| **Study****Country****USPSTF Quality** | **Study aim(s)** | **Study design** | **Inclusion criteria** | **Exclusion criteria** | **Intervention arm** | **N randomized** |
| --- | --- | --- | --- | --- | --- | --- |
| ACS113,115,186New ZealandFair | Assess the long-term effects of calcium on bone density and fracture incidence; determine effect of calcium supplementation on CVD and death | RCT | Women age >55 years, >5 years postmenopausal, and life expectancy >5 years | Women receiving therapy for osteoporosis or taking calcium supplements; any other major ongoing disease, creatinine >1.8 mg/dL, untreated hypo- or hyperthyroidism, liver disease, serum 25-hydroxyvitamin D <10 mcg/L, malignancy, metabolic bone disease; regular users of HRT, anabolic steroids, glucocorticoids, or bisphosphonates in the previous year; lumbar spine bone density above the age-appropriate normal levels | Calcium 1,000 mg bid | 732 |
| Placebo | 739 |
| AFPPS101,102United States and CanadaFair | Assess the safety and efficacy of folic acid supplementation for preventing colorectal cancer adenoma | RCT | Ages 21–80 years, had ≥1 of the following criteria: ≥1 histologically confirmed adenomas removed within 3 months before recruitment, ≥1 histologically confirmed adenomas removed within 16 months before recruitment, lifetime history of ≥2 confirmed adenomas, or a histologically confirmed adenoma of ≥1 cm in diameter before recruitment; complete colonoscopy with removal of all known polyps within 3 months of enrollment | History of familial polyposis syndromes, invasive large intestine cancer, malabsorption syndromes, any condition that could be worsened by supplemental aspirin or folic acid, or any condition commonly treated with aspirin, NSAIDs, or folate | Folic acid 1 mg qd | 516 |
| Placebo | 505 |
| ASAP79FinlandFair | Determine efficacy of vitamin E and vitamin C supplementation on progression of carotid atherosclerosis | RCT, 2x2 factorial design\* | Patients with hypercholesterolemia (serum cholesterol of ≥5.0 mmol/L) ages 45–69 years  | Premenopausal, had regular oral estrogen substitution therapy, regular intake of antioxidants, ASA or any other drug with antioxidative properties, severely obese (BMI >32 kg/m2), type 1 diabetes, uncontrolled hypertension (DBP >105 mm Hg), any condition limiting mobility making study visits impossible, severe disease-shortening life expectancy or other disease/condition worsening adherence to the measurements or treatment | Vitamin E 91 mg bid | 130 |
| Vitamin C 250 mg bid | 130 |
| Vitamin E 91 mg bid + vitamin C 250 mg bid | 130 |
| Placebo | 130 |
| ATBC59,66,69-73,76-78,87,88,155-157FinlandGood | Reduce the incidence of lung cancer with vitamin E and/or beta-carotene supplementation; reduce the incidence of other cancer, CVD, and other chronic diseases | RCT, 2x2 factorial design | Male smokers (≥5 cigarettes per day) ages 50–69 years living in southwestern Finland | History of cancer (other than NMSC or CIS) or serious disease that would prevent (or limit) participation (severe angina on exertion [Rose criteria grade 2], chronic renal insufficiency, cirrhosis of liver, chronic alcoholism, psychiatric disorder, physical disability); taking supplements of vitamin E (>20 mg), vitmain A (>20,000 IU) or beta-carotene (>6 mg) in excess of predefined doses; treated with anticoagulants; nonsmokers | Vitamin E 50 mg qd | 7,286 |
| Beta-carotene 20 mg qd | 7,282 |
| Vitamin E 50 mg qd + beta-carotene 20 mg qd | 7,278 |
| Placebo | 7,287 |
| CARET60,67,74,161-164United StatesGood | Determine the effect of beta-carotene plus vitamin A on preventing lung cancer in high-risk populations | RCT | Asbestos-exposed participants: men ages 45–69 years; exposed to asbestos on the job 15 years prior to randomization; chest x-ray positive for asbestos-related lung disease (fibrosis) or have worked in high-risk trades for 5 years; current smokers or have smoked in the last 15 years\*Heavy smokers: men and women ages 50–69 years; had ≥20 pack-years smoking history; either currently smoking or had quit smoking within the previous 6 years† | NR | Beta-carotene 30 mg qd + vitamin A 25,000 IU qd | 9,420 |
| Placebo | 8,894 |
| CPPS114,116United StatesFair | Determine if calcium intake increases the risk of prostate cancer; impacts the recurrence of colorectal adenoma | RCT | Age <80 years; in good health; no history of familial polyposis, invasive large-bowel cancer, malabsorption syndromes, or any condition that might be worsened by supplemental calcium; men without a history of prostate cancer for prostate cancer publication only | NR | Calcium 1,200 mg bid | 464 |
| Placebo | 466 |
| Dean 2011105AustraliaGood | Assess whether vitamin D supplementation would lead to improvement in cognitive and emotional functioning | RCT | Healthy volunteers age ≥18 years with sufficient English language skills required to complete study protocol | Current use of vitamin D or calcium supplements; history of adverse reactions to vitamin supplements; current or past diagnosis of mood or psychotic disorder; history of neurologic illness, including cerebrovascular accident, CNS tumors, head trauma, multiple sclerosis, epilepsy, movement disorder, or migraine treatment; current or recent (12 months) history of alcohol or illicit drug dependence; intellectual disability; pregnancy or currently breastfeeding or potential to become pregnant during the trial; history of severe renal impairment | Vitamin D 5,000 IU qd | 63 |
| Placebo | 65 |
| Graat 200252NetherlandsGood | Determine if long-term supplementation of a multivitamin and/or vitamin E reduces the incidence and severity of acute respiratory tract infections | RCT, 2x2 factorial design\* | Men and women age >60 years, noninstitutionalized | Used immunosuppressive treatment, anticoagulants interfering with vitamin K metabolism, dietary supplement in the previous 2 months or if they had a history of cancer, liver disease, or fat malabsorption during the 5 years prior to randomization | Multivitamin qd (vitamin A 600 mcg, beta-carotene 1.2 mg, vitamin C 60 mg, vitamin E 10 mg, vitamin D3 5 mcg, vitamin K 30 mcg, vitamin B1 1.4 mg, vitamin B2 1.6 mg, vitamin B3 18 mg, vitamin B5 6 mg, vitamin B6 2 mg, biotin 150 mcg, folic acid 200 mcg, vitamin B12 1 mcg, zinc 10 mg, selenium 25 mcg, iron 4 mg, Mg 30 mg, Cu 1 mg, iodine 100 mcg, calcium 74 mg, phosphor 49 mg, Mn 1 mg, Cr 25 mcg, Mo 25 mcg, silicium 2 mcg) | 163 |
| Vitamin E 200 mg | 164 |
| Multivitamin qd (see above) + vitamin E 200 mg qd | 172 |
| Placebo | 153 |
| IWHS96United StatesGood | Examine association between various lifestyle factors (e.g., supplement use) and morality, incidence of cancer, diabetes mellitus, hypertension, and fracture | Prospective cohort study | Women ages 55–69 years with a valid Iowa driver's license | Premenopausal at the time of the baseline questionnaire; had an implausible energy intake of <600 kcal or >5,000 kcal; failed to complete a substantial portion (>29 missing items) of the food frequency questionnaire; history of cancer other than skin cancer | Vitamin A† | 12,293 |
| Nonusers of vitamin A | 22,410 |
| Lappe 2007109,175United StatesFair | Determine the effect of calcium with or without vitamin Don skeletal status; determine efficacy in reducing incidence of cancer | RCT | Age >55 years, absence of known cancer, both mental and physical status sufficiently good to allow for 4-year participation in study; women only | NR | Calcium 1,400–1,500 mg qd§ | 445 |
| Calcium 1,400 mg qd + vitamin D3 25 mcg qd | 446 |
| Placebo | 288 |
| NHS53United StatesGood | Assess relationship between vitamin A supplementation and risk of hip fractures | Prospective cohort study | Postmenopausal (via natural or surgical menopause) registered nurses who responded to questionnaire in 1980 | Previous hip fracture or diagnosis of cancer, heart disease, stroke, or osteoporosis | Supplement users (vitamin A, multivitamin, or beta-carotene)‡ | NR |
| Nonusers of supplements | NR |
| NPC89,90,92-95,173United StatesFair | Determine if selenium supplementation reduces the incidence of BCC and SCC of the skin; reduces the incidence of other cancers | RCT | A history of ≥2 BCC or 1 SCC of the skin, with 1 of these occurring within the previous year; a 5-year life expectancy; no reported internal malignancies treated within the previous 5 years | History of significant kidney or liver disease | Selenium 200 mcg qd | 653 |
| Brewer’s yeast | 659 |
| NSCPS64,160AustraliaGood | Determine if beta-carotene can prevent skin cancer | RCT | Resident of Nambour, Queensland; ages 20–69 years when they took part in SCPS | Participants in prevalence study who were taking vitamin supplements containing beta-carotene and those already applying sunscreen on a strict daily basis were excluded | Beta-carotene 30 mg qd | 820 |
| Placebo | 801 |
| PHS-I61,65,68,158United StatesGood | Assess the impact of beta-carotene supplementation on the incidence of cancer and CVD | RCT, 2x2 factorial design\*§ | U.S. male physicians; no history of cancer (except NMSC), MI, stroke, or transient cerebral ischema | History of the above conditions;current liver or renal disease, peptic ulcer, or gout; contraindications to aspirin consumption; current use of aspirin, other platelet-active drugs, or NSAIDs; current use of vitamin A supplement | Beta-carotene 50 mg qod | 11,036 |
| No beta-carotene | 11,035 |
| PHS-II (vitamin C and E arms)80,83, 154United StatesGood | Evaluate whether long-term vitamin E or vitamin C supplementation decreases the risk of major cardiovascular events and cancer | RCT, 2x2x2x2 factorial design\*║ | Male physicians age ≥55 years; men from PHS I with a history of MI, stroke, or cancer were eligible for PHS II (new participants were not eligible if they had a history of CVD or cancer) | Those unwilling to avoid using outside supplements; a history of cirrhosis or active liver disease in the past 6 months, cancer (except NMSC) (new participants), CVD (new participants), current renal disease, peptic ulcer, or gout; currently on anticoagulants | Vitamin E 400 IU qd | 3,659 |
| Vitamin C 500 mg qd | 3,673 |
| Vitamin E 400 IU qd + vitamin C 500 mg qd | 3,656 |
| Placebo | 3,653 |
| PHS-II (multivitamin arm)50 United StatesGood | Evaluate whether long-term multivitamin supplementation decreases the risk of major cardiovascular events and cancer | RCT, 2x2x2x2 factorial design\*║ | Male physicians age ≥55 years; men from PHS I with a history of MI, stroke, or cancer were eligible for PHS II (new participants were not eligible if they had a history of CVD or cancer) | Those unwilling to avoid using outside supplements; a history of cirrhosis or active liver disease in the past 6 months, cancer (except NMSC) (new participants), CVD (new participants), current renal disease, peptic ulcer, or gout; currently on anticoagulants | Multivitamin | 7,317 |
| Placebo | 7,324 |
| Placebo | 730 |
| REACT51United States and United KingdomGood | Determine if multivitamin use would impact the progression of age-related cataracts | RCT | Age ≥40 years; ≥1 eyes met the following criteria: cataract extraction unlikely within 2 years, immature idiopathic "senile" cataract present, presence of minimal cataract by Lens Opacities Classification System criteria (U.S. patients), presence of cataract of minimal Oxford grade (U.K. patients), LogMAR acuity ≤0.5, no clinical signs of glaucoma and intraocular pressure by applanation tonometry ≤25 mm HG; no history of amblyopia, eye surgery, argon or YAG laser treatment, or major eye trauma; no history of iritis, renal crystalline deposits, or optic nerve disease; no extended use of ocular corticosteroid or glaucoma therapy; no participation in another clinical trial investigating an anticataract formulation within the last year | Pregnant; history of diabetes mellitus, severe renal failure, or kidney stones, fat malabsorption syndrome, major intestinal surgery, chronic diarrhea, alcoholism, extended use of corticosteroid treatment, use of anticoagulants, regular use of any vitamin supplement | Multivitamin tid (vitamin C 250 mg, vitamin E 200 mg, and beta-carotene 6 mg) | 149 |
| Placebo | 148 |
| RECORD103,107United KingdomFair | Investigate whether vitamin D or calcium supplementation affects mortality, vascular disease, and cancer in older people | RCT, 2x2 factorial design\* | Older adults age ≥70 years with a fragility fracture | Cancer likely to metastasize to bone within the previous 10 years; bed- or chairbound before fracture, Abbreviated Mental Test score <7, fracture associated with preexisting local bone abnormality, known hypercalcemia, renal stone in the last 10 years, life expectancy <6 months, known to be leaving the United Kingdom, taking >200 IU (5 µg) of vitamin D or >500 mg calcium supplements daily, treatment with fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERMs, or any vitamin D metabolite (e.g., calcitriol) in the last 5 years or vitamin D by injection in the last year | Calcium 1,000 mg qd | 1,311 |
| Vitamin D3 800 IU qd | 1,343 |
| Calcium 1,000 mg qd + vitamin D 800 IU qd | 1,306 |
| Placebo | 1,332 |
| SCPS63,75,159United StatesFair | Determine if beta-carotene supplementation increases the time to occurrence of first skin cancer | RCT | ≥1 biopsy-proven BCC or SCC since January 1, 1980; age <85 years; no potential childbearing; agree not to take vitamin supplements containing vitamin A or beta-carotene; not a vegan vegetarian | Active cancer other than skin cancer; xeroderma pigmentosum; basal cell nevus syndrome; significant known arsenic exposure; other major medical problems that might limit participation (e.g., disabling CVD, active liver disease, alcohol or drug dependence) | Beta-carotene 50 mg qd | 913 |
| Placebo | 892 |
| SELECT82,143,166-169United States, Canada, and Puerto RicoGood | Reduce the risk of prostate cancer with selenium and/or vitamin E, as well as other cancers and cardiovascular events | RCT, 2x2 factorial deign | Healthy men age ≥50 years (African American) or ≥55 years (all other races); normal blood pressure; serum PSA ≥4 ng/mL; DRE not suspicious for cancer; willing to restrict off-study supplement use; SWOG performance status = 0.  | Prior history of prostate cancer or high-grade prostatic intraepithelial neoplasia; anticoagulation therapy other than ≥175 mg/day ASA or ≥81 mg/day ASA with clopidogrel bisulfate; history of hemorrhagic stroke | Vitamin E 400 IU qd | 8,904 |
| Selenium 200 mcg qd | 8,910 |
| Vitamin E 400 IU qd + selenium 200 mcg qd | 8,863 |
| Placebo | 8,856 |
| SKICAPS-AK97,174United StatesFair | Determine the efficacy of vitamin A supplementation on the incidence of first NMSC in moderate-risk patients | RCT | Ages 21–85 years; ambulatory and capable of self-care; no diagnosis of life-threatening condition or internal cancer in past year; normal or near normal laboratory values in a routine screening panel of tests; planning to live within travel distance of SKICAP clinic for ≥5 years; willing to limit nonstudy vitamin A supplementation to ≤10,000 IU/day; history of ≥10 pathologically confirmed actinic keratoses (most recent diagnosed within preceding year) and a pathologically confirmed record of ≤1 prior SCC or BCC | NR | Vitamin A 25,000 IU qd | 1,157 |
| Placebo | 1,140 |
| SKICAPS-S/B98, 174United StatesFair | Determine the effect of vitamin A and isotretinoin on the incidence of NMSC in high-risk patients | RCT | Ages 21–85 years; ambulatory and capable of self-care; no diagnosis of life-threatening condition or internal cancer in past year; normal or near normal laboratory values in a routine screening panel of tests; planning to live within travel distance of SKICAP clinic for ≥5 years; history of ≥4 pathologically confirmed BCC or cutaneous SCC; triglyceride level <95% UL of normal; no childbearing potential or breastfeeding | Patients with a diagnosis of basal cell nevus syndrome or xeroderma pigmentosum | Vitamin A 25,000 IU qd | 173 |
| Placebo | 174 |
| SU.VI.MAX49,54-56,58,151-153FranceGood | Reduce the incidence of cancer and ischemic heart disease with multivitamin supplementation | RCT | Men (ages 45–60 years) and women (ages 35–60 years), free of any severe pathology that might limit participation, not be taking supplements containing any of the study vitamins or minerals, express no ambiguous motivations or obsessional behavior concerning diet and health; manifest no qualms about complying with protocol constraints | NR | Multivitamin qd (vitamin C 120 mg, vitamin E 30 mg, beta-carotene 6 mg, selenium 100 mcg, and zinc 20 mg) | 6,481 |
| Placebo | 6,536 |
| Trivedi 2003104United KingdomFair | Determine the effect of vitamin D supplementation on rate of fractures | RCT | Men and women ages 65–85 years | Already taking vitamin D supplements, conditions that were contraindications to vitamin D supplements (e.g., renal stones, sarcoidosis, or malignancy) | Vitamin D3 100,000 IU every 4 months | 1,345 |
| Placebo | 1,341 |
| U.K. PRECISE91United KingdomFai | Determine the effect of selenium supplementation on cancer prevention | RCT | Elderly volunteers ages 60–74 years | SWOG score >1, active liver or kidney disease, prior diagnosis of cancer (excluding NMSC), diagnosed HIV infection, immunosuppressive therapy, diminished mental capacity, taking ≥50 mcg/d of selenium supplements in the previous 6 months | Selenium 100 mcg qd | 127 |
| Selenium 200 mcg qd | 127 |
| Selenium 300 mcg qd | 126 |
| Placebo | 121 |
| WHI108,110,111,137,176-184United StatesGood | Evaluate the efficacy of calcium with vitamin D supplementation on preventing colorectal cancer; evaluate the efficacy of preventing hip and other fractures | RCT | Participants enrolled in the WHI dietary modification trial, hormone therapy trials, or both; women ages 50–79 years at initial screening; no evidence of a medical condition associated with a predicted survival of <3 years; no safety, adherence, or retention risks | Hypercalcemia; renal calculi; corticosteroid or calcitriol use; intention to continue to take ≥600 IU of vitamin D per day of personal supplements | Vitamin D3 200 IU bid + calcium 500 mg bid | 18,176 |
| Placebo | 18,106 |
| WHS62,81,165United StatesGood | Prevent cancer and CVD with vitamin E or beta-carotene supplementation | RCT, 2x2x2 factorial design\*¶ | Women age ≥45 years; post-menopausal or had no intention of becoming pregnant; no previous history of CHD, cerebrovascular disease, cancer (except NMSC), or any serious illness that might preclude participation; no reported history of serious side effects to any study treatment; not currently taking ASA, ASA-containing medications, or NSAIDs ≥1/week or willing to forgo the use of these; not currently taking anticoagulants or corticosteroids; and not taking vitamin A or E or beta-carotene supplements >1/week  | Participants in the ongoing Nurses' Health Study (an observational cohort study of registered nurses) | Vitamin E 600 IU qod | 19,937 |
| No vitamin E | 19.939 |
| Beta-carotene 50 mg qod | 19,939 |
| No beta-carotene | 19,937 |

\*Factorial design studies may have reported outcomes by original randomized arms and/or by factorial design; i.e., participants who were randomized to receive a specific supplement (e.g., vitamin C with or without vitamin E) vs. participants not randomized to receive the aforementioned specific supplement (e.g., vitamin E alone or placebo).

†IWHS: prospective cohort study among women taking vitamin A compared with nonusers of vitamin A; dosage not reported.

‡NHS: prospective cohort study among women taking one of the following supplements: multivitamin, vitamin A, or beta-carotene compared with nonusers; dosage or number of participants by supplement not reported.

§PHS-I: participants randomized to receive beta-carotene, beta-carotene + aspirin, aspirin, or placebo; numbers of participants allocated to original randomized arms not reported.

║PHS-II: participants randomized to receive vitamin E, vitamin C, multivitamin, beta-carotene (discontinued), or placebo.

¶WHS: participants randomized to receive vitamin E, beta-carotene, aspirin, or placebo; numbers of participants allocated to original randomized arms not reported.

**Abbreviations:** ACS =Auckland Calcium Study;AFPPS = Aspirin/Folate Polyp Prevention Study; ASA = acetylsalicylic acid; ASAP = Antioxidant Supplementation in Atherosclerosis Prevention; ATBC = Alpha-Tocopherol Beta-Carotene Cancer Prevention; bid = twice daily; BCC = basal cell carcinoma; BMI = body mass index; CARET = Carotene and Retinol Efficacy Trial; CHD = coronary heart disease; CIS = carcinoma in situ; CNS = central nervous system; CPPS = Calcium Polyp Prevention Study; CVD = cardiovascular disease; DBP = diastolic blood pressure; DRE = digital rectal examination; HRT = hormone replacement therapy; IWHS = Iowa Women’s Health Study; LogMAR = logarithm of the minimum angle of resolution; MI = myocardial infarction; NHS = Nurses’ Health Study; NMSC = nonmelanoma skin cancer; NPC = Nutritional Prevention of Cancer; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; NSCPS = Nambour Skin Cancer Prevention Study; PHS = Physician’s Health Study; PSA = prostate-specific antigen; qd = once daily; qod = every other day; RCT = randomized, controlled trial; REACT = Roche European American Cataract Trial; RECORD = Randomized Evaluation of Calcium or Vitamin D; SCC = squamous cell carcinoma; SCPS = Skin Cancer Prevention Study; SELECT = Selenium and Vitamin E Cancer Prevention Trial; SERM = selective estrogen receptor modulator; SKICAP-AK = Skin Cancer Prevention Trial-Actinic Keratoses; SKICAP=S/B = Skin Cancer Prevention Trial-SCC/BCC; SU.VI.MAX = Supplementation in Vitamins and Mineral Antioxidants Study; SWOG = Southwest Oncology Group; U.K. PRECISE = U.K. Prevention of Cancer by Intervention with Selenium; UL = upper intake limit; WHI = Women’s Health Initiative; WHS = Women’s Health Study; YAG = yttrium aluminium garnet.