Research Article

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Specialty Supplements and Breast Cancer Risk in the VITamins And Lifestyle (VITAL) Cohort

Theodore M. Brasky[1,2], Johanna W. Lampe[1,2], John D. Potter[1,2], Ruth E. Patterson[3], and Emily White[1,2]

Abstract

Background: Use of nonvitamin, nonmineral "specialty" supplements has increased substantially over recent decades. Several supplements may have anti-inflammatory or anticancer properties. Additionally, supplements taken for symptoms of menopause have been associated with reduced risk of breast cancer in two case-control studies. However, there have been no prospective studies of the association between the long-term use of these supplements and breast cancer risk.

Methods: Participants were female members of the VITamins And Lifestyle (VITAL) Cohort. Postmenopausal women, ages 50 to 76 years, who were residents of western Washington State, completed a 24-page baseline questionnaire in 2000 to 2002 (n = 35,016). Participants were queried on their recency (current versus past), frequency (days/week), and duration (years) of specialty supplement use. Incident invasive breast cancers (n = 880) from 2000 to 2007 were obtained from the Surveillance, Epidemiology, and End Results registry. Multivariable-adjusted hazards ratios (HR) and 95% confidence intervals (95% CI) were estimated by Cox proportional hazards models.

Results: Current use of fish oil was associated with reduced risk of breast cancer (HR, 0.68; 95% CI, 0.50-0.92). Ten-year average use was suggestive of reduced risk (P trend = 0.09). These results held for ductal but not lobular cancers. The remaining specialty supplements were not associated with breast cancer risk: Specifically, use of supplements sometimes taken for menopausal symptoms (black cohosh, dong quai, soy, or St. John's wort) was not associated with risk.

Conclusions: Fish oil may be inversely associated with breast cancer risk.

Impact: Fish oil is a potential candidate for chemoprevention studies. Until that time, it is not recommended for individual use for breast cancer prevention. *Cancer Epidemiol Biomarkers Prev; 19(7); 1696–708. ©2010 AACR.*

Introduction

The prevalence of regular dietary supplement use in the United States has risen in recent decades (1), with substantial increases in nonvitamin, nonmineral "specialty" supplement use (1-3). As supplements fall under the Dietary Supplements Health and Education Act of the U.S. Food and Drug Administration, oversight of these compounds is limited. Although several researchers have examined trends, lifestyle characteristics, and health-related behaviors and beliefs of specialty supplement users (1, 2, 4), relatively little is known about the long-term health consequences of these compounds for risk of cancer and, specifically, breast cancer.

Results from a growing body of literature suggest that some such supplements have anticancer properties *in vitro* and *in vivo* (5-13); however, the mechanisms of action for most compounds are not well understood. There is limited evidence that some specialty supplements, such as glucosamine, chondroitin, and fish oil, may have anti-inflammatory properties (14-16). Anti-inflammatory supplements are of interest because chronic inflammation has been linked to mutagenesis, mitogenesis, angiogenesis, antiapoptosis, and metastasis, factors associated with cancer initiation and progression (17, 18). Based on *in vitro* studies, one hypothesized mechanism by which inflammation contributes specifically to breast carcinogenesis is that increased prostaglandin E_2 (PGE_2) production promotes *de novo* estrogen synthesis in breast epithelia and stroma (19). A further rationale for examining use of anti-inflammatory supplements is that the use of nonsteroidal anti-inflammatory drugs (NSAID), which inhibit cyclooxygenase-2 (COX-2) and PGE_2 synthesis, has been inversely associated with several cancers (20), including breast (21). In addition,

Authors' Affiliations: [1]The Fred Hutchinson Cancer Research Center, Cancer Prevention Unit; [2]Department of Epidemiology, University of Washington, Seattle, Washington and [3]Department of Family and Preventive Medicine, University of California, San Diego, California

Corresponding Author: Theodore M. Brasky, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109-1024. Phone: 206-667-5881; Fax: 206-667-7850. E-mail: tbrasky@fhcrc.org

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supplements taken for symptoms of menopause have been recently associated with reduced risk of breast cancer in two case-control studies (22, 23).

To our knowledge, no prospective studies have evaluated the use of specialty supplements in relation to breast cancer risk. We describe here our investigation of the association between specialty supplement use and breast cancer risk in the VITamins And Lifestyle (VITAL) cohort.

Materials and Methods

Study population

Participants were female members of the VITAL cohort, a study of men and women designed to investigate prospectively the association of vitamin, mineral, and specialty supplements with cancer risk. Further details of the study design are provided by White et al. (24). Women who were 50 to 76 years of age at baseline and who lived in the 13-county area in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry were eligible to participate. Because this study is limited to women, we describe here recruitment of women. Between October 2000 and December 2002, we mailed baseline questionnaires and postcard reminders 2 weeks later to 168,953 women using names purchased from a commercial mailing list. Of these, 40,337 (23.9%) were returned and deemed eligible.

We excluded women who had a history of breast cancer or did not report cancer history at baseline (n = 3,164), were premenopausal (n = 1,347), or were missing menopausal status (n = 564). Women were considered postmenopausal if they had had a natural menopause with no periods in the year before baseline, had ever used hormone therapy, had had a bilateral oophorectomy, or were ≥60 years at baseline. Women who had had a hysterectomy without oophorectomy were considered to be postmenopausal if they had ever received hormone therapy or were ≥55 years at baseline. Because not all *in situ* breast cancers would be expected to progress to invasive disease, we excluded women who were diagnosed since baseline with *in situ* breast cancer (n = 240). In addition, we excluded women who had breast sarcoma, phyllodes, or lymphoma histologies (n = 6), as these histologies likely represent different etiologic pathways. After exclusions, there were 35,016 postmenopausal women available for study.

Data collection

The baseline questionnaire included a detailed assessment of supplement use. Respondents were queried on their use of herbal and specialty supplements during the 10-year period before baseline, in addition to use of vitamin and mineral supplements (including individual supplements and mixtures such as multivitamins). We previously reported on the validity and reliability of supplement assessment in VITAL (25). We inquired about current and past regular use, defined as ≥1 day/week for ≥1 year; questions included frequency in days per week and duration of use over the previous 10 years. We did not ascertain information on dose because of the lack of accurate information on the potency of specialty supplements.

In addition to dietary supplement use, we collected other information at baseline on known or suspected risk factors for breast cancer and correlates of supplement use. Participants reported on personal characteristics, including tallest height achieved and weight at baseline. From these data, body mass index (BMI; kg/m^2) was computed. Participants additionally answered a series of questions about physical activity over the past 10 years, including type of activity, minutes/day, days/week, and years of duration; average MET hours/week over the 10 years was computed from these data (26). Participants were queried on their medication use, including use of NSAIDs such as low-dose and regular strength aspirin, ibuprofen, and naproxen. Regular diet was measured using a 120-item food frequency questionnaire (24). We additionally ascertained information on family history of cancer, medical history, reproductive history, and other lifestyle characteristics. Participants who reported having had a heart attack, angina, angioplasty, or bypass surgery were considered to have a positive history of coronary artery disease (CAD).

Case ascertainment

Cohort members were followed for incident breast cancer diagnoses from baseline to December 31, 2007; the mean follow-up time was 6 years. Incident, primary, invasive breast cancers were ascertained by linking the study cohort to the western Washington SEER cancer registry, which is maintained by the Fred Hutchinson Cancer Research Center. All incident cancer cases except nonmelanoma skin cancer diagnosed within the 13-county area of western Washington State were reported to SEER along with stage, estrogen receptor (ER) and progesterone receptor (PR) status, histologic type, and other tumor characteristics. Cases were ascertained through all area hospitals; offices of pathologists, oncologists, and radiotherapists; and from state death certificates. Extensive quality control procedures ensure that registry data are accurate and complete. Linkage to SEER is based on ranking of the agreement between characteristics in common to VITAL and SEER, including name, social security number, and date of birth; matches with high concordance were automated, whereas visual inspection was done for matches in which some, but not all, criteria matched. Eight hundred eighty eligible cases of invasive breast cancer were diagnosed between November 2000 and December 2007.

Follow-up for censoring

Excluding the 2.5% of the cohort with incident breast cancer, the remaining participants were right censored

from the analysis at the earliest date of the following events: date they requested removal from the study (0.04%), date of death (4.5%), date of emigration out of the SEER catchment area (5.3%), or December 31, 2007, the most recent date that endpoints were ascertained (87.8%).

Deaths occurring in the cohort in Washington State were ascertained by linkage to the state death file using similar procedures to the SEER linkage. Emigrations out of the SEER catchment area were identified by linkage to the National Change of Address System and by active follow-up by telephone calls and mailings.

Statistical analyses

Statistical analyses were done using SAS (version 9.1). Cox proportional hazards regression models using age as the time component were used to estimate breast cancer hazards ratios (HR) and 95% confidence intervals (95% CI) associated with participant characteristics and supplement use. All reported *P* values are two sided. *P* values for trend (*P* trend) were calculated by treating categorical exposures as ordinal in proportional hazards models. *P* values for interaction between a specialty supplement and a potential effect modifier were computed by including a multiplicative term in the multivariable models.

For each specialty supplement, we categorized use by recency in relation to baseline (categorized as nonuser, former, and current) and by intake over the 10 years before baseline (nonuser; low use, <4 days/week or <3 years; and high use, ≥4 days/week and ≥3 years). For black cohosh, dong quai, garlic, ginkgo biloba, ginseng, grapeseed, and soy supplementation, intake from multivitamin sources was also included in estimation of 10-year average use. Participants whose supplement exposure was limited exclusively to multivitamin sources were categorized as low users. Analysis was categorized as only users/nonusers for the supplements with low prevalence (<5% use) of use.

We selected *a priori* potential confounders including known and suspected risk factors for breast cancer. Multivariable models were adjusted for age (time variable; years), race (white/non-white), education (≤high school, some college, college or advanced degree), BMI (<25, 25 to <30, ≥30 kg/m^2), height (<158, 158 to <165, 165 to <173, ≥173 cm), alcohol consumption (0 to <0.5, 0.5 to <1.5, 1.5 to <5, 5 to <10, ≥10 g/d), physical activity (0, >0 to <3.33, 3.33 to 10.62, >10.62 MET-hours/week), years of combined hormone therapy (never, 1 to <4, 4-9, >9), history of hysterectomy (none, simple, total or bilateral oophorectomy), age at menarche (≤11, 12, 13, ≥14 years), age at first birth (≤19, 20-24, 25-34, ≥35 years, nulligravid), age at menopause (≤44, 45-49, 50-55, ≥55 years), number of first-degree relatives with breast cancer (none, 1, ≥2), history of benign breast biopsy (yes/no), mammography in the 2 years before baseline (yes/no), fruit consumption (0-1.04, 1.05-2.14, >2.14 servings/day), vegetable consumption (0-1.73, 1.74-2.85, >2.85 servings/day), and 10-year average use of low-dose aspirin, regular strength aspirin, ibuprofen, or naproxen (none; low, <4 days/week or <4 years; high, ≥4 days/week and ≥4 years, respectively).

Further adjustments to multivariable models were made for *a priori* predictors of specialty supplement use, including multivitamin use (never, past, current). For specific supplements, additional adjustments were made for indications of their use, aided by baseline characteristics of supplement users previously described (27). Adjustments were made for personal histories of osteoarthritis or chronic joint pain (for analyses of glucosamine, chondroitin, methylsulfonylmethane), memory loss (fish oil, coenzyme q10, ginkgo biloba), CAD (fish oil, grapeseed), lactose intolerance (acidophilus), diabetes (dong quai), insomnia (melatonin), and depression (St. John's wort).

To assess whether differences in etiology exist for supplement exposures in association with biologically defined subsets of breast cancer, we stratified models on breast tumor ER and PR status, histologic type (ductal, lobular), and SEER summary stage (local versus regional/distant). Logistic regression models that were restricted to cases were used to calculate the *P* value for the difference (*P* difference) among associations between supplements and these subsets of breast tumors.

Results

Characteristics of VITAL participants and age-adjusted HR and 95% CI for the associations of these characteristics with breast cancer risk are presented in Table 1. Consistent with the literature, older age, greater body mass and height, higher alcohol consumption, later age at first birth or nulligravid status, longer duration of combined hormone therapy, a positive family history of breast cancer, and a personal history of benign breast biopsy were all associated with increased risk of breast cancer. Non-white race, later age at menarche, and a history of hysterectomy or oophorectomy were inversely associated with risk of breast cancer. Regular use of NSAIDs was not associated with risk [a more detailed investigation of NSAIDs in association with breast cancer in the VITAL cohort has been previously reported (ref. 28)]. In this population, age at menopause, fruit and vegetable consumption, and mammography were not statistically significantly associated with risk (data not shown).

Age- and multivariable-adjusted associations between specialty supplements and breast cancer risk are presented in Table 2. No differences were observed between the models. Among supplements with anti-inflammatory properties, we observed a statistically significant lower breast cancer risk among current (multivariable-adjusted HR, 0.68; 95% CI, 0.50-0.92) but not former users of fish oil (HR, 1.07; 95% CI, 0.71-1.60) compared with nonusers. Average use of fish oil in the 10 years before baseline suggested an inverse association, although the CI included 1.0, and there was

no clear trend. We observed no association between breast cancer and other anti-inflammatory supplements (glucosamine, chondroitin, methylsulfonylmethane, or grapeseed), whether expressed by recency of use or 10-year average use.

There was no association between specialty supplements taken to alleviate climacteric symptoms and breast cancer risk. Compared with nonuse, regular use of black cohosh (HR, 1.17; 95% CI, 0.75-1.82) or dong quai (HR, 1.27; 95% CI, 0.76-2.13) was not associated with risk. We further combined use of these two preparations with other supplements sometimes used for menopausal symptoms (soy, St. John's wort), as categorized in Obi et al. (22). Compared with nonuse, we observed no reduction in risk for use of any of these supplements (HR, 1.01; 95% CI, 0.80-1.27). The remaining specialty supplements were not associated with risk.

To further evaluate the association of current use of fish oil with breast cancer, we assessed the interaction of fish oil use (current user/nonuser) with characteristics thought to influence inflammation (29-31): BMI (<25, ≥25 kg/m^2), CAD (yes/no), any NSAID use (irregular, <4 days/week for <4 years; regular, ≥4 days/week for ≥4 years), smoking status [nonsmokers and former smokers (≥10 years since quitting), recent (<10 years since quitting), and current], and dietary arachidonic acid (g/d) in relation to risk of breast cancer using models of joint effects (Table 3). There was a statistically significant interaction ($P = 0.03$) between fish oil use and a history of CAD. Among those with a history of CAD, there was a 2-fold increased risk of breast cancer among users of fish oil versus nonusers (HR, 1.56 versus 0.84), whereas among those without a history of CAD, current use of fish oil was associated with reduced risk (HR, 0.62; 95% CI, 0.45-0.87). We observed no interactions between fish oil use and BMI, NSAID use, smoking status, or dietary arachidonic acid.

We further investigated the association of fish oil use with breast cancer characterized by histologic type (ductal versus lobular), SEER summary stage (local versus regional/distant), and hormone receptor status (ER and PR; Table 4). Current fish oil use was associated with decreased risk of ductal (HR, 0.56; 95% CI, 0.38-0.83) but not lobular carcinoma (HR, 1.08; 95% CI, 0.59-1.96). The P for difference was statistically significant (P difference < 0.05). The inverse association was additionally restricted to breast cancers diagnosed as local (HR, 0.57; 95% CI, 0.38-0.84) rather than regional or distant (HR, 0.97; 95% CI, 0.59-1.61), and the P for difference bordered on statistical significance (P difference = 0.06). There were no differences in the lower risk associated with current fish oil use when tumors were characterized by ER or PR status.

Discussion

In this cohort of 35,016 women living in western Washington State, current use of fish oil supplementation was associated with reduced risk of breast cancer. The reduced risk was restricted to women with ductal but not lobular carcinoma and, perhaps, local but not regional or distant disease. We observed no meaningful interaction with current use of fish oil and factors associated with chronic inflammation. Other specialty supplements were not associated with risk.

Fish oil primarily contains the long-chain ω-3 polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). It is generally marketed for its cardioprotective benefit. To our knowledge, there are no previous case-control or cohort studies that have examined the type of fish oil supplementation that is currently common in the United States (from fish high in EPA and DHA) with breast cancer risk. In one randomized trial, in which hypercholesterolemic patients were randomized to daily administration of a statin drug or to statin plus 1,800 mg EPA, investigators observed no significant difference in breast cancer incidence ($n = 16$ cases EPA + statin arm, $n = 21$ cases statin arm) after 4.6 years of follow-up (32). Investigators of a population-based case-control study in Ontario, Canada, examined cod liver oil supplementation with breast cancer risk (33, 34). They observed a 24% reduction in breast cancer risk with cod liver use ≥1/week during adolescence [odds ratio (OR), 0.76; 95% CI, 0.62-0.92; ref. 33]. Similar reductions in risk were evident for use up to age 54 years, although they did not reach statistical significance (33). It was further reported that the association did not differ by hormone receptor status (34). Cod liver oil differs from fish oil in its lower content of ω-3 PUFAs and is used primarily as a source of vitamins A and D (35). Because of these differences, it is unclear whether the observed associations in the Canadian study are attributable to the vitamin or fatty acid content of cod liver oil.

The association of fish or ω-3 PUFA intake from diet with breast cancer has been examined in several cohort studies (36-44). Generally, no association has been seen (45). However, results of a prospective study of women in Singapore, where fish intake is much higher than that of the United States, showed an inverse association between dietary ω-3 PUFA from marine sources and breast cancer risk [relative risk (RR), 0.72; 95% CI, 0.53-0.98; ref. 41]. The only cohort studies in which individual associations of EPA and DHA intake from diet with risk of breast cancer have been examined are the Nurses' Health Study and the Netherlands Cohort (36, 42). No association was found in either study (36, 42). In contrast, Saadatian-Elahi et al. (46) conducted a meta-analysis of studies that analyzed blood biomarkers of fatty acids in association with breast cancer risk. They found inverse associations for total ω-3 PUFAs (RR, 0.61; 95% CI, 0.40-0.93), as well as for EPA (RR, 0.69; 95% CI, 0.45-1.05) and DHA (RR, 0.68; 95% CI, 0.44-1.04; ref. 46). For all but EPA, the association persisted when the analysis was restricted to postmenopausal women (46). Thus, the associations we observed between fish oil supplement use and breast cancer risk are consistent with studies of

Table 1. Associations between participant characteristics and breast cancer risk among female VITAL participants (n = 35,016)

Characteristic	Cases (n = 880), n (%)	Noncases (n = 34,136), n (%)	Age-adjusted HR (95% CI)
Demographics			
Age at baseline (y)			
<55	101 (11.5)	7,224 (21.2)	N/A
55 to <60	190 (21.6)	8,333 (24.4)	
60 to <65	181 (20.6)	6,346 (18.6)	
65 to <70	183 (20.8)	5,492 (16.1)	
≥70	225 (25.6)	6,741 (19.8)	
Race			
White	828 (95.3)	31,103 (93.1)	1.00 (reference)
Non-white	41 (4.7)	2,297 (6.9)	0.69 (0.51-0.95)
Education			
≤High school graduate	223 (25.7)	8,149 (24.4)	1.00 (reference)
Some college	348 (40.1)	13,923 (41.7)	1.01 (0.86-1.20)
College or advanced degree	297 (34.2)	11,294 (33.9)	1.12 (0.94-1.33)
P trend			0.21
Anthropometrics			
BMI (kg/m^2)			
<25	313 (37.4)	13,061 (41.0)	1.00 (reference)
25 to <30	301 (36.0)	10,668 (33.5)	1.16 (0.99-1.36)
≥30	222 (26.6)	8,116 (25.5)	1.20 (1.01-1.42)
P trend			0.03
Height (cm)			
<158	66 (7.6)	3,043 (9.1)	1.00 (reference)
158 to <165	297 (34.1)	13,179 (39.5)	1.02 (0.78-1.34)
165 to <173	379 (43.5)	12,732 (38.2)	1.37 (1.05-1.77)
≥173	130 (14.9)	4,375 (13.1)	1.40 (1.04-1.88)
P trend			<0.0001
Lifestyle			
Fruit consumption (servings/day)			
0-1.04	272 (34.5)	10,115 (33.2)	1.00 (reference)
1.05-2.14	271 (34.4)	10,171 (33.4)	0.95 (0.81-1.13)
>2.14	246 (31.2)	10,186 (33.4)	0.86 (0.73-1.02)
P trend			0.09
Vegetable consumption (servings/day)			
0-1.73	270 (34.2)	10,173 (33.4)	1.00 (reference)
1.73-2.85	251 (31.8)	10,119 (33.2)	0.92 (0.77-1.09)
>2.85	268 (34.0)	10,180 (33.4)	0.97 (0.82-1.15)
P trend			0.74
Alcohol (g/d)			
0 to <0.5	367 (42.4)	15,072 (45.6)	1.00 (reference)
0.5 to <1.5	89 (10.3)	4,259 (12.9)	0.89 (0.71-1.13)
1.5 to <5	115 (13.3)	4,860 (14.7)	1.01 (0.82-1.24)
5 to <10	95 (11.0)	3,495 (10.6)	1.15 (0.92-1.44)
≥10	199 (23.0)	5,360 (16.2)	1.54 (1.30-1.83)
P trend			<0.0001
10-y physical activity (MET hours/week)			
0	138 (15.8)	5,112 (15.2)	1.00 (reference)
Tertile 1: 0 to <3.33	262 (30.1)	9,539 (28.3)	1.01 (0.82-1.24)
Tertile 2: 3.33-10.62	234 (26.9)	9,481 (28.2)	0.90 (0.73-1.11)
Tertile 3: >10.62	237 (27.2)	9,536 (28.3)	0.90 (0.73-1.11)

(*Continued on the following page*)

Table 1. Associations between participant characteristics and breast cancer risk among female VITAL participants (n = 35,016) (Cont'd)

Characteristic	Cases (n = 880), n (%)	Noncases (n = 34,136), n (%)	Age-adjusted HR (95% CI)
P trend			0.15
Reproductive history			
Age at menarche (y)*			
≤11	181 (20.6)	6,279 (18.5)	1.00 (reference)
12	671 (30.9)	10,123 (29.8)	0.93 (0.77-1.12)
13	242 (27.7)	9,987 (29.4)	0.83 (0.68-1.00)
≥14	183 (20.8)	7,593 (22.3)	0.80 (0.65-0.98)
P trend			0.01
Age at first birth (y)			
≤19	134 (15.3)	6,227 (18.4)	1.00 (reference)
20-24	379 (43.4)	14,095 (41.5)	1.20 (0.98-1.46)
25-34	205 (23.5)	8,707 (25.7)	1.15 (0.92-1.43)
≥35	25 (2.9)	677 (2.0)	1.95 (1.27-3.00)
Nulligravid	131 (15.0)	4,229 (12.5)	1.64 (1.29-2.09)
P trend			<0.0001
Hysterectomy			
None	564 (64.1)	20,332 (59.6)	1.00 (reference)
Simple	168 (19.1)	7,615 (22.3)	0.73 (0.62-0.87)
Total or bilateral oopherectomy	148 (16.8)	6,189 (18.1)	0.83 (0.69-0.99)
Combined hormone therapy (y)			
Never	462 (56.0)	20,281 (63.0)	1.00 (reference)
1-4	91 (11.0)	4,432 (13.8)	1.04 (0.82-1.30)
5-9	110 (13.3)	3,592 (11.2)	1.40 (1.14-1.73)
≥10	162 (19.6)	3,898 (12.1)	1.68 (1.40-2.01)
P trend			<0.0001
Medical history			
Number of first-degree relatives with breast cancer			
None	675 (78.7)	28,532 (84.7)	1.00 (reference)
1	162 (18.9)	4,616 (13.7)	1.46 (1.23-1.73)
≥2	21 (2.5)	475 (1.4)	1.75 (1.13-2.70)
P trend			<0.0001
Had benign breast biopsy			
No	652 (74.1)	27,916 (81.8)	1.00 (reference)
Yes	228 (25.9)	6,220 (18.2)	1.50 (1.29-1.75)
NSAID use†			
Irregular	672 (77.5)	25,975 (77.0)	1.00 (reference)
Regular	195 (22.5)	7,765 (23.0)	0.91 (0.78-1.07)

*Among women who have had a period.
†Ten-year average use: irregular, <4 d/week or <4 y; regular, ≥4 d/week and ≥4 y.

biomarkers of ω-3 PUFA intake and breast cancer but not with prior studies of self-report of dietary intakes of ω-3 PUFAs.

These differences among studies may be explained by the poor measurement precision of self-reported diet. Another explanation may be that the daily dose of ω-3 PUFA intake from fish oil supplements is likely to be much higher than most people in the United States consume from diet. Eighty-three percent of fish oil users in our study took fish oil ≥4 times a week; 60% were daily users. Although concentrations vary by manufacturer, participants who used fish oil supplements probably consumed the equivalent of 33% to 77% of a serving of high ω-3 fish each day that the supplement was used.

Current but not former use of fish oil was inversely associated with breast cancer risk. It may be that current use reported at baseline is a surrogate for use after baseline closer to the incident cancer (0-7.3 years after baseline). If use in the more distant past does not represent

Table 2. Associations between specialty supplement use and breast cancer risk among female VITAL participants (n = 35,016)

Supplement	Cases (n = 880), n (%)	Noncases (n = 34,136), n (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
Anti-inflammatory supplements				
Glucosamine†				
Nonuser	649 (74.1)	25,766 (75.9)	1.00 (reference)	1.00 (reference)
Former	46 (5.3)	1,510 (4.5)	1.21 (0.89-1.63)	1.27 (0.93-1.74)
Current	181 (20.7)	6,694 (19.7)	1.02 (0.86-1.20)	1.07 (0.90-1.29)
P trend			0.68	0.36
10-y average use‡				
Nonuser	649 (74.1)	25,766 (75.9)	1.00 (reference)	1.00 (reference)
Low	155 (17.7)	5,369 (15.8)	1.11 (0.93-1.32)	1.18 (0.98-1.42)
High	72 (8.2)	2,835 (8.4)	0.95 (0.75-1.22)	0.98 (0.75-1.27)
P trend			0.84	0.56
Chondroitin†				
Nonuser	724 (82.7)	28,409 (83.5)	1.00 (reference)	1.00 (reference)
Former	31 (3.5)	1,094 (3.2)	1.10 (0.77-1.58)	1.12 (0.77-1.64)
Current	121 (13.8)	4,513 (13.3)	1.00 (0.82-1.21)	1.07 (0.87-1.31)
P trend			0.96	0.51
10-y average use‡				
Nonuser	724 (82.7)	28,409 (83.5)	1.00 (reference)	1.00 (reference)
Low	101 (11.5)	3,721 (10.9)	1.02 (0.83-1.26)	1.09 (0.87-1.36)
High	51 (5.8)	1,886 (5.5)	1.00 (0.75-1.33)	1.05 (0.78-1.42)
P trend			0.91	0.54
Methylsulfonylmethane†				
Nonuser	826 (94.1)	32,056 (94.1)	1.00 (reference)	1.00 (reference)
Former	10 (1.1)	397 (1.2)	0.99 (0.53-1.85)	1.01 (0.52-1.96)
Current	42 (4.8)	1,612 (4.7)	0.99 (0.73-1.35)	1.02 (0.74-1.42)
P trend			0.95	0.89
10-y average use‡				
Nonuser	826 (94.1)	32,056 (94.1)	1.00 (reference)	1.00 (reference)
Low	45 (5.3)	1,612 (4.7)	1.07 (0.79-1.44)	1.10 (0.80-1.51)
High	7 (0.8)	397 (1.2)	0.68 (0.32-1.44)	0.69 (0.31-1.54)
P trend			0.67	0.82
Fish oil†				
Nonuser	802 (91.2)	30,331 (89.2)	1.00 (reference)	1.00 (reference)
Former	30 (3.4)	998 (2.9)	1.16 (0.81-1.67)	1.07 (0.71-1.60)
Current	47 (5.4)	2,668 (7.9)	0.67 (0.50-0.90)	0.68 (0.50-0.92)
P trend			0.02	0.02
10-y average use‡				
Nonuser	802 (91.2)	30,331 (89.2)	1.00 (reference)	1.00 (reference)
Low	41 (4.7)	2,160 (6.4)	0.74 (0.54-1.01)	0.75 (0.54-1.04)
High	36 (4.1)	1,506 (4.4)	0.89 (0.64-1.24)	0.82 (0.57-1.18)
P trend			0.14	0.09
Grapeseed†				
Nonuser	848 (96.8)	32,672 (95.9)	1.00 (reference)	1.00 (reference)
User	28 (3.2)	1,381 (4.1)	0.80 (0.55-1.16)	0.78 (0.52-1.17)
Taken for climacteric symptoms				
Black cohosh				
Nonuser	858 (97.6)	33,087 (97.2)	1.00 (reference)	1.00 (reference)
Users	21 (2.4)	964 (2.8)	1.04 (0.67-1.60)	1.17 (0.75-1.82)

(*Continued on the following page*)

Table 2. Associations between specialty supplement use and breast cancer risk among female VITAL participants (n = 35,016) (Cont'd)

Supplement	Cases (n = 880), n (%)	Noncases (n = 34,136), n (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
Dong quai[†]				
Nonuser	864 (98.2)	33,459 (98.7)	1.00 (reference)	1.00 (reference)
Users	16 (1.8)	426 (1.3)	1.18 (0.72-1.93)	1.27 (0.76-2.13)
Soy supplement				
Nonuser	843 (95.9)	32,510 (95.4)	1.00 (reference)	1.00 (reference)
User	36 (4.1)	1,553 (4.6)	0.98 (0.70-1.37)	1.04 (0.74-1.48)
St. John's wort[†]				
Nonuser	827 (94.5)	31,909 (93.8)	1.00 (reference)	1.00 (reference)
Former	28 (3.2)	1,396 (4.1)	0.87 (0.59-1.26)	0.83 (0.55-1.24)
Current	20 (2.3)	713 (2.1)	1.16 (0.75-1.81)	1.18 (0.74-1.89)
P trend			0.89	0.95
10-y average use[‡]				
Nonuser	827 (94.5)	31,909 (93.8)	1.00 (reference)	1.00 (reference)
Low	40 (4.6)	1,595 (4.7)	1.07 (0.78-1.47)	1.05 (0.75-1.47)
High	8 (0.9)	514 (1.5)	0.66 (0.33-1.33)	0.63 (0.30-1.33)
P trend			0.54	0.46
Combined climacteric supplements[†]				
Nonuser	782 (89.27)	29,983 (88.25)	1.00 (reference)	1.00 (reference)
User	94 (10.73)	3,991 (11.75)	1.01 (0.81-1.26)	1.01 (0.80-1.27)
Other specialty supplements				
Acidophilus[†]				
Nonuser	842 (95.7)	32,040 (94.4)	1.00 (reference)	1.00 (reference)
Former	17 (1.9)	881 (2.6)	0.78 (0.48-1.26)	0.73 (0.55-1.23)
Current	21 (2.4)	1,034 (3.1)	0.79 (0.52-1.23)	0.83 (0.52-1.31)
P trend			0.18	0.23
10-y average use[‡]				
Nonuser	842 (95.7)	32,040 (94.4)	1.00 (reference)	1.00 (reference)
Low	28 (3.2)	1,320 (3.9)	0.84 (0.58-1.23)	0.82 (0.55-1.23)
High	10 (1.1)	595 (1.8)	0.67 (0.36-1.25)	0.69 (0.36-1.33)
P trend			0.12	0.15
Coenzyme Q10[†]				
Nonuser	815 (92.8)	31,503 (92.6)	1.00 (reference)	1.00 (reference)
Former	16 (1.8)	792 (2.3)	0.81 (0.50-1.33)	0.76 (0.45-1.30)
Current	47 (5.4)	1,744 (5.1)	1.04 (0.77-1.39)	1.05 (0.77-1.43)
P trend			0.99	0.99
10-y average use[‡]				
Nonuser	815 (92.8)	31,503 (92.6)	1.00 (reference)	1.00 (reference)
Low	37 (4.2)	1,603 (4.7)	0.92 (0.66-1.27)	0.92 (0.65-1.29)
High	26 (3.0)	933 (2.7)	1.06 (0.71-1.56)	1.04 (0.69-1.58)
P trend			0.96	0.92
Garlic pills				
Nonuser	789 (90.2)	30,101 (88.6)	1.00 (reference)	1.00 (reference)
Former	34 (3.9)	1,612 (4.8)	0.81 (0.57-1.14)	0.86 (0.60-1.22)
Current	52 (5.9)	2,252 (6.6)	0.83 (0.63-1.10)	0.84 (0.62-1.13)
P trend			0.11	0.18
10-y average use[‡ §]				
Nonuser	779 (89.0)	29,871 (88.0)	1.00 (reference)	1.00 (reference)
Low	56 (6.4)	2,346 (6.9)	0.92 (0.70-1.20)	0.99 (0.74-1.31)

(*Continued on the following page*)

Table 2. Associations between specialty supplement use and breast cancer risk among female VITAL participants (n = 35,016) (Cont'd)

Supplement	Cases (n = 880), n (%)	Noncases (n = 34,136), n (%)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
High	40 (4.6)	1,748 (5.2)	0.82 (0.60-1.13)	0.83 (0.59-1.16)
P trend			0.19	0.31
Ginkgo biloba†				
Nonuser	774 (88.3)	29,592 (87.1)	1.00 (reference)	1.00 (reference)
Former	47 (5.4)	1,707 (5.0)	1.09 (0.81-1.47)	1.06 (0.77-1.45)
Current	56 (6.4)	2,664 (7.8)	0.81 (0.62-1.06)	0.85 (0.64-1.13)
P trend			0.21	0.36
10-y average use‡ §				
Nonuser	755 (86.1)	28,794 (84.8)	1.00 (reference)	1.00 (reference)
Low	82 (9.4)	3,441 (10.1)	0.94 (0.75-1.18)	0.98 (0.77-1.25)
High	40 (4.6)	1,728 (5.1)	0.88 (0.64-1.21)	0.88 (0.63-1.24)
P trend			0.36	0.51
Ginseng				
Nonuser	835 (95.0)	31,986 (94.1)	1.00 (reference)	1.00 (reference)
Former	22 (2.5)	963 (2.8)	0.94 (0.62-1.44)	0.91 (0.58-1.44)
Current	22 (2.5)	1,045 (3.1)	0.87 (0.57-1.32)	0.94 (0.61-1.46)
P trend			0.48	0.69
10-y average use‡ §				
Nonuser	811 (92.3)	31,167 (91.7)	1.00 (reference)	1.00 (reference)
Low	53 (6.0)	2,160 (6.4)	1.02 (0.77-1.35)	1.08 (0.80-1.44)
High	15 (1.7)	667 (2.0)	0.91 (0.55-1.52)	0.85 (0.48-1.50)
P trend			0.87	0.92
Melatonin†				
Nonuser	831 (94.8)	32,007 (94.1)	1.00 (reference)	1.00 (reference)
Former	26 (3.0)	920 (2.7)	1.01 (0.68-1.49)	0.93 (0.61-1.42)
Current	20 (2.3)	1,090 (3.2)	0.86 (0.55-1.34)	0.87 (0.54-1.39)
P trend			0.56	0.51
10-y average use‡				
Nonuser	831 (94.8)	32,007 (94.1)	1.00 (reference)	1.00 (reference)
Low	33 (3.8)	1,583 (4.7)	0.85 (0.60-1.21)	0.86 (0.60-1.23)
High	13 (1.5)	427 (1.3)	1.25 (0.72-2.16)	1.09 (0.58-2.04)
P trend			0.97	0.70

*Adjusted for age, race, education, BMI, height, fruit consumption, vegetable consumption, alcohol consumption, physical activity, age at menarche, age at menopause, age at first birth, history of hysterectomy, years of combined hormone therapy, family history of breast cancer, history of benign breast biopsy, mammography, low-dose aspirin use, regular aspirin use, ibuprofen use, naproxen use, and use of multivitamins.

†Additionally adjusted for history of osteoarthritis (glucosamine, chondroitin, methylsulfonylmethane), chronic joint pain (glucosamine, chondroitin, methylsulfonylmethane), memory loss (fish oil, coenzyme q10, ginkgo biloba), CAD (fish oil, grapeseed), lactose intolerance (acidophilus), diabetes (dong quai), insomnia (melatonin), and depression (St. John's wort).

‡Ten-year average use: nonuser; low use, <4 d/week or <3 y; and high use, ≥4 d/week and ≥3 y.

§Including multivitamin sources; those with only multivitamin source coded as "low" 10-y average use.

the exposure window of etiologic relevance, our finding of no association with former use and no clear trend with amount of use in the 10 years before baseline is explained.

In this study, current use of fish oil was associated with reduced risk of invasive ductal carcinoma but not invasive lobular carcinoma. Although the mechanism is not clear, other exposures are differentially associated with ductal versus lobular cancer. For example, exposures that act by modifying circulating hormones, such as alcohol use and combined postmenopausal hormone therapy, seem to have greater associations with lobular or mixed ductal-lobular cancers (47, 48). We additionally found a reduction in risk of local but not regional or distant disease. It may be that any anticancer effect of fish oil may be insufficient to protect against aggressive phenotypes. Similar phenomena have been

previously reported. Authors of the Prostate Cancer Prevention Trial found a protective effect of finasteride on early-stage, but not late-stage, prostate cancer (49). In the Women's Health Initiative trial of combined hormone therapy, a protective effect was observed only for early-stage colorectal tumors (50).

Fish oil may be associated with a reduction of breast cancer risk because of its anti-inflammatory properties. EPA and DHA are thought to reduce inflammation through the inhibition of NF-κB (16), which acts as a transcription factor for targets associated with inflammation, including interleukin-6 and COX-2 (51). Because EPA and DHA are incorporated into cell phospholipids at the expense of arachidonic acid (ω-6 PUFA), they reduce the reservoir of arachidonic acid for COX-2 to synthesize PGE_2 (16).

Animal and human studies support fish oil as having anti-inflammatory and possibly other properties that could reduce breast cancer risk. Experimental studies in rodents have shown a reduction in PGE_2 levels and mammary tumor incidence with diets high in ω-3 PUFAs found in fish oil (52-54). In humans, dietary intake of ω-3 PUFAs or fish has been inversely associated with blood concentrations of inflammatory markers C-reactive protein, tumor necrosis factor-α, and interleukin-6 (31, 55). A recent randomized trial of ω-3 PUFA supplements reported that the supplements reduced circulating C-reactive protein and tumor necrosis factor-α (56); moreover, these markers have been associated with breast cancer risk in some epidemiologic studies (57-59). However, earlier findings from randomized trials of ω-3 PUFA supplementation in humans have been inconsistent in observing an effect on these or other immune markers, in part due to limited power (60).

We found no association of other specialty supplements with breast cancer risk. Our findings are in contrast to previously published work. Obi et al. (22) conducted a large, population-based case-control study

Table 3. Interaction of fish oil supplement use with factors associated with chronic inflammation in relation to breast cancer risk among female VITAL participants (*n* = 35,016)

	Fish oil*			
	Nonuser		Current user	
	Cases/noncases	HR (95% CI)†	Cases/noncases	HR (95% CI)†
BMI				
<25 kg/m^2	327/13,594	1.00 (reference)	21/1,270	0.67 (0.41-1.07)
≥25 kg/m^2	475/16,737	1.24 (1.06-1.44)	26/1,398	0.84 (0.56-1.27)
P interaction				0.94
CAD‡				
No	767/28,734	1.00 (reference)	41/2,539	0.62 (0.45-0.87)
Yes	35/1,591	0.84 (0.58-1.20)	6/129	1.56 (0.64-3.78)
P interaction				0.03
NSAID use§				
Irregular	616/23,119	1.00 (reference)	33/2,025	0.64 (0.44-0.91)
Regular	177/6,853	0.88 (0.74-1.05)	12/613	0.72 (0.41-1.28)
P interaction				0.52
Smoking status‖				
Nonsmoker/former smoker	672/25,743	1.00 (reference)	43/2,360	0.72 (0.53-1.00)
Current/recent smoker	119/4,391	1.06 (0.86-1.31)	4/299	0.41 (0.13-1.27)
P interaction				0.30
Dietary arachidonic acid				
<0.09 g/d	362/13,633	1.00 (reference)	21/1,129	0.62 (0.38-1.00)
≥0.09 g/d	358/13,365	0.99 (0.85-1.15)	22/1,299	0.69 (0.44-1.06)
P interaction				0.71

*Former users dropped from analysis.

†Adjusted for age, race, education, BMI, height, fruit consumption, vegetable consumption, alcohol consumption, physical activity, age at menarche, age at menopause, age at first birth, history of hysterectomy, years of combined hormone therapy, family history of breast cancer, history of benign breast biopsy, mammography, low-dose aspirin use, regular aspirin use, ibuprofen use, naproxen use, use of multivitamins, memory loss, and CAD.

‡Participants with a positive history of heart attack, angina, angioplasty, or bypass surgery.

§Ten-year average use: irregular, <4 d/week or <4 y; regular, ≥4 d/week and ≥4 y.

‖Former smokers, ≥10 y since quit; recent smokers, <10 y since quit.

Table 4. Associations of fish oil supplement use with subsets of breast cancer defined by histology and stage, among female VITAL participants (n = 35,016)

	Fish oil*			
	Nonuser		Current user	
	Cases/noncases	HR (95% CI)†	Cases/noncases	HR (95% CI)†
Histology				
Ductal carcinoma (n = 632)	579/30,331	1.00 (reference)	29/2,668	0.56 (0.38-0.83)
Lobular carcinoma (n = 172)	153/30,331	1.00 (reference)	13/2,668	1.08 (0.59-1.96)
P difference				<0.05
SEER summary stage				
Local (n = 626)	578/30,331	1.00 (reference)	29/2,668	0.57 (0.38-0.84)
Regional/distant (n = 251)	221/30,331	1.00 (reference)	18/2,668	0.97 (0.59-1.61)
P difference				0.06
Hormone receptor status				
ER^+ (n = 737)	669/30,331	1.00 (reference)	29/2,668	0.64 (0.46-0.91)
ER^- (n = 125)	118/30,331	1.00 (reference)	1/2,668	0.61 (0.27-1.40)
P difference				0.49
PR^+ (n = 640)	584/30,331	1.00 (reference)	22/2,668	0.63 (0.43-0.92)
PR^- (n = 221)	202/30,331	1.00 (reference)	8/2,668	0.67 (0.36-1.23)
P difference				0.96

*Former users dropped from analysis.

†Adjusted for age, race, education, BMI, height, fruit consumption, vegetable consumption, alcohol consumption, physical activity, age at menarche, age at menopause, age at first birth, history of hysterectomy, years of combined hormone therapy, family history of breast cancer, history of benign breast biopsy, mammography, low-dose aspirin use, regular aspirin use, ibuprofen use, naproxen use, use of multivitamins, memory loss, and CAD.

of 10,121 postmenopausal women in northern and southwestern Germany. They reported inverse associations with breast cancer for use of black cohosh (OR, 0.80; 95% CI, 0.63-1.00) and a borderline inverse association with phytoestrogens from soy and red clover supplements (OR, 0.64; 95% CI, 0.39-1.05; ref. 22). When the authors combined several herbal preparations including black cohosh, St. John's wort, soy, and other preparations, they reported a 25% reduction in breast cancer risk (ever versus never: OR, 0.74; 95% CI, 0.63-0.87; ref. 22). We attempted to replicate their findings and combined ever use of specialty supplements taken for climacteric symptoms; we observed no association. In another population-based case-control study, Rebbeck et al. (23) observed a reduction in breast cancer risk with ever use of black cohosh (OR, 0.47; 95% CI, 0.27-0.82) and a borderline risk reduction with use of ginseng (OR, 0.74; 95% CI, 0.53-1.06). Our finding of no association of ginkgo biloba with breast cancer risk is also in contrast to a recently completed randomized trial of ginkgo biloba, which reported a borderline significant excess risk of breast cancer in the intervention group (RR, 2.15; 95% CI, 0.97-4.80; ref. 61). Differences between our results and those of the prior studies may be explained by differences in study design, differences in dose under study, or chance; in the study by Rebbeck et al. (23), exposure frequencies were quite low, and in the ginkgo trial, the number of breast cancer cases was low (n = 27; ref. 61).

Our study has several strengths. To our knowledge, ours is the first prospective study designed specifically to investigate the association of specialty supplements with cancer risk. We targeted supplement users for recruitment, and we had detailed assessment of current and long-term specialty supplement exposure. Another strength of the study is that we were able to adjust our analyses for known and suspected indications for supplement use, thereby correcting for potential confounding by indication. Additionally, follow-up on the cohort was 95% complete; therefore, bias due to differential loss to follow-up is not likely to explain our findings.

This study is not without limitations. First, we did not query participants on the dose used for specialty supplements. One reason for this is that there is evidence that the advertised dose can vary substantially from that of the actual supplement (35). Another limitation is that supplement use was ascertained from participants through self-report. Although we did not conduct a validity study on our data on specialty supplements, we did conduct a study on the reliability and validity of our measures of 10-year average use of vitamin and mineral supplements (25). The intraclass correlation coefficients for test-retest reliability at baseline and after 3 months varied between 0.69 for β-carotene and 0.84

for folic acid, which provides some assurance that our measure of specialty supplements is reasonably accurate. An additional limitation is that we did not update exposure information after baseline. However, the prospective nature of the study design ensures that any error from self-report is likely to be nondifferential. Power was limited by the relatively low prevalence of use of some specialty supplements (e.g., black cohosh and dong quai). Finally, despite the support from epidemiologic studies of biomarkers of fatty acids and breast cancer risk and the biological plausibility, our finding for fish oil supplements could be due to chance because we examined 15 specialty supplements.

In summary, this is the first prospective study to report on the association of specialty supplements with breast cancer risk. Our finding of a reduced risk of breast cancer with use of fish oil warrants further study of this agent, focused particularly on timing of exposure and dose, as well as on mechanisms of action that might explain differences by tumor stage or histologic type. Until these results are replicated, fish oil supplements should not be promoted for reduction of breast cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 1998;280:1569–75.
2. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Anderson TE, Mitchell AA. Recent trends in use of herbal and other natural products. Arch Intern Med 2005;165:281–6.
3. Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997-2002. Altern Ther Health Med 2005;11:42–9.
4. Greenlee H, Kwan ML, Ergas IJ, et al. Complementary and alternative therapy use before and after breast cancer diagnosis: the Pathways Study. Breast Cancer Res Treat 2009;117:653–65.
5. Al-Akoum M, Dodin S, Akoum A. Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an *in vitro* study. Can J Physiol Pharmacol 2007;85:1153–9.
6. Rao CV, Sanders ME, Indranie C, Simi B, Reddy BS. Prevention of colonic preneoplastic lesions by the probiotic *Lactobacillus acidophilus* NCFMTM in F344 rats. Int J Oncol 1999;14:939–44.
7. Gonzalez MJ, Schemmel RA, Dugan L, Jr., Gray JI, Welsch CW. Dietary fish oil inhibits human breast carcinoma growth: a function of increased lipid peroxidation. Lipids 1993;28:827–32.
8. Dixon-Shanies D, Shaikh N. Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncol Rep 1999;6:1383–7.
9. Kramer F, Johnson IT, Doleman JF, Lund EK. A comparison of the effects of soya isoflavonoids and fish oil on cell proliferation, apoptosis and the expression of oestrogen receptors α and β in the mammary gland and colon of the rat. Br J Nutr 2009;102:29–36.
10. Kaur M, Singh RP, Gu M, Agarwal R, Agarwal C. Grape seed extract inhibits *in vitro* and *in vivo* growth of human colorectal carcinoma cells. Clin Cancer Res 2006;12:6194–202.
11. Grant SG, Melan MA, Latimer JJ, Witt-Enderby PA. Melatonin and breast cancer: cellular mechanisms, clinical studies and future perspectives. Expert Rev Mol Med 2009;11:e5.
12. Oh HJ, Lee JS, Song DK, et al. D-Glucosamine inhibits proliferation of human cancer cells through inhibition of p70S6K. Biochem Biophys Res Commun 2007;360:840–5.
13. Sakano K, Takahashi M, Kitano M, Sugimura T, Wakabayashi K. Suppression of azoxymethane-induced colonic premalignant lesion formation by coenzyme Q10 in rats. Asian Pac J Cancer Prev 2006;7:599–603.
14. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000;283:1469–75.
15. Iovu M, Dumais G, du Souich P. Anti-inflammatory activity of chondroitin sulfate. Osteoarthritis Cartilage 2008;16 Suppl 3:S14–8.
16. Chapkin RS, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. Prostaglandins Leukot Essent Fatty Acids 2009;81:187–91.
17. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.
18. Kundu JK, Surh YJ. Inflammation: gearing the journey to cancer. Mutat Res 2008;659:15–30.
19. Howe LR. Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. Breast Cancer Res 2007;9:210.
20. Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. Inflammopharmacology 2009;17:55–67.
21. Takkouche B, Regueira-Méndez C, Etminan M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst 2008;100:1420–3.
22. Obi N, Chang-Claude J, Berger J, et al. The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study. Cancer Epidemiol Biomarkers Prev 2009;18:2207–13.
23. Rebbeck TR, Troxel AB, Norman S, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer 2007;120:1523–8.
24. White E, Patterson RE, Kristal AR, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol 2004;159:83–93.
25. Satia-Abouta J, Patterson RE, King IB, et al. Reliability and validity of self-report of vitamin and mineral supplement use in the vitamins and lifestyle study. Am J Epidemiol 2003;157:944–54.
26. Littman AJ, White E, Kristal AR, Patterson RE, Satia-Abouta J, Potter JD. Assessment of a one-page questionnaire on long-term recreational physical activity. Epidemiology 2004;15:105–13.
27. Gunther S, Patterson RE, Kristal AR, Stratton KL, White E. Demographic and health-related correlates of herbal and specialty supplement use. J Am Diet Assoc 2004;104:27–34.
28. Ready A, Velicer CM, McTiernan A, White E. NSAID use and breast cancer risk in the VITAL cohort. Breast Cancer Res Treat 2008;109:533–43.
29. Fredrikson GN, Hedblad B, Nilsson JA, Alm R, Berglund G, Nilsson J. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. Metabolism 2004;53:1436–42.

30. Pitsavos C, Panagiotakos DB, Tzima N, et al. Diet, exercise, and C-reactive protein levels in people with abdominal obesity: the ATTICA epidemiological study. Angiology 2007;58:225–33.
31. Cavicchia PP, Steck SE, Hurley TG, et al. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr 2009;139:2365–72.
32. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090–8.
33. Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. Vitamin D and reduced risk of breast cancer: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2007;16:422–9.
34. Blackmore KM, Lesosky M, Barnett H, Raboud JM, Vieth R, Knight JA. Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. Am J Epidemiol 2008; 168:915–24.
35. Ako H, Ota E, Ogasawara A. ω-3 Fatty acids in Hawaii seafood. Hawaii Med J 1994;53:142–5.
36. Voorrips LE, Brants HA, Kardinaal AF, Hiddink GJ, van den Brandt PA, Goldbohm RA. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002;76: 873–82.
37. Stripp C, Overvad K, Christensen J, et al. Fish intake is positively associated with breast cancer incidence rate. J Nutr 2003;133: 3664–9.
38. Holmes MD, Colditz GA, Hunter DJ, et al. Meat, fish and egg intake and risk of breast cancer. Int J Cancer 2003;104:221–7.
39. Key TJ, Sharp GB, Appleby PN, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer 1999;81:1248–56.
40. Vatten LJ, Solvoll K, Loken EB. Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. Int J Cancer 1990;46:12–5.
41. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: the Singapore Chinese Health Study. Br J Cancer 2003;89:1686–92.
42. Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281: 914–20.
43. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079–85.
44. Kim EH, Willett WC, Colditz GA, et al. Dietary fat and risk of postmenopausal breast cancer in a 20-year follow-up. Am J Epidemiol 2006; 164:990–7.
45. MacLean CH, Newberry SJ, Mojica WA, et al. Effects of ω-3 fatty acids on cancer risk: a systematic review. JAMA 2006;295:403–15.
46. Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer 2004;111:584–91.
47. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006;7:910–8.
48. Li CI, Daling JR, Malone KE, et al. Relationship between established breast cancer risk factors and risk of seven different histologic types of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2006; 15:946–54.
49. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.
50. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004;350:991–1004.
51. Pahl HL. Activators and target genes of Rel/NF-κB transcription factors. Oncogene 1999;18:6853–66.
52. Karmali RA, Marsh J, Fuchs C. Effect of ω-3 fatty acids on growth of a rat mammary tumor. J Natl Cancer Inst 1984;73:457–61.
53. Kort WJ, Weijma IM, Bijma AM, van Schalkwijk WP, Vergroesen AJ, Westbroek DL. ω-3 Fatty acids inhibiting the growth of a transplantable rat mammary adenocarcinoma. J Natl Cancer Inst 1987; 79:593–9.
54. Sasaki T, Kobayashi Y, Shimizu J, et al. Effects of dietary n-3-to-n-6 polyunsaturated fatty acid ratio on mammary carcinogenesis in rats. Nutr Cancer 1998;30:137–43.
55. Pot GK, Geelen A, Majsak-Newman G, et al. Increased consumption of fatty and lean fish reduces serum C-reactive protein concentrations but not inflammation markers in feces and in colonic biopsies. J Nutr 2010;140:371–6.
56. Micallef MA, Garg ML. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis 2009;204:476–82.
57. Heikkila K, Harris R, Lowe G, et al. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.
58. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2413–8.
59. Zeleniuch-Jacquotte A, Gu Y, Bruning PF, et al. Re: C-reactive protein and risk of breast cancer. J Natl Cancer Inst 2008;100:443–4, author reply 444–5.
60. Fritsche K. Fatty acids as modulators of the immune response. Annu Rev Nutr 2006;26:45–73.
61. Biggs ML, Sorkin BC, Nahin RL, Kuller LH, Fitzpatrick AL. Ginkgo biloba and risk of cancer: secondary analysis of the Ginkgo Evaluation of Memory (GEM) Study. Pharmacoepidemiol Drug Saf. In press 2010.