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Vitamin Supplement Use and Risk for Breast Cancer: The Shanghai Breast Cancer Study.

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Abstract

Objective: The influence of vitamin supplements on risk for breast cancer is unclear. Also the interactive effects of vitamins from dietary and supplemental sources are unknown. This study investigated the association between self-reported vitamin supplement use (A, B, C, E and multivitamin) and breast cancer among urban Chinese women. It also examined the combined effect of vitamin supplements in relation to particular dietary vitamin intakes on breast cancer risk.

Methods: Study subjects were identified from The Shanghai Breast Cancer Study (SBCS) and was a population-based case-control study conducted in Shanghai in 1996-1998 (Phase I) and 2002-2004 (Phase II). Participants were aged 25 to 64 and 20 to 70 years for phase I and for phase II, respectively. The analyses included 3,454 incident breast cancer cases and 3,474 controls. Unconditional logistic regression models were used to determine adjusted odds ratios (ORs) for breast cancer risk associated with vitamin supplement use.

Results: Overall, the breast cancer risk was not related to intakes of any vitamin supplement. However, an approximately 20% reduction in breast cancer risk was observed with use of vitamin E supplement among women with low-dietary vitamin E intake (OR=0.8; 95% confidence interval (CI), 0.6-0.9) with a significant dose-response inverse association ($P_{trend}=0.01$ for duration). Modest risk reduction was observed among vitamin B supplement users with low dietary intake of the same vitamin (OR=0.9; 95% CI, 0.6-1.0). However, vitamin B supplement was adversely associated with breast cancer risk among those with high dietary vitamin B intake with a significant dose-response effect ($P_{trend}=0.04$ for duration).

Conclusions: This study suggests that vitamins E and B supplement may confer a prevention of breast cancer among women who have low dietary intake of those vitamins.

Keywords

antioxidants; breast cancer epidemiology; dietary supplements; vitamins

INTRODUCTION

Due to their importance in biological functions, vitamins have been extensively studied over the past few decades for their relationship with a wide-variety of health outcomes, including

breast cancer [1-4]. Vitamins are hypothesized to affect breast cancer risk through an assortment of mechanisms, including their antioxidant capabilities against free-radical induced DNA damage, maintenance of cellular integrity, coenzyme and immune, and reproductive system functions [3,5-10]. However, despite laboratory-based findings [8,11-14], epidemiological studies have been unable to provide unequivocal evidence for preventive effect of both dietary and supplemental vitamin intakes in preventing breast cancer for most common vitamins [6,15-23].

Vitamin supplements, including vitamins A, C, E and B, first became available in the early 1930s. Today, these supplements often contain substantially higher concentrations of vitamins than are available from typical dietary sources and populations in many countries have extensive availability to these preparations [1,3,7,24-27]. However, despite their prevalent use, few studies have specifically evaluated use of specific vitamin supplements (multivitamin, A, C, B and E) with breast cancer risk. In this study, we examine the relationship between breast cancer risk and vitamin supplements use in a large population-based cases and controls in urban Shanghai, China.

METHODS

Study population

The Shanghai Breast Cancer Study is a large population-based case control study conducted in Shanghai, China during August 1996-March 1998 (Phase I) and April 2002-February 2005 (Phase II). Detailed methods have been published elsewhere [28]. Cases were identified by a rapid case-ascertainment system, supplemented by the population-based Shanghai Cancer Registry and diagnoses were confirmed by medical record review. Participants were excluded if they were not permanent residents of urban Shanghai or if they had a prior history of cancer. Controls were randomly selected from female permanent residents and frequency-matched to the expected case age distribution. A total of 1,455 (91.1%) and 1,999 (83.7%) cases and 1,556 (90.3%) and 1,918 (70.4%) controls were recruited in Phase I and II respectively, comprising for a total of 3,454 cases and 3,474 controls for this analysis. The study protocols were approved by the Institutional Review Boards of all institutes involved in the study, and written, informed consent was obtained from all study participants prior to interview.

Data Collection

Information on demographic characteristics, personal and family history of cancer, other diseases, and various behavioral and dietary habits and vitamin supplement use were collected by in-person interviews conducted by trained staff. With few exceptions, the questionnaires from both phases were identical. The food frequency questionnaire (FFQ) from Phase II included ten additional food items and use of folic acid supplement. Participants in both phases were asked whether they had ever taken any vitamin supplement at least 3 times per week for more than 2 months continuously per year during the past 5 years period prior to breast cancer diagnosis (cases) or enrollment (controls). These included multivitamin, vitamins A, B, C, E, and, for Phase II only, folic acid. If participants were ever taken any vitamin supplement and for each supplement they used, participants were asked for how many months in total they had used the supplement (duration), and during those months how many times per day or week they used them (frequency). Vitamin supplement intake frequency was categorized to less than or equal to once daily and greater than once daily per week and duration was categorized to less than 1 year, 1-2 years, and more than 3 years. The folic acid supplement users were excluded in this study due to very small sample size (n=49). Information regarding specific brand and dosage of vitamin supplement was not available. Total dietary intakes of vitamins A, B (a composite of B1, B2 and niacin), E, and C were derived from the FFQ and the Chinese

food composition tables [28,29]. Dietary vitamin intake was divided into two categories based on the median daily intake value in the control population.

STATISTICAL ANALYSIS

Statistical tests were based on a two-sided probability with a significance level of 0.05. Odds ratios (OR) were used to measure the association between breast cancer risk with various exposures. Unconditional logistic regression (LR) was used to estimate odds ratios and 95% confidence intervals (CI), with adjustment for breast cancer risk factors identified in this population. The latter included age (continuous), education, age at menarche (≤ 12 , 13-14, 15-16, and > 16 years), age at first life birth (≤ 25 , 26-29, 30-35, and > 35 years), live birth (Y/N), body mass index (BMI in quartiles), menopausal status (pre- and post-), physical activity in the past 10 years (Y/N), history of fibroadenoma (Y/N), family history of breast cancer (Y/N). We also adjusted for study phase (I and II) in the analyses.

For our analyses we grouped the cases and controls in to six categories based on their supplement use patterns : any vitamin supplement users, multivitamin only users and specific supplement users (vitamins A, B, C, and E) with multivitamins, which is similar to previously reported studies [4,30]. To evaluate the impact of vitamin supplement use on breast cancer risk in the context of dietary status, we conducted stratified analyses by median dietary intake of vitamins. Use of other vitamin supplements was also controlled in the analyses. Tests for trend were performed by entering the categorical variables as continuous parameters in the model. Tests for interaction were performed using the log likelihood test. All data management and statistical analyses were performed using SAS.9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the participants of two study phases are presented in Table 1. The average age was 47.9 and 50.8 for cases and 47.2 and 51.6 years for controls for Phase I and Phase II, respectively. In general, participants of the two phases are comparable with the exception that phase II subjects were slightly older and more frequently post-menopausal as a result of wide age eligibility. As compared to controls, cases were more likely to have higher educational attainment, an earlier age at menstruation ($P = 0.0001$ for both phases), later age at first birth or menopause, a family history of breast cancer among first degree of relatives, a personal history of breast fibroadenoma, and a higher red meat intake. They were also more likely to be nulliparous and overweight or obese and less likely to have breast fed or exercised regularly ($P = < .001$ for both phases). There were no differences in intakes of total energy, or vegetables and fruits between cases and controls in both phases.

Characteristics of vitamin supplement users and non-users were compared within the control populations (Table 2). The use of supplements increased from 1996-1998 (14.5 %, Phase I) to 2002-2004 (24.8 %, Phase II) in all subjects. Among cases, this difference was even larger; in phase I only 11.5 % and in phase II over 26.5 % were users (data not shown in table).

Supplement users had higher educational attainment than non-users ($P = < .0001$ for both phases). They also were more likely to have an earlier age at menstruation, more likely to be menopausal, more often engaged in leisure physical activities in the past 10 years, and more likely to have a lower BMI or a lower waist-to-hip ratio (WHR), and a family history of breast cancer or a personal history of fibroadenoma in both phases. In phase I, users were also more likely to be older, less likely to be parous, and more likely to have a family history of breast cancer. In comparison with Phase II non-users, users were more likely to have a higher vegetables and fruit intake. Neither energy intake nor meat intake were statistically significantly different between users and non-users in either study phase.

Presented in Table 3 are the comparisons of cases and controls for use of specific vitamin supplements. Most vitamin supplements users reported using specific vitamins together with multivitamins (data not shown in table). Thus, the multivariate models were additionally controlled for other vitamin supplements. Among users, multivitamin was the most used a supplement on a daily basis. When use of multivitamins or specific vitamin supplements was evaluated we did not find any statistically significant associations between any use, duration, or frequency of use in this population. We analyzed the associations between vitamin supplement intake and breast cancer for each phase of study. Results were similar for both phases so only the results from the combined phases are presented. Additionally, results from the analyses stratified by menopausal status did not appreciably differ from the unstratified analyses as reported above (data not shown in table).

To evaluate the association between use of individual vitamin supplements in the context of dietary intake for these same vitamins, we stratified all analyses by low and high dietary intakes (Table 4). Use of vitamin A or vitamin C supplements was not associated with risk for breast cancer regardless of dietary intake of the same vitamins. Among those with high dietary intake of B vitamins, there was an increased risk associated with long-term intake ($P_{\text{for trend}}=0.04$) and a suggestive increased risk with frequency of use of a B vitamin, although this result was not statistically significant. Among those with low intake, there was also a borderline decreased risk with ever use of vitamins B supplement (OR =0.8; 95% CI, 0.6-1.0) and its frequency of use ($P_{\text{trend}}=0.05$), however compare to the duration of use this result is more likely to be non-significant. The interactions between ever use or frequency of use of any B vitamin supplement and across the dietary B vitamin intake were statistically significant ($P_{\text{interaction}}=0.008$ and $P_{\text{interaction}}=0.03$, respectively) levels. Among women with low dietary intake of vitamin E, use of a vitamin E supplement was associated with a decreased risk for breast cancer (OR=0.8; 95% CI, 0.6-0.9). Longer durations of use of vitamin E supplement may confer additional protection ($P_{\text{for trend}}=0.01$).

DISCUSSION

In Shanghai, vitamin supplement use among women increased substantially between the years 1996 and 2002. In this case-control study, we found little evidence that overall use of vitamin supplements was associated with breast cancer risk. However, we did observe a statistically significant decreased risk of breast cancer associated with use of a vitamins E and B supplement among those with low dietary intake of these vitamins. We also found that use of a vitamin B supplement was associated with an increased risk among those with high dietary intake.

Breast cancer occurs as a culmination of a multistep process. Vitamins, through their effect in many cellular functions, may potentially affect breast carcinogenesis [5,11,31]. The B family of vitamins, including B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), and B12 (cyanocobalamin), function in one-carbon metabolism, oxidative stress pathways, the immune and nervous systems, and cell growth and division. Antioxidants, including vitamins C, E, and carotenoids are important in the defense against oxidative damage, such as DNA damage, from free radicals [5-9,14,31,32]. Although the mechanisms are not clearly understood, oxidative damage is thought to occur during the promotional stage of carcinogenesis. For this reason, antioxidants may cause regression of premalignant lesions or inhibit their development into cancer [6,7,10,25,33,34]. These antioxidants also have other important roles in cellular processes. Vitamin C (ascorbic acid) is essential for metabolic reactions in the body [32,35]. Vitamin A (retinol) is needed for the cell differentiation, normal functioning of the immune or reproductive systems, and vision [12,32,33]. The lipid-soluble Vitamin E also helps the immune response, maintenance of cell membranes, anti-inflammatory reaction and DNA synthesis. Among animal models, Vitamin E may counteract cellular proliferation and protect against carcinogen-induced mammary tumor development [14,32,34,36], however there are

research reports that this protection may be affected by the presence of other dietary components, such as polyunsaturated fatty acids [3,34,37].

Overall, the results of this study support previous epidemiological findings in which vitamin supplementation alone does not substantially affect the risk of breast cancer [17,30,38]. In this study vitamin A intake, from both dietary intake and supplemental, was not associated with breast cancer risk or incidence as seen in several previous studies [21,31,38-42]. However, other studies did find significant inverse [43,44] or borderline inverse associations [15,17, 44-48]. Likewise, Vitamin C intake, has also had conflicting reports of both null and non-significant inverse associations with breast cancer risk [18,39-41,44,48]. However, several case-control studies [16,49,50] and one meta-analysis [20] reported a significant inverse association for vitamin C intake. In our study, we found breast cancer risk associated with use of a B-vitamin supplement varied according to dietary intake. In studies which have evaluated use of supplemental B vitamins including folic acid and breast cancer risk, supplemental use has not been associated with risk of breast cancer [45,51-53], although dietary intake of some B vitamins (B12, B6 and folate) [54-58], and adequate levels of serum B12, B12 and folate have been associated with a decreased risk in other studies [58,59] including in a previous report from our own study [60]. There have also been recent reports that folic acid, and possibly other B vitamins, may have dual effects on breast cancer [61,62]. In the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial, folic acid supplementation was associated with an increased risk of breast cancer [52].

In both the Nurses' Health Study and the Iowa Women's Health study, dietary intake of vitamin E alone was not sufficient to protect against breast cancer [18,63]. In contrast to some cohort [17,18,38-41,48,63] and case control studies [15,16,55,64,65] on dietary intake or supplemental intakes only [17,30], we found that vitamin E supplementation was associated with a decreased risk of breast cancer among women who had lower dietary intakes. It has been previously suggested that the effect of supplemental vitamin E intake on breast cancer risk may be dependent upon the dietary intake level within the population or possibly food sources [32,44,47]. In our population median dietary intake is below recommended levels and lower than many of the previous studies [3,32]. Thus, it is possible use of a vitamin E supplement may confer protection against breast cancer among women with insufficient intake.

In our study, an association between vitamin supplements use and breast cancer risk could have been obscured by the short duration of use (etiological window) or the use of supplements among those at high risk. In many population, vitamin supplement use is a marker of a healthy lifestyle [66-68]. In our study population, use of vitamin supplement was associated with income and education, but not related dietary intake. We have carefully controlled for many of these factors in statistical analyses, although the possibility of residual confounding remains. As in all case-control studies, the possibility of recall bias must also be considered. However, nearly all users reported taking the vitamin supplement at least once daily indicating that, in this population of users, vitamin supplement use is a frequent habit which may facilitate recall for both cases and controls. We also evaluated vitamin supplement use that lasted at least one year's duration and found similar results. Lack of specific dosages of vitamins has prevented a further a depth analysis.

This study has several strengths. This is a population-based study with a large sample size and high response rates. We were able to evaluate both the frequency and duration of supplement use, and to evaluate it in the context of dietary intake. We were also able to evaluate both pre- and post-menopausal breast cancer risk. Unlike populations in many Western countries, the Chinese food supply is not fortified with vitamins which enabled us to investigate the effect of vitamin preparations.

In summary, this large population-based breast cancer case-control study does not support a strong role for vitamin supplements in the prevention of breast cancer among population with sufficient dietary intake of vitamins. However, supplemental use of vitamins E and B may be inversely associated with breast cancer risk among women with low dietary intake of these vitamins.

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REFERENCES

1. Satia-Abouta J, Kristal AR, Patterson RE, Littman AJ, Stratton KL, White E. Dietary supplement use and medical conditions: the VITAL study. *Am J Prev Med* 2003;24(1):43–51. [PubMed: 12554023]
2. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. *JAMA* 2002;287(23):3127–3129. [PubMed: 12069676]
3. Vitamin and Mineral Requirements in Human Nutrition. Second edition. WHO and FAO Publications; 2004. Joint Expert Consultation on Human Vitamin and Mineral requirements FW; p. 1-340.
4. Hoggatt KJ, Berstein L, Reynolds P, et al. Correlates of vitamin supplement use in the United States: data from the California Teachers Study cohort. *Cancer Causes Control* 2002;13(8):735–740. [PubMed: 12420952]
5. Machlin LJ, Bendich A. Free radical tissue damage: protective role of antioxidant nutrients. *FASEB J* 1987;1:441–445. [PubMed: 3315807]
6. Garland M, Willett WC, Manson JE, Hunter DJ. Antioxidant micronutrients and breast cancer. *J Am Coll Nutr* 1993;12:400–11. [PubMed: 8409102]
7. Rose RC. Vitamin supplementation and breast cancer: is homeostasis a factor? *Medical Hypotheses* 1998;51:239–242. [PubMed: 9792202]
8. Kumaraguruparan R, Subapriya R, Kabalimoorthy J, Nagini S. Antioxidant profile in the circulation of patients with fibroadenoma and adenocarcinoma of the breast. *Clinical Biochemistry* 2002;35:275–279. [PubMed: 12135688]
9. Fenech M. Biomarkers of genetic damage for cancer epidemiology. *Toxicology* 2002;181-182:411–6. [PubMed: 12505344]
10. Galan P, Briancon S, Favier A, Bertrails S, et al. Antioxidant status and risk of cancer in the SU.VI.MAX study: is the effect of supplementation dependent on baseline levels? *Br J Cancer* 2005;94:125–132.
11. Collins AR. Molecular epidemiology in cancer research. *Mol Aspects Med* 1998;19(6):359–432. [PubMed: 10385877]
12. Willett WC. Diet and breast cancer. *J Intern Med* 2001;249(5):395–411. [PubMed: 11350564]
13. Maillard V, Hoinard C, Arab K, Jourdan ML, Bougnoux P, Chajes V. Dietary beta-carotene inhibits mammary carcinogenesis in rats depending on dietary alpha-linolenic acid content. *Br J Nutr* 2006;96(1):18–21. [PubMed: 16869986]
14. Chamras H, Barsky SH, Ardashian A, Navasartian D, Heber D, Glaspy JA. Novel interactions of vitamin E and estrogen in breast cancer. *Nutr Cancer* 2005;52(1):43–48. [PubMed: 16091003]
15. Sato R, Helzlsouer KJ, Alberg AJ, et al. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11:451–457. [PubMed: 12010859]
16. Howe GR, Hirohata T, Hisop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst (Bethesda)* 1990;82:561–569.
17. Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of the intake of vitamins C, E and A and the risk of breast cancer. *N Engl J Med* 1993;329(4):234–240. [PubMed: 8292129]

18. Kushi LH, Fee RM, Sellers TA, Zheng W, Folsom AR. Intake of vitamins A, C, and E and postmenopausal breast cancer. The Iowa Women's Health Study. *Am J Epidemiol* 1996;144(2):165–174. [PubMed: 8678048]
19. Lee MM, Chang IY, Horng CF, et al. Breast cancer and dietary factors in Taiwanese women. *Cancer Causes and Control* 2005;16(8):929–937. [PubMed: 16132802]
20. Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer* 2000;36(5):636–646. [PubMed: 10738129]
21. Nissen SB, Tjonneland A, Stripp C, et al. Intake of vitamins A, C, and E from diet and supplements and breast cancer in postmenopausal women. *Cancer Causes and Control* 2003;695–704. [PubMed: 14674733]
22. Stanner SA, Hughes J, Kelly CN, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. *Public Health Nutr* 2004;7(3):407–422. [PubMed: 15153272]
23. Horn-Ross PL, Hoggatt KJ, West DW, et al. Recent diet and breast cancer risk: the California Teachers Study (USA). *Cancer Cause Control* 2002;13(5):407–415.
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(1):83–93. [PubMed: 14693663]
25. World Cancer Research Fund. World cancer Research Fund/American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. American Ins for Cancer Research; Washington DC: 1997. Vitamins.
26. Shikany JM, Patterson RE, Agurs-Collins T, Anderson G. Antioxidant supplement use in Women's Health Initiative participants. *Prev Med* 2003;36(3):379–387. [PubMed: 12634029]
27. Rock CL. Multivitamin-multimineral supplements: who uses them? *Am J Clin Nutr* 2007;85(1):277S–279S. [PubMed: 17209209]
28. Malin AS, Dai Q, Shu XO, et al. Intake of fruits, vegetables and selected micronutrients in relation to the risk of breast cancer. *Int J Cancer* 2003;105:413–8. [PubMed: 12704679]
29. Sciences CAoM. Food composition table. People's Health Publishing House; Beijing: 1991.
30. Moorman PG, Ricciuti MF, Millikan R, Newman B. Vitamin supplement use and breast cancer in a North Carolina population. *Public Health Nutrition* 2001;4(3):821–7. [PubMed: 11415490]
31. Dorgan JF, Schatzkin A. Antioxidant micronutrients in cancer prevention. *Hematol Onco Clin North Am* 1991;5(1):43–68.
32. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention. *JAMA* 2002;187(23):3117–3126.
33. Zhang SM. Role of vitamins in the risk, prevention, and treatment of breast cancer. *Curr Opin Obstet Gynecol* 2004;16(1):19–25. [PubMed: 15128003]
34. Stroll BA. Breast cancer and the Western diet: Role of fatty acids and antioxidant vitamins. *Eur J Cancer* 1998;34(12):1852–1856. [PubMed: 10023305]
35. Diplock AT. Antioxidants and disease prevention. *Molecular Aspects of Medicine* 1994;15:293–376. [PubMed: 7845187]
36. Jiang Q, Christen S, Shigenaga MK, Ames BN. Gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. *Am J Clin Nutr* 2001;74(6):714–722. [PubMed: 11722951]
37. Bonilla-Fernandez P, Lopez-Cervantes M, Torres-Shanchez LE, et al. Nutritional factors and breast cancer in Mexico. *Nutr Cancer* 2003;45(2):148–155. [PubMed: 12881007]
38. Michels KB, Holmberg L, Bergkvist L, et al. Dietary antioxidant vitamins, retinol, and breast cancer incidence in a cohort of Swedish women. *Int J Cancer* 2001;91:563–567. [PubMed: 11251982]
39. Jarvinen R, Knekt P, Seppanen R, Teppo L. Diet and breast cancer risk in a cohort of Finnish women. *Cancer Lett* 1997;114(12):251–253. [PubMed: 9103304]
40. Verhoeven DT, Assen N, Goldbohm RA, et al. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. *Br J Cancer* 1997;75:149–155. [PubMed: 9000614]
41. Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C and E and risk of breast cancer: a cohort study. *Cancer Cause Control* 1993;4:29–37.

42. Lee IM, Cook NR, Manson JE, Buring JE. Randomised beta-carotene supplementation and incidence of cancer and cardiovascular disease in women: is the association modified by baseline plasma level? *Br J Cancer* 2002;86(5):698–701. [PubMed: 11875728]
43. Tamimi RM, Hankinson SE, Campos H, et al. Plasma carotenoids, retinol and tocopherols and risk of breast cancer. *Am J Epidemiol* 2005;161(2):153–160. [PubMed: 15632265]
44. Bohlke K, Spiegelman D, Trichopoulos A, Katsouyanni K, Trichopoulos D. Vitamins A, C and E and the risk of breast cancer: results from a case-control study in Greece. *Br J Cancer* 1999;79(1):23–9. [PubMed: 10408688]
45. Potischman N, Swanson CA, Coates RJ, Gammon MD, Brogan DR, Curtin J, et al. Intake of food groups and associated micronutrients in relation to risk of early-stage breast cancer. *Int J Cancer* 1999;82:315–21. [PubMed: 10399945]
46. Hulten K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, Riboli E. Carotenoids, alpha-tocopherols, and retinol in plasma and breast cancer risk in northern Sweden. *Cancer Causes Control* 2001;12(6):529–37. [PubMed: 11519761]
47. Wald NJ, Hayward JL, Bulbrook RD. Plasma retinol, beta-carotene and vitamin E levels in relation to the future risk of breast cancer. *Br J Cancer* 1984;49(3):321–324. [PubMed: 6704307]
48. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C and E and risk of breast cancer. *J Natl Cancer Inst (Bethesda)* 1999;91:547–56.
49. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary intake of selected micronutrients and breast-cancer risk. *Int J Cancer* 2001;91(2):260–3. [PubMed: 11146455]
50. Do MH, Lee SS, Jung PJ, Lee MH. Intake of dietary fat and vitamin in relation to breast cancer risk in Korean women: a case-control study. *J Korean Med Sci* 2003;18(4):534–40. [PubMed: 12923330]
51. Wu K, Helzlsouer KJ, Comstock GW, Hoffman SC, Nadeau MR, Selhub J. A prospective study on folate, B12, and pyridoxal 5'-phosphate (B6) and breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8(3):209–217. [PubMed: 10090298]
52. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, Johnson KA, Johnson C, Buys SS, Hoover RN, Ziegler RG. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Clin Nutr* 2006;83(4):895–904. [PubMed: 16600944]
53. Lewis SJ, Harbord RM, Harris R, Smith GD. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. *J Natl Cancer Inst (Bethesda)* 2006;98(22):1607–1622.
54. Lajous M, Lazcano-Ponce E, Henandez-Avila M, et al. Folate, vitamin B6, and B12 intake and the Risk of Breast Cancer Among Mexican Women. *Cancer Epidemiology, Biomarkers & Prevention* 2006;15(3):443–448.
55. Lajous M, Romieu I, Sabia S, et al. Folate, vitamin B12 and postmenopausal breast cancer in a prospective study of French women. *Cancer Causes and Control* 2006;17:1209–1213. [PubMed: 17006726]
56. Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, et al. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 1996;88:340–348. [PubMed: 8609642]
57. Zhang S, Hunter DJ, Hankinson SE, Giovannucci EL, et al. A prospective study of folate intake and the risk of breast cancer. *JAMA* 1999;281(17):1632–1637. [PubMed: 10235158]
58. Zhang SM, Willett WC, Selhub JS, Hunter DJ, et al. Plasma folate, vitamin B6, B12, homocysteine, and risk of breast cancer. *J Natl Cancer Inst (Bethesda)* 2003;95(5):373–380.
59. Beilby J, Ingram D, Hahnel R, Rossi E. Reduced breast cancer risk with increasing serum folate in a case-control study of the C677T genotype of the methylenetetrahydrofolate reductase gene. *Eur J Cancer* 2004;40(8):1250–1254. [PubMed: 15110890]
60. Shrubsole MJ, Jin F, Dai Q, et al. Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Res* 2001;61:7136–7141. [PubMed: 11585746]
61. Eichholzer M, Luthy J, Moser U, Fowler B. Folate and the risk of colorectal, breast and cervix cancer: the epidemiological evidence. *Swiss Med Wkly* 2001;131(3738):539–49. [PubMed: 11759174]
62. Kim YI. Does a high folate intake increase the risk of breast cancer? *Nutr Rev* 2006;64:468–475. [PubMed: 17063929]

63. Cho E SD, Hunter DJ, et al. Premenopausal intakes of vitamins A, C and E, folate and carotenoids, and risk of breast cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2003;12:713–720.
64. Willett WC. Selenium, vitamin E, fiber, and the incidence of human cancer: an epidemiologic perspective. *Adv Exp Med Biol* 1986;206:27–34. [PubMed: 3035899]
65. London SJ, Stein EA, Henderson IC, Stampfer MJ, Wood WC, Remine S, Dmochowski JR, Robert NJ, Willett WC. Carotenoids, retinol, and vitamin E and risk of proliferative benign breast disease and breast cancer. *Cancer Causes Control* 1992;3(6):503–512. [PubMed: 1420852]
66. Jarvinen R, Knekt P, Seppanen R, Reunanen A, Heliovaara M, Maatela J, Aromaa A. Antioxidant vitamins in the diet: relationships with other personal characteristics in Finland. *J Epidemiol Community Health* 1994;48(6):549–554. [PubMed: 7830008]
67. Touvier M, Kesse E, Volatier JL, Clavel-Chapelon F, Boutron-Ruault MC. Dietary and cancer-related behaviors of vitamin/mineral dietary supplement users in a large cohort of French women. *Eur J Nutr* 2006;45(4):205–214. [PubMed: 16382374]
68. Patterson RE, Neuhouser ML, White E, et al. Cancer-related behaviour of vitamin supplement users. *Cancer Epidemiol Biomarker Prev* 1998;7(1):79–81.

Table 1
Comparison of baseline characteristics between cases and controls by study phase (SBCS I, 1996-1998 and II, 2002-2004)

	Study phase I			Study phase II		
	Cases (n=1455)	Controls (n=1556)	<i>P</i> ¹	Cases (n=1999)	Controls (n=1918)	<i>P</i> ¹
Age at interview, yrs (mean ± SD)	47.9 ± 8.0	47.2 ± 8.8	0.03	50.8±8.3	51.6±8.4	0.003
	18.1	25.7		7.5	5.7	
≤40 (%)	48.3	40.0		47.5	46.5	
41-50	23.5	24.2		29.7	31.1	
51-60	10.1	10.1	<.0001	15.3	16.7	0.07
>60						
Education (%)						
None / elementary	12.2	13.8		5.9	11.5	
Junior high school	42.7	41.9		36.7	40.4	
Senior high school	31.5	33.6		41.3	36.6	
Professional/College +	13.6	10.6	0.04	16.1	11.5	<.0001
Age at menarche (mean ± SD)	14.5 ± 1.6	14.7 ± 1.7	0.0001	14.4±1.7	14.6±1.8	<.0001
Ever had a life birth (%)	94.9	96.1	0.12	94.7	96.3	0.04
Age at first live birth (mean ± SD)	26.8 ± 4.1	26.2 ± 3.8	<.0001	26.2±3.6	25.7±3.8	<.0001
Ever breastfed (%)	77.5	79.2	0.28	69.5	76.3	0.05
Menopausal women (%)	34.7	36.4	0.34	43.5	49.3	0.0003
Age at menopause (mean ± SD)	48.1 ± 4.5	47.4 ± 4.9	0.02	48.5±4.3	48.2±4.6	0.13
Body mass index, kg/m ² (%)						
Q1 (<21.00)	22.8	28.2		19.9	22.4	
Q2 (21.00-23.01)	24.7	24.1		24.0	25.7	
Q3 (23.02-25.16)	24.0	23.7		26.9	26.2	
Q4 (≥25.6)	28.5	24.0	0.002	29.2	25.7	0.04
Waist to hip ratio (%)						
Q1 (<0.772)	25.1	30.9		11.3	20.4	
Q2 (0.772-0.805)	23.3	23.5		20.8	25.8	
Q3 (0.806-0.842)	26.4	25.7		26.0	25.2	
Q4 ≥0.843)	25.2	19.9	0.0003	41.9	28.6	<.0001
Regularly exercised during past 10 yrs (%)	18.7	25.2	<.0001	29.3	34.2	0.001
Family history of breast cancer (%)	3.6	2.4	0.05	5.5	3.0	0.0002
Breast fibroadenoma (%)	9.5	5.0	<.0001	10.1	5.8	<.0001
Energy intake, kcal (mean±sd)	1840±455	1813±454	0.09	1705±410	1707±417	0.98
Veg/fruit intake, g/day (mean±sd)	490.1±274.8	489.7±283.9	0.84	556.2±274.7	560±279	0.75
Red meat consumption, g/day (mean±sd)	84.4±57.7	75.0±47.3	<.0001	76.6±47.1	70±47	0.006

Note: missing data (<0.2%) was excluded from calculation.

¹ Derived from t-test for continues variables and chi-square test for categorical variables

Table 2
Characteristics of controls in the case -control study according to any vitamin supplement use, SBCS and II

Selected characteristics	Study phase I		p [*]	Study phase II		p [*]
	Non-user (n=1330)	User (n=226)		Non-user (n=1442)	User (n=476)	
Age, yrs (mean ± SD)	46.8±8.7	49.6±8.7	<.0001	51.5±8.4	51.9±8.1	0.37
Education level (%)						
Elementary/below	14.7	8.9		14.0	4.0	
Junior high school	43.8	29.6		42.4	34.5	
Senior high school	32.2	42.5		34.1	44.1	
Professional/College +	9.3	19.0		9.5	17.4	
Age at menarche, yrs (mean ± SD)	14.7±1.7	14.4±1.7	<.0001	14.7±1.8	14.4±1.7	<.0001
Ever had a live birth (%)	96.6	92.8	0.008	96.6	95.2	0.0002
Age at first live birth, yrs (mean ± SD)	26.0±3.8	25.9±3.9	0.70	25.6±3.9	26.0±3.6	0.11
Ever breastfed (%)	79.5	77.2	0.45	75.5	78.4	0.58
Menopausal women (%)	34.7	48.2	<.0001	47.7	53.9	0.02
Age at menopause, yrs (mean ± SD)	47.5±4.7	47.3±5.5	0.77	48.2±4.5	48.2±4.6	0.86
Body mass index, kg/m ² (mean ± SD)	23.2±3.3	22.7±3.8	0.04	23.6±3.3	23.0±2.8	<.0001
Waist-to-hip ratio (mean ± SD)	0.801±0.06	0.794±0.06	0.08	0.818±0.05	0.809±0.06	0.005
Physically active in past 10 yrs (%)	23.8	33.6	0.002	32.2	40.3	0.001
Family history of breast cancer (%)	2.2	3.9	0.10	2.7	4.0	0.15
History of fibroadenoma (%)	4.2	9.7	0.0004	4.7	9.2	0.0003
Energy intake, kcal (mean±sd)	1813±449	1807±482	0.85	1717±384	1716.8±383.7	0.47
Vegetable/fruit intake, g/day (mean±sd)	487.5±282.0	494.7±294.0	0.73	548.5±268.4	592.1±273.6	0.002
Red meat intake, g/day (mean±sd)	59.8±4640.1	59.8±43.0	0.98	53.4±38.7	55.1±37.4	0.41

* Derived from t-test for continues variables and chi-square test for categorical variables

Table 3
Breast cancer in relation to Any-vitamin supplement intake, SBCS I and II

	Both phases					<i>P</i> _{trend}
	Cases (n=3454)	%	Controls (n=3474)	%	OR (95% CI) ¹	
<u>Any Vitamin</u>						
Never	2758	79.8	2772	79.8	1.0 (ref)	
Ever	696	20.2	702	20.2	0.9 (0.8-1.0)	
Longest duration (years)						
<1	247	7.2	245	7.2	0.9 (0.8-1.1)	
1-2	237	6.9	251	7.5	0.9 (0.7-1.0)	
≥3	212	6.1	202	6.0	1.0 (0.8-1.2)	0.33
Frequency per week						
≤Once daily	503	14.6	505	14.5	0.9 (0.8-1.0)	
>Once daily	193	5.6	194	5.6	1.0 (0.8-1.2)	0.40
<u>Multivitamin only</u>						
Never	3174	91.9	3248	93.4	1.0 (ref)	
Ever	280	8.1	228	6.6	1.1 (0.9-1.3)	
Longest duration (years)						
<1	100	2.9	90	2.6	1.0 (0.7-1.4)	
1-2	95	2.7	80	2.3	1.0 (0.8-1.4)	
≥3	85	2.5	57	1.7	1.3 (0.9-1.9)	0.12
Frequency per week						
≤Once daily	266	7.7	211	6.1	1.1 (0.9-1.3)	
>Once daily	14	0.4	17	0.5	0.8 (0.4-1.6)	0.33
<u>Any vitamin A supplement²</u>						
Never	3129	90.8	3188	92.1	1.0 (ref)	
Ever	319	9.2	275	7.9	1.0 (0.8-1.2)	
Longest duration (years)						
<1	114	3.3	106	3.1	1.0 (0.7-1.3)	
1-2	111	3.2	98	2.8	1.0 (0.7-1.3)	
≥3	94	2.7	70	2.0	1.2 (0.8-1.6)	0.45
Frequency per week						
≤Once daily	293	8.5	246	7.1	1.1 (0.9-1.3)	
>Once daily	26	0.7	29	0.8	0.9 (0.5-1.6)	0.82
<u>Any vitamin B supplement²</u>						
Never	3070	89.0	3124	90.2	1.0 (ref)	
Ever	378	11.0	339	9.8	1.0 (0.8-1.2)	
Longest duration (years)						
<1	188	5.5	172	5.0	1.0 (0.8-1.2)	
1-2	72	2.1	75	2.2	0.9 (0.6-1.3)	
≥3	118	3.4	91	2.6	1.1 (0.9-1.5)	0.65
Frequency per week						
≤Once daily	303	8.8	266	7.7	1.0 (0.8-1.2)	
>Once daily	75	2.2	72	2.1	1.0 (0.7-1.4)	0.91
<u>Any vitamin C supplement²</u>						
Never	2981	86.5	3017	87.1	1.0 (ref)	
Ever	467	13.5	446	12.9	0.9 (0.8-1.1)	
Longest duration (years)						
<1	162	4.7	159	4.6	0.9 (0.7-1.2)	
1-2	164	4.8	152	4.4	1.0 (0.8-1.2)	
≥3	140	4.0	134	3.9	0.9 (0.7-1.2)	0.70
Frequency per week						
≤Once daily	351	10.2	322	9.3	1.0 (0.8-1.2)	
	115	3.3	124	3.6	0.9 (0.7-1.2)	0.49

	Both phases					<i>P</i> _{trend}
	Cases (n=3454)	%	Controls (n=3474)	%	OR (95% CI) ¹	
Any vitamin E supplement ²						
>Once daily	2869	83.2	2882	83.2	1.0 (ref)	
Never	579	16.8	581	16.8	0.9 (0.8-1.0)	0.98
Longest duration (years)						
<1	203	5.9	209	6.0	0.9 (0.7-1.1)	
1-2	207	6.0	209	6.0	0.9 (0.7-1.1)	
≥3	168	4.9	158	4.6	0.9 (0.7-1.2)	0.33
Frequency per week						
≤Once daily	485	14.1	474	13.7	0.9 (0.8-1.1)	
>Once daily	93	2.7	103	3.0	0.9 (0.7-1.2)	0.33

Note: *P* derived from chi-square, and *P*_{trend} of the categorical variable

Note: Missing data (<0.3%) was not included in calculation

¹ Adjusted for age (continuous), education, age at menarche categories), age at 1st birth (categories), livebirth (Y/N), BMI (categories), menopausal status (pre- vs. post-), physical activity in the past 10 years (Y/N), history of fibroadenoma (Y/N), family history of breast cancer (Y/N), and study phase.

² Additional adjustment for total intake of the other vitamin supplements

Table 4
Breast cancer in relation to any specific vitamin supplement use and Dietary vitamin intake (both phases)

Pattern of use	Low-dietary vitamin intake (<median) ¹				High-dietary vitamin intake (≥median) ¹			
	Cases n (%)	Controls n (%)	OR (95% CI) ¹	P _{trend}	Cases n (%)	Controls n (%)	OR (95% CI) ¹	P _{trend}
Any vitamin A supplement²								
Never	1621 (92.4)	1609 (92.8)	1.0 (ref)		1508 (89.0)	1579 (91.3)	1.0 (ref)	
Ever	133(7.6)	124 (7.2)	0.9 (0.7-1.2)		186(11.0)	151 (8.7)	0.9 (0.7-1.2)	0.24
Longest duration (years)								
<1	54 (3.1)	55 (3.2)	0.8 (0.6-1.3)		60 (3.5)	51 (2.9)	1.1 (0.7-1.6)	
1-2	45 (2.6)	43 (2.5)	0.9 (0.6-1.4)		66 (3.9)	55 (3.2)	1.1 (0.8-1.6)	
≥3	34 (1.9)	25 (1.5)	1.2 (0.7-2.0)	0.96	62 (3.6)	45 (2.6)	1.2 (0.8-1.8)	0.35
Frequency per week								
≤Once daily	123 (7.1)	112 (6.5)	0.9 (0.7-1.3)		170 (10.0)	134 (7.9)	1.1 (0.9-1.4)	
>Once daily	10(0.5)	12 (0.7)	0.7 (0.3-1.7)	0.77	16(1.0)	17 (0.9)	1.0 (0.5-2.1)	0.48
Any vitamin B supplement²								
Never	1428 (90.4)	1556 (89.5)	1.0 (ref)		1642 (87.9)	1568 (90.9)	1.0 (ref)	
Ever	152 (9.6)	183 (10.5)	0.8 (0.6-1.0)		226 (12.1)	156 (9.1)	1.2 (1.0-1.6)	0.008
Longest duration (years)								
<1	81 (5.1)	95 (5.5)	0.8 (0.6-1.1)		107 (5.7)	77 (4.6)	1.2 (0.8-1.6)	
1-2	24 (1.7)	39 (2.3)	0.6 (0.3-1.0)		48 (2.6)	36 (2.1)	1.2 (0.8-1.9)	
≥3	47 (3.0)	48 (2.7)	0.9 (0.6-1.4)	0.11	71 (3.8)	43 (2.5)	1.4 (0.9-2.1)	0.04
Frequency per week								
≤Once daily	126 (8.0)	147 (8.4)	0.8 (0.6-1.0)		177 (9.5)	119(6.0)	1.2 (0.9-1.6)	
>Once daily	26 (1.6)	36 (2.1)	0.7(0.4-1.2)	0.05	49 (2.6)	36 (2.1)	1.3(0.8-2.0)	0.03
Any vitamin C supplement²								
Never	1560 (88.2)	1527 (88.3)	1.0 (ref)		1421 (84.6)	1490 (86.0)	1.0 (ref)	
Ever	208 (11.8)	203 (11.7)	0.9 (0.7-1.1)		259 (15.4)	243 (14.0)	1.0 (0.8-1.2)	0.47
Longest duration (years)								
<1	79 (4.5)	80 (4.6)	0.8 (0.6-1.2)		83 (5.0)	81 (4.6)	1.0 (0.7-1.4)	
1-2	73 (4.1)	70 (4.0)	0.9 (0.7-1.3)		91 (5.4)	83 (4.7)	1.0 (0.8-1.4)	
≥3	56 (3.2)	53 (3.1)	0.9 (0.6-1.4)	0.48	84 (5.0)	84 (4.7)	1.0 (0.7-1.4)	0.87
Frequency per week								
≤Once daily	157(8.9)	143 (8.2)	0.9 (0.7-1.2)		194 (11.6)	179 (11.0)	1.0 (0.8-1.2)	
>Once daily	51 (2.9)	60 (3.5)	0.8 (0.5-1.2)	0.66	64 (3.8)	63 (3.9)	1.1 (0.7-1.5)	0.58
Any vitamin E supplement²								
Never	1519 (86.1)	1464 (84.6)	1.0 (ref)		1350 (80.2)	1418 (81.9)	1.0 (ref)	
Ever	246 (13.9)	267 (15.4)	0.8 (0.6-0.9)		333 (19.8)	314(18.1)	1.0(0.9-1.3)	0.04
Longest duration (years)								
<1	94 (5.3)	95 (5.5)	0.8 (0.6-1.1)		109 (6.5)	114 (6.6)	1.0 (0.7-1.3)	
1-2	90 (5.1)	100 (5.8)	0.8 (0.6-1.0)		117(7.0)	109 (6.3)	1.1 (0.8-1.4)	
≥3	62 (3.5)	70 (4.1)	0.7 (0.5-1.0)	0.01	106 (6.3)	88 (5.2)	1.2 (0.9-1.6)	0.16
Frequency per week								
≤Once daily	204 (11.6)	216 (12.5)	0.8 (0.6-0.9)		281 (16.8)	258 (14.9)	1.1 (0.9-1.3)	
>Once daily	42 (2.3)	50 (2.9)	0.7(0.5-1.1)	0.57	51 (3.0)	53 (3.2)	1.0 (0.7-1.5)	0.43

Note: P derived from chi-square, P_{trend} of the categorical variable and P_{interaction} of the dietary vitamin intake levels

¹ Adjusted for age (continuous), education, age at menarche (categories), age at 1st birth (categories), livebirth (Y/N), BMI (categories), menopausal status (pre- vs. post-), physical activity in the past 10 years (Y/N), history of fibroadenoma (Y/N), family history of breast cancer (Y/N), and study phase.

² Additional adjustment for total intake of the other vitamin supplements

⁴Each vitamin supplement intake is stratified by the same dietary vitamin intake (median ranges: 597.7 for vitamin A, 16.5 for vitamins B, 78.6 for vitamin, and 12.9 for vitamin E