specificity.[1] In particular, the test was sensitive to stage I carcinoma. The onco-antibody test was found to have 64% sensitivity and 85% specificity. The epigenetic studies are at an exploratory stage, so prior results are not available.

2.3 Risks and benefits

The only risks to subjects from this study are those associated with having a blood sample drawn. No benefits are anticipated for the participants in this study during the period of the study. However, in the event of the study's results validating the test, those women with a positive blood test but no diagnosis of breast cancer as yet can be offered further diagnostic investigation and surveillance. Also, in this event, the potential benefits to future patients in terms of early diagnosis and treatment are substantial.

2.4 Administration of the intervention

It is planned to take two blood samples every six months from the participants over two years, i.e. taking 4 double samples in total from each participant. Follow-up for occurrence of breast cancer will continue for a further two years thereafter. The subjects have already consented to flagging and follow-up for breast cancer. No further commitment is required from the participants for purposes of this study. Samples will be analysed for the gene expression and onco-antibody test for those who are subsequently diagnosed with breast cancer and for ten control subjects for each breast cancer case. The first sample will be taken using a kit designed for stable extraction of RNA. The second will use a kit which suitable for subsequent

separation, using serum for the onco-antibody assay with ELISA, and plasma for the epigenetic testing. Results will not be communicated to the subjects as at this stage, they have no implications for the treatment or surveillance of the subjects. For the epigenetic markers, we propose to test the first 1,000 samples to ascertain the profile of this risk group. As cases are diagnosed, their stored plasma samples will be tested, and compared with the population profile, to generate hypotheses on predisposition, for confirmation in future validation studies.

2.5 Compliance

The study will comply with good clinical practice guidelines and all regulatory requirements.

2.6 Population to be studied

FH01 is a study of annual mammography in 6,669 women aged under 50 with an enhanced risk of breast cancer due to family history of the disease.[5] Women of this age tend to have radiologically dense tissue, reducing the sensitivity of mammography, and a biological marker of early breast cancer would be of great value in this population. We propose to investigate the blood tests in a subgroup of 4,000 of the FH01 population, taking 6-monthly blood samples over two years.

2.7 References

1. Sharma P, Sahni NS, Tibshirani R, *et al*. Early detection of breast cancer based on gene expression patterns in peripheral blood cells. *Breast Cancer Res* 2005;**7**:R634–44.
2. Chapman C, Murray A, Chakrabarti J, *et al*. Autoantibodies in breast cancer: their use as an aid to early diagnosis. *Ann Oncol* 2007;**18**:868–73.
3. Nelson WG, Yegnasubramanian S, Agoston AT, Bastian PJ, Lee BH, Nakayama M, De Marzo AM. Abnormal DNA methylation, epigenetics, and prostate cancer. *Fron Biosci* 2007;**12**:4254–66
4. Cooper CS, Foster CS. Concepts of epigenetics in prostate cancer development. *Br J Cancer* 2009;**100**:240–5.
5. FH01 management committee, steering committee and collaborators. The challenge of evaluating annual mammography screening for young women with a family history of breast cancer. *J Med Screening* 2006;**13**:177–182.

3. Objectives and purpose

As noted above, cross-validation exercises suggest that the gene expression test can identify early breast cancers with approximately 87% sensitivity and 76% specificity.[1] Recent improvements suggest that 86% specificity can be achieved (Christensen, in preparation). The corresponding results for the onco-antibody test indicate 64% sensitivity and 85% specificity.

A number of questions regarding the first two tests can be clarified using the FH01 cohort.[5] In the first instance, are the promising first results replicated in FH01: can the tests prospectively detect early cancers in this particular familial risk group as already observed in other settings? A related important point is: are they equally efficacious in women with dense breast tissue as in women with fatty replaced breast tissue?

More interesting, do the tests show positive results in some time in advance of suspicious imaging followed by a diagnosis of breast cancer? Does this apply equally to those with dense and non-dense breasts?

The epigenetic work is at the exploratory, hypothesis-generating stage. It is anticipated that a small number of DNA methylation markers will be identified as possible risk markers. These will need to be confirmed in future validation studies.

Thus, the objectives can be summarised as:

1. Prospective estimation of sensitivity of the tests in women with a significant family history of breast cancer.
2. Prospective estimation of specificity of the tests in women with a significant family history of breast cancer.
3. If the test proves sensitive to breast cancer in this setting, estimation of how far in advance of diagnosis a positive test is observed.
4. Do the answers to (1–3) above differ between those women with dense breasts and those with fatty replaced breasts?
5. What is the typical profile of this moderate familial risk group with respect to the epigenetic markers?
6. Do the epigenetic markers correlate with risk factors for breast cancer?
7. Are any of the epigenetic markers correlated with risk of breast cancer in this population?

4. Study design

From the seven highest recruiting Cancer Research networks to FH01 (Wales, Greater Manchester, Scotland, Avon, Merseyside/Cheshire, South-West London and Mid Trent) we can recruit 4,200 subjects so far free of cancer. We assume 4,000 to be conservative. These subjects will be asked to provide a blood sample every six months for two years. In addition to mammographic surveillance within FH01, the subjects are flagged with ONS, so that all breast cancers, whether detected at surveillance or outwith the study, will be ascertained. A dedicated member of staff at each centre will be trained by Diagenic staff in the use of the sample kits, and will be responsible for taking all samples.

The Diagenic staff will also provide training to laboratory staff in extraction and storage of the RNA. RNA will be extracted within a month of taking the samples, however the extracted RNA will be analysed for the gene expression test only for those who are subsequently diagnosed with breast cancer and for ten control subjects for each breast cancer case. Results will then be analysed for questions (1–4) in section 3 above.

The second blood sample will be separated, with plasma stored for epigenetic testing and the serum for the onco-antibody assays. The latter will be carried out by Oncimmune, a small company in Nottingham, UK. Under the scientific direction of Professor John Robertson at the University of Nottingham (UoN), the company has been working for over 4 years, optimizing the blood based assay for the detection of breast cancer.

The epigenetic markers will be measured in the Molecular Epidemiology Laboratory, Wolfson Institute of Preventive Medicine, which has considerable experience in these markers.

A basic summary of the study milestones is given below:

1. Obtain consent for four 6-monthly blood samples in 4,000 unaffected recruits in the seven largest participating CRN's in FH01.
2. The 4,000 subjects are already flagged for cancer and death along with the rest of the FH01 cohort.
3. Continue to take 6-monthly samples from the 4,000 for two years.
4. RNA will be extracted from the first blood sample, and stored. The second sample will be separated, and the plasma and serum stored separately.
5. The first 1,000 plasma samples will be tested for the epigenetic markers and results correlated with breast cancer risk factors.
6. As breast cancers are diagnosed, retrieve the stored samples for the entire sequence of samples for each cancer and for 10 controls per cancer, and apply the expression and antibody tests to these. For the epigenetic markers, only the cases will be tested, since 1,000 test results will already be available for comparison.

7. Calculate prospective estimates of sensitivity, specificity and predictive values, from the cancers and the 930 controls, first for the overall performance of the expression and antibody tests, then for the performance by time before diagnosis of the cancers, and by breast density. This analysis is to be carried out at two years and four years. Assess associations of the epigenetic markers with risk using unconditional logistic regression.

4.1 Endpoints

In view of the objectives above, the primary endpoints are the test results up to the time of diagnosis in breast cancer cases, and in disease free controls. From these, prospective sensitivity and specificity will be estimated, along with the lead time of the tests. Comparison of expression and antibody results between cases and controls will be made using conditional logistic regression, taking account of the matching. Unmatched comparison for the epigenetic markers will be carried out using unconditional logistic regression.

4.2 Type of study

This is a single-arm prospective cohort study.

4.3 Measures taken to avoid bias

The gene expression testing of the blood samples will be carried out blind to the diagnostic category (cancer/no cancer). All samples tested from cancer cases will be taken prediagnosis. PaxGene blood kits will be used which contain a solution to prevent RNA deterioration. Extraction of RNA will be carried out using state of the art Qiagen equipment. Separation and storage of serum and plasma are standard. Testing for the oncoantibodies and the epigenetic markers will be carried out in two laboratories with proven track experience in the respective areas (Oncimmune and the Molecular Epidemiology Laboratory, London).

4.4 Regimen

Blood samples of 2.5 ml will be taken every six months using PaxGene blood kits. A second sample of 5 ml will be taken using standard equipment.

4.5 Duration

Four sets of two blood samples will be taken over two years. Aside from providing these blood samples, no further commitment is asked of the subjects.

4.6 Stopping rules

NA.

4.7 Accountability procedures

The products under investigation are potential diagnostic tests which are under validation. They have no bearing on the treatment or clinical outcome of the study subjects. The only indemnity issues relate to taking the blood samples, and these will be covered by the sponsor. Results of the blood tests will not be communicated to the subjects, as at this validation stage they have no implications for the treatment or surveillance of the subjects.

4.8 Maintenance of treatment codes

NA.

4.9 CRF data

NA.

5. Selection and withdrawal of subjects

5.1 Inclusion criteria

Subjects must be participants in FH01.

Only subjects with no prior diagnosis of breast cancer will be included.

Only subjects who give informed consent will be included.

5.2 Exclusion criteria

Prior breast cancer.

Failure to give informed consent.

Presence of any condition contraindicating regular venepuncture.

5.3 Withdrawal criteria

- Subjects who decide to withdraw will be removed from the study, and their wishes respected with regard to treatment of data and biological material collected so far.
- Subjects for whom complications or adverse events occur as a result of the blood sampling will be withdrawn.
- Subjects who develop a breast cancer will no longer be asked to provide blood samples, and their active period in the study will be truncated at their date of surgical treatment.
- Subjects who develop comorbidity contraindicating the taking of blood samples or rendering it personally inconvenient for them to continue will be removed from the study and their wishes respected with regard to treatment of data and biological material collected so far.
- Subjects who are removed from the study for any reason will not be replaced.

6. Treatment of subjects

NA.

7. Assessment of efficacy

In this context it must be emphasised that we are referring to screening and diagnostic efficacy, not treatment efficacy. The subjects in this study are healthy female population members, not patients.

7.1 Efficacy parameters

Sensitivity, specificity, positive and negative predictive values of the test, in the population as a whole and separately for those with dense and fatty replaced breast tissue. Odds ratio estimates of relative risk will also be calculated.

7.2 Timing, assessing and recording efficacy parameters

When a cancer is notified to the CPTU, the informatic staff will select ten controls matched for date of birth within one year, who have not as yet developed breast cancer. The identification numbers of the eleven subjects will be notified to the laboratory staff who will arrange for testing of the entire blood sample history of these subjects for the gene expression and onco-antibody tests. The laboratory staff will not be informed which subject is the cancer case. The laboratory staff will then communicate the test results to the informatic staff at CPTU. These will be stored securely for future statistical analysis when the study is complete.

8. Assessment of safety

8.1 Safety parameters

The only such parameter is the outcome of each blood sampling episode.

8.2 Methods for timing, assessment, recording and analysis of safety parameters

The study will have an independent data monitoring and ethics committee (DMEC). Any adverse events in relation to blood samples will be recorded and reported immediately to the investigators and the DMEC chair (see below). The DMEC will meet six-monthly.

8.3 Procedures for eliciting reports, etc.

The staff taking the blood samples will also receive as part of their training instructions as to immediate reporting of any adverse events or any condition arising in a participant which might affect her suitability for continued blood sampling. A standard adverse event and intercurrent illness form will be provided for reporting. The only adverse events related to the research are untoward sequelae of venepuncture, including vasovagal attack (faint) and possible consequences such as indirect injury, bruising, tissue injury, cellulitis and accidental arterial puncture.

8.4 Follow-up of subjects with adverse events

All blood sampling will cease in those subjects with serious adverse events consequent upon having a sample taken. They will be referred immediately for medical attention. Their follow-up in the study for breast cancer incidence will continue unless they request otherwise.

9. Statistics

9.1 Statistical methods and timing of analysis

Gene expression and onco-antibody tests

We shall calculate sensitivities, specificities and predictive values, and will carry out ROC analysis in relation to test cut-off points, estimating the area under the ROC curve. We shall also estimate the likely benefit in terms of additional cases detected early as a result of augmenting mammography with the test. This will be based on the performance characteristics of testing one year or more before cancers are diagnosed. Analyses will be carried out twice, once of cases and controls accrued at two years, when the blood sampling ceases, and again after a further two years of follow-up, i.e. after four years. We shall also compare cases and controls with respect to test status using conditional logistic regression, including adjusting for risk factors and testing for effect modifications (interactions).

Epigenetic markers

We shall first estimate associations of the markers with risk factors for breast cancer using unconditional logistic regression. Cases will be compared with the original sample of 1,000 (excluding any who have subsequently been diagnosed with breast cancer) also using unconditional logistic regression.

9.2 Number of subjects

Approximately half of our cohort have mixed or dense breast patterns. The incidence of breast cancer in the last four years in FH01 was 4.2 per 1000 per year. In the coming four years, we can expect this to be 38% higher due to the ageing of the cohort. We would therefore expect 5.8 cancers per 1000 per year in the next four years. Thus in a subcohort of 4,000 followed up over four years we would expect 93 cancers.

We propose to select 10 controls from the population for each breast cancer case. Then the entire blood sample history of the cases and controls will be tested. From the anticipated 93 cancers and 930 controls, we shall estimate the sensitivities and specificities specified in objectives (1–4) above.

Based on the previous 87% estimate of sensitivity and 76% estimate of specificity, this would have a 95% confidence interval of no more than 7% in either direction on the sensitivity, and a 95% CI of no more than 3% in either direction on the specificity. For the antibody study, 93 cancers and 930 controls will give a 95% confidence interval on the sensitivity of 64% of no more than 10% in either direction, and on a specificity of 85% of no more than 3% in either direction.

This will give prospective confirmation of the tests' predictive power for breast cancer. If we assume that testing one year before mammographic diagnosis has a lesser sensitivity, say 70%, 93 cancers would give a 95% CI on the sensitivity of no more than 10% in either direction.

Because density is associated with increased risk of breast cancer one would expect 60% of the tumours to be in those with dense breast tissue, even though only 50% of the screened subjects in FH01 are likely to have dense tissue. So, to assess sensitivity to tumours in dense breasts, we might expect to have 60% of 93 cancers, i.e. 56 cancers, which would give a 95% CI on a sensitivity of 87% with no more than 9% in either direction.

9.3 Level of significance

5% will be used throughout, although the emphasis in the statistical analysis will be point and interval estimation rather than significance testing.

9.4 Criteria for termination

None. The study will run for four years and no early stopping is anticipated.

9.5 Missing, unused and spurious data

The FH01 co-ordinator in Breast Test Wales will continue to actively solicit routine FH01 data, particularly on mammography episodes and cancer diagnoses, which is delayed in arriving at the data centre. FH01 data is subject to routine logic cross-checks. The data manager in CPTU will monitor data on blood sampling and will investigate if a particular centre appears to have a hiatus in recruitment or inflow of data.

9.6 Procedures for reporting any deviations from the statistical plan

No such deviations are anticipated. Loss of information or failure to recruit the anticipated numbers will be reported in full in the final report.

9.7 Selection of subjects

All subjects at each of the seven centres listed in section 4 above will be considered eligible unless otherwise indicated. For details of selection and withdrawal, see section 5 above.

10. Direct access to source data/documents

The investigators undertake to comply with authorised audits, regulatory inspections, ethics committee reviews, etc. All documents and data will be made available to the inspecting authorities on request.

11. Quality control and quality assurance

The RNA extraction procedures in the laboratory have inbuilt quality indicators which will be monitored in real time. Any centre which is out of the control range for these will be subject to immediate retraining.

12. Ethics

The major issue is that the participants are asked to provide eight blood samples over two years (two samples every six months) for no clinical benefit to themselves. This will be made clear in the information sheet. In addition, data will be stored on subjects and they are flagged and followed up for breast cancer. They have already given consent for this. The study will undergo ethical scrutiny by NRES.

13. Data handling and record keeping

Data for statistical analysis will be pseudonymised. Data will be held, password and firewall protected, at the Cancer Trials Prevention Unit (CPTU), Wolfson Institute of Preventive Medicine.

14. Financing and insurance

FH01 is financed by HTA. The blood study will be conducted with considerable contributions in kind (testing and training) from DiaGenic and oncimmune. We believe there are no serious insurance/indemnity issues but will take advice from the R and D department of the sponsoring institution.

15. Publication policy

Results, whether positive or negative, will be published in peer-reviewed medical journals.

16. Supplements

See attached protocol of FH01 main study.

Appendix 3 Information sheet used in England and Wales for potential FH01 recruits

BREAST SCREENING FOR WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

(FH01)

An evaluation funded by the NHS Research and Development Programme.

INFORMATION SHEET

You are being invited to take part in a project to evaluate the effectiveness of mammographic screening in women with a family history of breast cancer. Before you decide to take part in the project, it is important for you to understand why the evaluation is being done and what it will involve. Please take time to think about the following information on breast screening and discuss it with others if you wish. If you require further information on breast screening, or on the evaluation project, please ask us. Take time to decide whether or not you wish to take part.

What's the purpose of screening?

The purpose of breast screening is to detect breast cancer as early as possible by picking up changes to the breast that often cannot be seen or felt. In the UK, around one in every 9 women will develop breast cancer at some point in their life-time. Women with a family history of the disease have a higher risk. Early diagnosis of breast cancer offers the best chance of a successful recovery, however it is not known whether or not breast screening is effective in women under 50 with a family history of breast cancer.

What's the purpose of the evaluation?

The purpose of this evaluation is to look at the effectiveness of providing annual mammographic screening in women under 50 with a family history of breast cancer. The evaluation will involve collecting data from 10,000 women aged 40–44 with a significant family history of breast cancer, who are offered regular mammographic surveillance over 5 years.

How does screening work?

X-ray pictures called mammograms are taken of the breast. Two views of each breast are taken at every screening appointment. Women having a mammogram are asked to undress to the waist, so wearing a separate top rather than a dress may be preferable. The actual X-ray only takes a few minutes and the level of radiation is very low.

Who can have screening?

In the UK women aged between 50 and 64 are routinely invited for breast screening every three years by the National Breast Screening Programme. Work is being carried out to extend the programme to all women up to and including the age of 70. Continued three yearly screening from the age of 64 is available in those areas where the programme has not been extended if requested by the woman and for those over 70 where the programme has been extended.

Why does screening not start until the age of 50?

Research studies have shown that screening significantly reduces deaths from breast cancer in women aged 50–64 who attend for screening. For women under 50 the effectiveness of screening is controversial.

Experts in the UK currently believe the disadvantages of screening outweigh the advantages for women in the general population under 50, hence it is not routinely offered.

Why am I being offered screening before I am 50?

For younger women who have an increased risk of developing breast cancer on account of their family history, the collective view of experts in the UK is currently that the benefits of screening are likely to outweigh the harms. However, it is important to realise that, as yet, there is no strong evidence to prove whether or not breast screening in younger women with a family history is effective and will reduce deaths from breast cancer.

Is there anything else I need to know?

For the purposes of this evaluation we need to hold personal information on you to issue regular invitations and to check on the performance of the programme. We take great care to keep your personal details confidential and only share information with people who have a statutory or medical requirement for it, for example your General Practitioner.

We are centralising personal data from everyone involved in this evaluation. The data will be held in a database on behalf of the NHS by Breast Test Wales, the Welsh equivalent of the NHS Breast Screening Programme, which is based in Cardiff. These personal details will remain confidential to Breast Test Wales. Only anonymised details will be released to the research teams involved in the evaluation.

If this evaluation provides evidence to the NHS that regular mammography is not beneficial then this will be formally reported to the National Screening Committee who reserve the right to advise that regular mammography will not be available to women under 50.

How reliable is screening?

Mammography is currently the best way of detecting breast cancer early. However, like other screening tests it is not perfect:

- Some cancers are very difficult to see on the X-ray
- Some cancers, even though they are there, cannot be seen on the X-ray at all
- The person reading the X-ray may miss the cancer (this will happen occasionally, no matter how experienced the reader is)

Does screening hurt?

Each breast needs to be held firmly in position and compressed as the X-ray is taken, in order to obtain a clear picture. Some women describe a mammogram as uncomfortable, while others describe it as painful. Any discomfort only lasts for a brief period of time.

At what age does screening start for women with a family history?

In women with a family history screening usually starts at age 40, although in some women with a strong family history, regular mammography will be offered from a younger age.

How often would I have a mammogram?

Screening is currently recommended every year for younger women with a family history. This is because breast cancer in younger women may appear more quickly than in older women.

How would I get my results?

When you have had the mammogram, a member of the screening team will tell you how and approximately when you will get your result.

What does it mean if I am called back for more tests?

Some women (about 1 in every 20 who goes for screening) are asked to come back for a further appointment because the appearance of the X-ray is not completely normal. It may be necessary to perform further mammographic views, or other investigations such as ultrasound or a biopsy may be needed. In the majority of cases, these further tests will show there is nothing to worry about.

What should I do if I notice any breast symptoms?

As breast cancer can occur between screens it is important you see your doctor immediately if you notice any unusual changes in your breasts, even if you have just had a normal screen or are due for a screen in a month or so.

So should I go for screening or not?

To help you decide whether or not **you** want to attend for breast screening, the main advantages and disadvantages of regular mammography in women under 50 with a family history of breast cancer are outlined below:

- Screening is currently believed to provide the best chance of detecting cancers at an early stage when treatment can offer the best chance of a successful recovery. However there is no good evidence that this is the case.
- Around seventy per cent of the cancers found at screening are still small enough to be removed from the breast. This means that the whole breast does not have to be removed.
- Screening will **not** detect all breast cancers, so some cancers will be missed at screening and some women may be falsely reassured.
- Screening will **not** prevent breast cancer from developing.
- Approximately one in every 20 women who go for screening will be called back for further investigations. Most of the women who have further tests will turn out not to have cancer. However, women who are called back often find this a very anxious time.
- Each mammogram gives a small dose of radiation. The expert view is that the dose is so small it is unlikely to cause any harm. However, it is theoretically possible that regular mammography in younger women could actually promote the development of a breast cancer.
- Many women find mammography uncomfortable or painful.

What if I may be/am pregnant?

The radiation dose to the abdomen during mammography is extremely low, so you could still be screened. However, you may prefer to wait until you know you are not pregnant.

What do I do now?

If you would like to be part of the evaluation including regular mammography, please sign the consent form and return it to the person named on the form

What if I do not want regular mammography?

You do not have to choose screening now. You will be invited automatically for screening after the age of 50 by the NHS Breast Screening Programme. If you change your mind before then and decide that you do wish to have screening please contact the person named on the consent form.

How will the evaluation affect me?

Your treatment will not be affected in any way if you participate in the evaluation. You will receive exactly the same mammographic screening if you participate in the evaluation as you would outside the evaluation. You may withdraw from the evaluation at any time if you wish, without this affecting your treatment. Your mammograms and the results of any further tests, which you may have, may be reviewed by a panel of national experts.

Appendix 4 Information sheet for primary care staff

BREAST SCREENING FOR WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

An evaluation funded by the NHS Research and Development Programme.

INFORMATION FOR PRIMARY CARE

The importance of breast screening

In the UK, 1 in 9 women develops breast cancer at some time in her life. Screening by mammography finds early changes that often cannot be seen or felt. Early diagnosis offers the best chance of full recovery. Most cases of breast cancer detected early are successfully treated with the modern treatments now available. Screening does not prevent cancer and like most tests is not 100% accurate. This means that some cancers may not be detected. It also means that some women may receive unnecessary investigations and/or procedures.

Who is offered screening?

The NHS Breast Screening Programme invites all women in the UK between the ages of 50 and 64 for screening mammography every three years. Breast cancer is more common in women over 50 than in younger women (approximately 4 out of 5 women diagnosed with breast cancer are over 50) and screening with mammography has been proven to be effective in this age group. Invitations will continue to be offered up to the age of 70.

Women with a family history of breast cancer

Women with a family history of breast cancer may benefit from starting regular mammography earlier than 50. In order to investigate whether this practice is beneficial or not the NHS Research and Development Programme have funded a large prospective evaluation of regular mammography in women under 50 with a family history of breast cancer.

Eligible women will be offered annual mammography in their local breast care clinic from the age of 40, until they become eligible for the National Programme.

Results will be sent by post within 3 weeks to each woman, and a copy sent to their primary care team. If the mammogram shows an abnormality, the woman will be recalled directly for further assessment, including possible biopsy at the breast clinic.

Women entering this evaluation give written consent after reading the information leaflet 'Breast Screening for Women with a Family History of Breast Cancer'. They agree to personal information being stored in a database held on behalf of the NHS by Breast Test Wales in Cardiff. Only anonymous data will be released by Breast Test Wales to research teams involved in the evaluation.

This evaluation will produce evidence to the NHS, which will be reported to the National Screening Committee. If that evidence shows no benefit, the National Screening Committee reserves the right to advise the NHS that regular screening mammography should not be offered to women under 50.

Appendix 5 Data proformas

1. Baseline data not pertaining to family history recorded at recruitment				
Name				
Address 1				
Address 2				
Address 3				
Address 4				
Postcode				
NHS number				
Hospital Number				
Study number (Study number as used by centre)				
Date of birth				
Date of recruitment (Date consent form signed)				
BRCA1 mutation identified in family	Not tested	Positive	Negative	Unknown
BRCA2 mutation identified in family	Not tested	Positive	Negative	Unknown
Personal search (If yes to either of above, has subject been tested for relevant mutation)	Yes	No	Unknown	
Personal BRCA status (If yes, to above, was subject positive for relevant mutation?)	Yes	No	Unknown	
Menopausal status	Pre (regular periods)	Peri- (7–12 months since last period)		
	Post (>12 months since last period)	Unknown		
Age at menopause (years) (0 if pre- or perimenopausal)				
Age at hysterectomy/opherectomy (years)				
HRT use	Never	Previously		
	Currently	Unknown		
Parity (Number of pregnancies to at least 30 weeks)				
Age at first pregnancy (Age at first pregnancy of at least 30 weeks duration)				
Age at menarche				
Previous screening mammography	Yes	No	N/K	
Time since last mammogram (Months)				
Previous Breast biopsy?	No	ADH		
	LCIS	Benign NOS		
Previous breast surgery? (Yes/no)	Yes	No	N/K	
How many sisters has the participant?				
How many sisters has the participant's mother?				
How many sisters has the participant's father?				
Has the family history data been verified from medical records?	Yes	No	N/K	

1a. Family history of breast and ovarian cancer taken at baseline – list only relatives with a diagnosis						
Relative (first or second degree only)	Maternal or paternal	Breast cancer (Y/N)	Bilateral (Y/N)	Age first diagnosed	Ovarian cancer (Y/N)	Age first diagnosed

2. Screening and assessment data recorded for each screening episode						
Name						
NHS number						
Screening Centre						
Study number						
Date of mammogram						
Screening round	**1**	**2**	**3**	**4**	**5**	**6**
Suspicion left breast (5 point score)						
Suspicion right breast (5 point score)						
Mammographic pattern (Fatty/mixed/dense)						
Recall for assessment (Yes/No)						
Percutaneous biopsy (Yes/No)						
Physical examination – not done (1) done after mammography result (2) done before mammography result (3) mammography and physical examination results each assessed with knowledge of the other (4)						
Ultrasound scan performed – not done (1) done after mammography result (2) done before mammography result (3) mammography and USS results each assessed with knowledge of the other (4)						
Palpable lump (Yes/No)						
Other tests 1						
Other test 1 result						
Other tests 2						
Other test 2 result						
Surgery/open biopsy (Yes/No)						
Final diagnosis (Breast cancer, BBD, normal- if cancer, form below required)						

3. Cancer data – all cancers, whether detected by screening or clinically	
Name	
NHS number	
Screening Centre	
Study number	
Date of diagnosis (Date of surgery, or date of most definitive test otherwise)	
Mode of detection (Prevalence screen, incidence screen, interval cancer, clinically diagnosed after non-attendance at last scheduled screen)	
Date of mammogram (prompting diagnosis if screen detected)	
Date of last scheduled mammogram (if clinically detected)	
Date of last actual mammogram (if clinically detected)	
Tumour palpable (on physical examination)	
Symptoms (yes/no)	
Invasive or in situs	
Neoadjuvant chemotherapy Preoperative chemotherapy (yes/no)	
Tumour size Pathological size of invasive component (mm)	
Lymph nodes examined Number of lymph nodes examined pathologically	
Lymph nodes positive (Number of pathologically examined nodes with tumour)	
Axillary surgery (None, sentinel only, sampling, clearance (either immediately or after positive sentinel finding))	
Histological grade (1, 2 or 3)	
Histological type (DCIS, invasive ductal, lobular, medullary, tubular, mucinous)	
Ultrasound size (Ultrasonically assessed size, if pathology not available (mm))	
Mammographic size (if pathology and ultrasound size both unavailable (mm))	
Surgery (None, local excision, mastectomy)	
Radiotherapy (Yes/no)	
Hormone therapy (Yes/no)	
Chemotherapy (Yes/no)	

3. Cancer data – all cancers, whether detected by screening or clinically	
Oestrogen receptor status (Positive/negative)	
Progesterone receptor status (Positive/negative)	

EME
HS&DR
HTA
PGfAR
PHR

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