Dietary Carotenoids and Vitamins A, C, and E and Risk of Breast Cancer

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Background: **Data on intake of specific carotenoids and breast cancer risk are limited. Furthermore, studies of vitamins A, C, and E in relation to breast cancer risk are inconclusive. We have conducted a large, prospective study to evaluate long-term intakes of these nutrients and breast cancer risk.** ***Methods:*** **We examined, by use of multivariate analysis, associations between intakes of specific carotenoids, vitamins A, C, and E , consumption of fruits and vegetables, and breast cancer risk in a cohort of 83 234 women (aged 33–60 years in 1980) who were participating in the Nurses' Health Study. Through 1994, we identified 2697 incident cases of invasive breast cancer (784 premenopausal and 1913 postmenopausal).** ***Results:*** **Intakes of β-carotene from food and supplements, lutein/zeaxanthin, and vitamin A from foods were weakly inversely associated with breast cancer risk in premenopausal women. Strong inverse associations were found for increasing quintiles of α-carotene, β-carotene, lutein/zeaxanthin, total vitamin C from foods, and total vitamin A among premenopausal women with a positive family history of breast cancer. An inverse association was also found for increasing quintiles of β-carotene among premenopausal women who consumed 15 g or more of alcohol per day. Premenopausal women who consumed five or more servings per day of fruits and vegetables had modestly lower risk of breast cancer than those who had less than two servings per day (relative risk [RR] = 0.77; 95% confidence interval [CI] = 0.58–1.02); this association was stronger among premenopausal women who had a positive family history of breast cancer (RR = 0.29; 95% CI = 0.13–0.62) or those who consumed 15 g or more of alcohol per day (RR = 0.53; 95% CI = 0.27–1.04).** ***Conclusions:*** **Consumption of fruits and vegetables high in specific carotenoids and vitamins may reduce premenopausal breast cancer risk. [J Natl Cancer Inst 1999;91:547–56]**

Because of their antioxidant properties, dietary carotenoids and vitamins C and E can neutralize reactive oxygen species, may reduce oxidative DNA damage, genetic mutations *(1)*, and also may enhance host immunologic functions *(2)*. All of these reactions may help to protect against breast carcinogenesis. Preformed vitamin A (retinol and retinyl esters) is involved in cell differentiation *(3)*, and certain carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) found in fruits and vegetables can be metabolized to retinol *(4,5)*. Case–control studies of breast cancer support a weak protective effect of carotenoids rather than preformed vitamin A *(6)*, and in three of six cohort studies *(7–12)*, risk of breast cancer was lower with increasing intakes of total or preformed vitamin A and carotenoids with vitamin A activity *(7,8,12)*. A significant inverse association between vitamin C intake and breast cancer risk was found in a

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See "Notes" following "References."

meta-analysis of 12 case–control studies *(13)*. Prospective studies *(6–12)*, however, have not supported associations between vitamins C or E and breast cancer risk.

Food composition data have recently become available for specific carotenoids *(14,15)*. In a case–control study using the new U.S. Department of Agriculture–National Cancer Institute (USDA–NCI) carotenoid food composition database, an inverse association between risk of premenopausal breast cancer and intakes of β-carotene and lutein/zeaxanthin was observed *(16)*. Inverse associations were also observed between these nutrients measured in breast adipose tissue and breast cancer risk *(17)*.

In an earlier report from the Nurses' Health Study, we examined the relationships between baseline intakes of vitamins A, C, and E and breast cancer risk during 8 years of follow-up *(7)*, but at that time, a carotenoid food composition database was not available. We now examine intakes of specific carotenoids; vitamins A, C, and E; and fruit and vegetable consumption in relation to risk of breast cancer in this cohort during 14 years of follow-up using repeated measures of diet to better represent long-term intakes. As a secondary hypothesis, we also evaluated whether these relations vary by family history of breast cancer and alcohol intake.

METHODS

Study Cohort

In 1976, 121 700 female nurses aged 30–55 years living in 11 states of the United States completed a mailed questionnaire and provided medical history and health-related information. Every 2 years, a mailed questionnaire was sent to cohort members to update information on potential risk factors and to ascertain newly diagnosed cancers and other diseases. Through May 31, 1994, the follow-up rate was 95% complete as percentage of potential person-years. In 1980, a 61 food-item semiquantitative food-frequency questionnaire was included to assess dietary intake. The 1984 food-frequency questionnaire was expanded to 126 items. Similar questionnaires were used in 1986 and in 1990 to update the dietary intakes of the participating women.

For the analyses presented here, women were excluded at baseline if their responses to the 1980 dietary questionnaire had implausible total energy intake (<500 or >3500 kcal/day), if they left 10 or more food items blank, or if they had a previous diagnosis of cancer (other than nonmelanoma skin cancer). The final 1980 baseline population consisted of 83 234 women. Among the women included, response rates were 80% for the 1984 dietary questionnaire and 76% for the 1986 and 1990 dietary questionnaires. Approximately 61% of the women had all four dietary questionnaires, and 72% of the women had all three most recent dietary questionnaires. Women also were excluded if they reported uncertain menopausal status or had incomplete information on menopausal status.

Women were classified as postmenopausal from the time they returned a questionnaire on which they reported natural menopause or hysterectomy with bilateral oophorectomy. Women who reported hysterectomy without bilateral oophorectomy were classified as uncertain menopausal status until they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers), in which case they were classified as postmenopausal. Menopause status was updated every 2 years. There were 53 938 premenopausal women in 1980 and 59 426 postmenopausal women in 1994.

The 1976 questionnaire included a question on a history of breast cancer in the mother or sister. We updated information on family history (yes/no) in 1982, 1988, and 1992. The study was approved by the Human Research Committee at the Brigham and Women's Hospital. Data on alcohol consumption were obtained from food-frequency questionnaires.

The Semiquantitative Food-Frequency Questionnaire

The validity and reliability of the food-frequency questionnaires in the Nurses' Health Study have been described elsewhere *(18–20)*. For each food in the questionnaires, a commonly used unit or portion size (e.g., one tomato or one slice of bread) was specified, and women were asked how often, on average, over the previous year they had consumed that amount of each food. There were nine possible responses, ranging from "never" to "six or more times per day." Nutrient intake was computed by multiplying the frequency of response by the nutrient content of the specific portion sizes. We also asked questions on the use of specific vitamins and brand and type of multivitamins as well as dose and duration of use; vitamin supplement use was updated biennially. A comprehensive database on multivitamin preparations that provides the dose of vitamins A, C, and E in each preparation was developed at Harvard University.

Values for nutrients in foods were derived from the USDA sources *(21)* and supplemented with information from manufacturers. Food composition data for specific types of carotenoids were based on the USDA–NCI carotenoid database developed by Chug-Ahuja et al. *(14)* and Mangels et al. *(15)*. Values for lutein and zeaxanthin were reported as combined. The carotenoid content of tomato-based food products was updated with values from the USDA *(22)*.

Nutrient intakes calculated from the 1980 food-frequency questionnaire were reasonably correlated with those recorded by 173 Boston women who kept diet diaries for four 1-week periods more than 1 year *(18,19)*. Pearson correlation coefficients between estimates from the food-frequency questionnaire and from the four 1-week dietary records were .49 and .75 for total vitamins A and C from food and supplements and .36 and .66 for intakes from foods, respectively *(18)*. Vitamin E intake was positively correlated with its plasma concentrations in two studies [$r = .34$ *(23)*; $r = .52$ *(24)*]. The estimates of specific dietary carotenoids from the 1986 food-frequency questionnaire were correlated with their respective plasma concentrations; among nonsmoking women, the Pearson correlation coefficients were .48 for α-carotene, .27 for β-carotene and lutein/zeaxanthin, .32 for β-cryptoxanthin, and .21 for lycopene *(25)*.

Ascertainment of Breast Cancer Cases

Incident cases of invasive breast cancer were identified by self-report on each biennial questionnaire from the period 1982 through 1994. Deaths in the cohort were identified by reports from family members, the postal service, and a search of the National Death Index *(26)*; we estimate that 98% of all deaths were identified. Women who reported breast cancer (or their next of kin if the study participant had died) were asked for permission to obtain hospital records and pathology reports. Physicians without knowledge of dietary information of all study participants reviewed the records. During 14 years of follow-up, we documented 784 incident cases of invasive breast cancer among premenopausal women, 1913 cases among postmenopausal women, and 259 cases among women with uncertain menopausal status (excluded from this analysis). The mean age at diagnosis was 47 years for premenopausal case patients and 60 years for postmenopausal case patients. We included in the data analysis 145 breast cancer case patients for whom no medical records could be obtained because the accuracy of self-reporting was extremely high (>99%) among those for whom we were able to obtain medical records.

Statistical Analysis

Person-years of follow-up for each participant were calculated from the date of returning the 1980 questionnaire to the date of diagnosis of breast cancer, death, or June 1, 1994, whichever came first. For nutrient analyses, women were categorized by quintile of nutrient intakes with adjustment for total energy by the residual method *(27)*. For analysis of association between the consumption of fruits and vegetables and the risk of breast cancer, frequencies were summed over all fruits and vegetables. Cruciferous vegetables include broccoli, kale, cauliflower, cabbage or cole slaw, and Brussels sprouts. In addition, we classified women by their use of specific supplements of vitamins A, C or E and multivitamins and by dose and duration among current users.

For each category of nutrient intake, we calculated incidence rate by dividing the number of breast cancer cases by the number of person-years of follow-up. Relative risk was calculated by dividing the incidence rate in an exposure category by the corresponding rate in the reference category. Age-adjusted relative risks were calculated with the use of 5-year age categories by the Mantel–Haenszel method *(28)*. In multivariate analyses using pooled logistic regression models with 2-year time increments *(29,30)*, we simultaneously adjusted for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0,1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of breast cancer in mother or a sister (yes or no), history of benign breast disease (yes or no), alcohol intake (0, 0.1–4.9, 5–14.9, or ⩾15 g/day), body mass index at age 18 years (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to

<27, or ⩾27 kg/m^2), weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), and height in inches. For the analyses among postmenopausal women, the models also included indicator variables for age at menopause (<45, 45–49, 50–54, or ⩾55 years) and postmenopausal hormone use (never, past <5 years, past ⩾5 years, current <5 years, or current ⩾5 years).

To reduce within-person variation and represent long-term dietary intake of participants, we modeled the incidence of breast cancer in relation to the cumulative average of dietary intake from all available dietary questionnaires up to the start of each 2-year follow-up interval *(31)*. For example, the incidence of breast cancer from the period 1980 through 1984 was related to the dietary information from the 1980 questionnaire, and the incidence of breast cancer during the 1984 through 1986 time period was related to the average intake from the 1980 and 1984 questionnaires. In these models, nondietary covariates, e.g., age, parity, history of breast cancer in mother or a sister, history of benign breast disease, weight change from age 18 years, age at menopause, and postmenopausal hormone use, were updated biennially. For all relative risks, 95% confidence intervals (CIs) were calculated and all *P* values were two-tailed. Since the results of age-adjusted relative risks were virtually identical to those of multivariate adjusted analysis; only the multivariate adjusted relative risks were reported. The test for linear component of trend was conducted by use of the median value of the cumulative updated nutrient intake for each quintile analyzed as a continuous variable.

Analyses were stratified by menopausal status, family history of breast cancer, or alcohol intake (<15 or ⩾15 g/day; 15 g of alcohol roughly equals about one drink). Log likelihood ratio tests were used to compare models with or without interaction terms between nutrient intake and menopausal status or family history of breast cancer and alcohol intake.

RESULTS

Among premenopausal women, intakes of β-carotene from food and supplements, lutein/zeaxanthin, and total vitamin A from foods were weakly inversely associated with risk of breast cancer after adjustment for age, length of follow-up, total energy intake, parity, age at first birth, age at menarche, history of breast cancer in mother or a sister, history of benign breast disease, alcohol intake, body mass index at age 18 years, weight change from age 18 years, and height (Table 1). Women in the highest quintile of intakes of lutein/zeaxanthin and preformed vitamin A from food and supplements had statistically significant 21% and 22% reductions in risk of breast cancer as compared with those in the lowest quintile. Additionally, a weak positive association was seen with total vitamin E from food and supplements.

No associations were seen between overall risk of postmenopausal breast cancer and intakes of specific dietary carotenoids and total vitamins A, C, and E, except for a weak inverse association for total vitamin E from food and supplements (Table 1). Tests for interactions between nutrients and menopausal status and breast cancer risk were statistically significant only for intakes of preformed vitamin A from food and supplements and total vitamin E from food and supplements. Because postmenopausal women currently taking hormones have biologic similarities with premenopausal women *(32)*, we stratified our analyses by use of postmenopausal hormone therapy. Among current hormone users, the multivariate relative risks for women in the highest quintile as compared with those in the lowest quintile were 0.78 (95% CI = 0.60–1.01) for carotenoid vitamin A, 0.89 (95% CI = 0.69–1.15) for α-carotene, 0.77 (95% CI = 0.59–0.99) for β-carotene from food and supplements, 0.79 (95% CI = 0.61–1.03) for β-carotene from foods, 0.90 (95% CI = 0.69–1.18) for lutein/zeaxanthin, 0.77 (95% CI = 0.58–1.01) for β-cryptoxanthin, 0.95 (95% CI = 0.74–1.23) for lycopene, 0.83 (95% CI = 0.64–1.07) for preformed vitamin A from food and supplements, 1.13 (95% CI = 0.86–1.49) for preformed vitamin A from foods, 0.79 (95% CI = 0.61–1.03) for total vitamin A from food and supplements, and 0.94 (95% CI = 0.72–1.22) for total vitamin A from foods.

Etiologic mechanisms of carcinogenesis may vary according to family history of breast cancer *(33,34)*. Among women with a positive family history (n = 90 case patients) of breast cancer, α-carotene, β-carotene from food and supplements, β-carotene from foods, lutein/zeaxanthin, carotenoid vitamin A, total vitamin A from food and supplements, total vitamin A from foods, and vitamin C from foods were associated with 53%–63% lower risk of breast cancer when comparing women in the extreme quintiles of intakes of these nutrients (*P* for trend ⩽.01) (Table 2, A). Tests for interactions between nutrients and family history of breast cancer and breast cancer risk were statistically significant for intakes of β-carotene from food and supplements, β-carotene from foods, carotenoid vitamin A, total vitamin A from foods, and vitamin C from foods (*P*<.05).

The inverse associations of β-carotene from food and supplements, β-carotene from foods, carotenoid vitamin A, and total vitamin A from foods were also stronger (*P*<.05) among premenopausal women who consumed greater than or equal to 15 g/day of alcohol (n = 120 case patients), whereas no difference was observed with intake of preformed vitamin A (Table 2, B). These inverse associations remained after further adjustment for total folate intake but were attenuated after further controlling for total vitamin C from food and supplements. Tests for interactions between nutrients and alcohol consumption and breast cancer risk were not statistically significant. Among postmenopausal women who consumed greater than or equal to 15 g/day of alcohol, intake of preformed vitamin A from food and supplements was significantly related to lower risk of breast cancer; the relative risks for increasing quintiles were 1.00, 0.82, 0.91, 0.67, and 0.66 (95% CI for the highest quintile compared with the lowest quintile = 0.47–0.93).

Intakes of fruits or vegetables were associated with lower risk of premenopausal breast cancer (Table 3). When fruits and vegetables were grouped together, women who consumed greater than or equal to five servings/day had a 23% lower risk of premenopausal breast cancer (*P* for trend = .05) (Table 3). The association did not change when we further divided the highest category into six to 6.9 or greater than or equal to seven servings/day. No significant association was observed between consumption of fruits or vegetables and overall risk of postmenopausal breast cancer (Table 3). Fruit consumption was inversely associated with risk of postmenopausal breast cancer among women currently taking hormones; the relative risk was 0.57 (95% CI = 0.33–1.00) for women who consumed greater than or equal to five servings/day. The comparable relative risks were 0.87 (95% CI = 0.63–1.20) for vegetable consumption and 0.86 (95% CI = 0.54–1.39) for fruit and vegetable consumption. Intakes of cruciferous vegetables had only weak, nonsignificant inverse associations with breast cancer risk among premenopausal women. The associations with fruits and vegetables were stronger among premenopausal women who had a positive family history of breast cancer or consumed alcohol. The relative risks for intake of greater than or equal to five servings/day of fruits and vegetables were 0.29 (95% CI = 0.13–0.62; *P* for trend = .003) for premenopausal women who had a positive family history and 0.53 (95% CI = 0.27–1.04; *P*

Table 1. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for breast cancer* according to the quintile group for cumulative updated average intake of specific dietary carotenoids and vitamins A, C, and E by menopausal status†,‡ in a cohort of 83 234 women, for the period from 1980 through 1994

	Quintile (Q) of nutrient intake§						
Nutrient	1 (low) [referent]	2	3	4	5 (high)	95% CI‖ for Q5	*P* for trend¶
Carotenoid vitamin A, IU/day#	**1037**	**1633**	**2253**	**3087**	**4680**		
Premenopausal†	1.00	0.88	1.00	0.73	0.84	0.67–1.05	.06
Postmenopausal†,‡	1.00	1.01	1.02	1.01	0.95	0.82–1.10	.38
α-Carotene, μg/day	**220**	**373**	**507**	**818**	**1453**		
Premenopausal†	1.00	0.97	0.88	0.89	0.84	0.67–1.06	.14
Postmenopausal†,‡	1.00	0.98	1.11	0.97	0.98	0.85–1.13	.48
β-Carotene from food and supplements, μg/day	**1683**	**2685**	**3719**	**5082**	**7694**		
Premenopausal†	1.00	0.89	0.99	0.75	0.83	0.66–1.04	.04
Postmenopausal†,‡	1.00	0.97	1.01	1.00	0.94	0.81–1.09	.42
β-Carotene, food only, μg/day	**1677**	**2669**	**3687**	**5030**	**7609**		
Premenopausal†	1.00	0.90	1.00	0.78	0.84	0.67–1.05	.07
Postmenopausal†,‡	1.00	1.01	0.98	1.04	0.94	0.81–1.09	.42
Lutein/zeaxanthin, μg/day	**1376**	**2292**	**3186**	**5106**	**8796**		
Premenopausal†	1.00	0.92	0.86	0.82	0.79	0.63–0.99	.04
Postmenopausal†,‡	1.00	1.11	1.05	1.04	0.95	0.82–1.10	.12
β-Cryptoxanthin, μg/day	**20**	**45**	**69**	**102**	**175**		
Premenopausal†	1.00	1.03	0.97	1.05	0.89	0.70–1.13	.34
Postmenopausal†,‡	1.00	0.98	0.96	1.05	0.97	0.84–1.12	.91
Lycopene, μg/day	**1520**	**4090**	**6077**	**8405**	**12 688**		
Premenopausal†	1.00	0.99	0.94	1.04	1.10	0.87–1.38	.34
Postmenopausal†,‡	1.00	1.03	0.97	0.96	1.02	0.88–1.18	.97
Preformed vitamin A from food and supplements, IU/day	**1021**	**1968**	**3108**	**5307**	**9366**		
Premenopausal†	1.00	0.76	0.83	1.02	0.78	0.62–0.99	.44
Postmenopausal†,‡	1.00	0.96	1.03	0.91	0.95	0.83–1.10	.40
Preformed vitamin A, food only, IU/day	**800**	**1427**	**1954**	**2630**	**4391**		
Premenopausal†	1.00	0.89	0.84	0.89	0.88	0.70–1.10	.34
Postmenopausal†,‡	1.00	1.03	1.05	1.05	1.05	0.91–1.21	.63
Total vitamin A from food and supplements, IU/day	**5873**	**8842**	**11 525**	**14 823**	**21 379**		
Premenopausal†	1.00	0.92	0.88	0.72	0.87	0.70–1.09	.07
Postmenopausal†,‡	1.00	1.08	0.97	0.98	1.03	0.89–1.20	.98
Total vitamin A, food only, IU/day	**5293**	**7590**	**9680**	**12 260**	**17 073**		
Premenopausal†	1.00	0.93	0.94	0.72	0.82	0.65–1.04	.02
Postmenopausal†,‡	1.00	1.01	1.00	1.05	1.03	0.89–1.19	.59
Total vitamin C from food and supplements, mg/day	**83**	**130**	**177**	**277**	**710**		
Premenopausal†	1.00	0.91	0.96	0.97	1.01	0.81–1.26	.59
Postmenopausal†,‡	1.00	0.98	0.91	0.97	0.99	0.85–1.14	.77
Total vitamin C, food only, mg/day	**70**	**103**	**128**	**156**	**205**		
Premenopausal†	1.00	0.99	0.78	0.91	1.01	0.81–1.26	.82
Postmenopausal†,‡	1.00	1.03	1.05	1.01	1.06	0.91–1.22	.57
Total vitamin E from food and supplements, IU/day	**5**	**7**	**11**	**22**	**251**		
Premenopausal†	1.00	0.89	0.96	1.01	1.22	0.98–1.52	.007
Postmenopausal†,‡	1.00	0.81	0.85	0.82	0.84	0.72–0.96	.50
Total vitamin E, food only, IU/day	**5**	**6**	**7**	**8**	**10**		
Premenopausal†	1.00	0.77	0.89	0.95	0.81	0.64–1.02	.29
Postmenopausal†,‡	1.00	0.99	0.85	0.90	0.96	0.83–1.11	.55

*A total of 784 incident cases of invasive breast cancer were diagnosed in premenopausal women, and 1913 cases were diagnosed in postmenopausal women.

†The model included indicator variables for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0, 1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of breast cancer in mother or a sister (yes or no), history of benign breast disease (yes or no), alcohol intake (0, 0.1–4.9, 5–14.9, or ⩾15 g/day), body mass index (weight in kg/height in m^2) (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to <27, or ⩾27) at age 18 years, weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), and height in inches.

‡The model also included indicator variables for age at menopause (<45, 45–49, 50–54, or ⩾55 years) and for postmenopausal hormone use (never, past <5 years, past ⩾5 years, current <5 years, or current ⩾5 years).

§Values for intake are medians for each quintile, computed as the cumulative updated average (*see* "Methods" section).

‖95% CI for Q5 = 95% CIs for RRs for quintile 5 (Q5).

¶*P* values are two-sided (Wald's test).

#One international unit of vitamin A activity is defined as equal to 0.60 μg of β-carotene.

for trend = .007) for women consuming greater than or equal to 15 g/day of alcohol. When we examined individual foods that were the major or primary contributors to carotenoid intake, nonsignificant inverse trends were seen for most; no single food accounted for the overall associations.

The use of specific vitamin supplements and multivitamins was not significantly associated with overall risk of breast cancer (Table 4) or among premenopausal or postmenopausal women separately, even when taken in high doses or for long periods.

Discussion

To our knowledge, this is the first prospective cohort study to examine the risk of breast cancer among premenopausal and postmenopausal women by dietary intakes of specific carotenoids and vitamins A, C, and E. In this cohort, intakes of lutein/zeaxanthin, β-carotene from food and supplements, total vitamin A from foods, and consumption of fruits and vegetables were inversely associated with risk of premenopausal breast cancer. These inverse associations were strongest among women at elevated risk due to a positive family history of breast cancer or consumption of greater than or equal to 15 g/day of alcohol. Intakes of these nutrients had no appreciable overall associations with risk of postmenopausal breast

Table 2, A. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for premenopausal breast cancer* according to family history of breast cancer† for cumulative updated average intake of specific dietary carotenoids and vitamins A, C, and E among 53 938 women who were premenopausal at baseline, for the period from 1980 through 1994

Nutrient	Quintile (Q) of nutrient intake‡					95% CI§ for Q5	*P* for trend‖
	1 (low) [referent]	2	3	4	5 (high)		
Carotenoid vitamin A, IU/day							
Family history, yes†	1.00	0.69	0.57	0.27	0.38	0.19–0.77	.001
Family history, no†	1.00	0.90	1.09	0.80	0.93	0.73–1.19	.41
α-Carotene, μg/day							
Family history, yes†	1.00	1.05	0.67	0.48	0.47	0.23–0.98	.01
Family history, no†	1.00	0.96	0.90	0.96	0.89	0.70–1.14	.46
β-Carotene from food and supplements, μg/day							
Family history, yes†	1.00	0.67	0.58	0.23	0.42	0.21–0.83	.002
Family history, no†	1.00	0.91	1.07	0.83	0.91	0.71–1.16	.33
β-Carotene, food only, μg/day							
Family history, yes†	1.00	0.71	0.57	0.23	0.38	0.19–0.77	<.001
Family history, no†	1.00	0.91	1.08	0.87	0.93	0.73–1.18	.48
Lutein/zeaxanthin, μg/day							
Family history, yes†	1.00	0.89	0.56	0.47	0.38	0.18–0.81	.004
Family history, no†	1.00	0.93	0.92	0.89	0.88	0.69–1.12	.32
β-Cryptoxanthin, μg/day							
Family history, yes†	1.00	0.64	0.88	0.45	0.57	0.28–1.15	.09
Family history, no†	1.00	1.09	0.99	1.15	0.94	0.73–1.22	.71
Lycopene, μg/day							
Family history, yes†	1.00	1.83	0.76	1.21	1.42	0.70–2.88	.75
Family history, no†	1.00	0.91	0.96	1.03	1.05	0.82–1.34	.43
Preformed vitamin A from food and supplements, IU/day							
Family history, yes†	1.00	0.75	0.70	1.02	0.59	0.29–1.21	.38
Family history, no†	1.00	0.76	0.86	1.04	0.82	0.64–1.04	.67
Preformed vitamin A, food only, IU/day							
Family history, yes†	1.00	0.75	0.76	0.67	0.62	0.31–1.23	.19
Family history, no†	1.00	0.91	0.85	0.93	0.92	0.72–1.17	.63
Total vitamin A from food and supplements, IU/day							
Family history, yes†	1.00	0.50	0.66	0.38	0.41	0.20–0.84	.01
Family history, no†	1.00	1.00	0.92	0.77	0.96	0.76–1.22	.34
Total vitamin A, food only, IU/day							
Family history, yes†	1.00	0.65	0.47	0.23	0.38	0.19–0.77	<.001
Family history, no†	1.00	0.99	1.02	0.81	0.92	0.72–1.17	.23
Total vitamin C from food and supplements, mg/day							
Family history, yes†	1.00	0.95	0.77	0.55	0.97	0.52–1.79	.91
Family history, no†	1.00	0.88	0.97	1.03	1.02	0.80–1.28	.53
Total vitamin C, food only, mg/day							
Family history, yes†	1.00	0.78	0.78	0.42	0.37	0.17–0.80	.002
Family history, no†	1.00	1.03	0.76	1.00	1.12	0.89–1.41	.43
Total vitamin E from food and supplements, IU/day							
Family history, yes†	1.00	1.34	1.64	1.27	1.41	0.69–2.89	.77
Family history, no†	1.00	0.84	0.89	0.98	1.21	0.96–1.53	.004
Total vitamin E, food only, IU/day							
Family history, yes†	1.00	0.62	0.81	0.91	0.57	0.28–1.15	.27
Family history, no†	1.00	0.79	0.90	0.95	0.84	0.66–1.07	.43

Table 2, B. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for premenopausal breast cancer¶ according to alcohol intake# for cumulative updated average intake of specific dietary carotenoids and vitamin A among 53 938 women who were premenopausal at baseline, for the period from 1980 through 1994

Nutrient	Quintile (Q) of nutrient intake‡					95% CI§ for Q5	*P* for trend‖
	1 (low) [referent]	2	3	4	5 (high)		
Carotenoid vitamin A, IU/day							
Alcohol, <15 g/day†	1.00	0.94	1.08	0.81	0.90	0.70–1.15	.23
Alcohol, ⩾15 g/day†	1.00	0.64	0.63	0.43	0.59	0.33–1.04	.04
α-Carotene, μg/day							
Alcohol, <15 g/day†	1.00	1.02	0.95	0.97	0.87	0.67–1.12	.23
Alcohol, ⩾15 g/day†	1.00	0.84	0.56	0.58	0.71	0.41–1.25	.23
β-Carotene from food and supplements, μg/day							
Alcohol, <15 g/day†	1.00	0.97	1.09	0.83	0.90	0.70–1.15	.20
Alcohol, ⩾15 g/day†	1.00	0.60	0.55	0.47	0.55	0.31–0.97	.04
β-Carotene, food only, μg/day							
Alcohol, <15 g/day†	1.00	0.97	1.09	0.87	0.91	0.71–1.17	.28
Alcohol, ⩾15 g/day†	1.00	0.60	0.55	0.47	0.55	0.32–0.97	.03
Lutein/zeaxanthin, μg/day							
Alcohol, <15 g/day†	1.00	0.98	0.92	0.92	0.82	0.64–1.06	.11
Alcohol, ⩾15 g/day†	1.00	0.72	0.78	0.44	0.73	0.43–1.24	.29
β-Cryptoxanthin, μg/day							
Alcohol, <15 g/day†	1.00	1.08	1.07	1.11	0.95	0.73–1.24	.67
Alcohol, ⩾15 g/day†	1.00	0.79	0.59	0.83	0.62	0.32–1.22	.19
Lycopene, μg/day							
Alcohol, <15 g/day†	1.00	0.95	1.02	1.16	1.17	0.91–1.51	.07
Alcohol, ⩾15 g/day†	1.00	1.12	0.51	0.56	0.72	0.41–1.28	.07
Preformed vitamin A from food and supplements, IU/day							
Alcohol, <15 g/day†	1.00	0.67	0.80	0.98	0.78	0.61–1.00	.62
Alcohol, ⩾15 g/day†	1.00	1.31	1.01	1.30	0.78	0.41–1.48	.45
Preformed vitamin A, food only, IU/day							
Alcohol, >15 g/day†	1.00	0.87	0.80	0.84	0.88	0.69–1.13	.41
Alcohol, ⩾15 g/day†	1.00	0.91	1.14	1.39	0.73	0.38–1.43	.71
Total vitamin A from food and supplements, IU/day							
Alcohol, <15 g/day†	1.00	0.96	0.97	0.77	0.92	0.72–1.18	.23
Alcohol, ⩾15 g/day†	1.00	0.75	0.54	0.49	0.68	0.39–1.20	.08
Total vitamin A, food only, IU/day							
Alcohol, <15 g/day†	1.00	0.97	1.03	0.82	0.87	0.68–1.12	.14
Alcohol, ⩾15 g/day†	1.00	0.70	0.60	0.34	0.61	0.35–1.08	.02

*A total of 90 incident cases of invasive breast cancer were diagnosed among women with a positive family history of breast cancer, and 689 cases were diagnosed among women without such a history. Information on some covariates was not available for five case patients and, therefore, these five patients were excluded from this analysis.

†The model included indicator variables for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0, 1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of benign breast disease (yes or no), alcohol intake (0, 0.1–4.9, 5–14.9, or ⩾15 g/day), body mass index (weight in kg/height in m^2) (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to <27, or ⩾27) at age 18 years, weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), and height in inches.

‡Median values for quintiles of all nutrient variables are given in Table 1.

§95% CI for Q5 = 95% CIs for RRs for quintile 5 (Q5).

‖*P* values are two-sided (Wald's test).

¶A total of 120 incident cases of invasive breast cancer were diagnosed among women who consumed greater than or equal to 15 g/day of alcohol, and 657 cases were diagnosed among women who consumed less than 15 g/day of alcohol. Information on certain covariates was not available for seven patients and, therefore, these seven patients were excluded from the analysis.

#The model included indicator variables for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0, 1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of breast cancer in mother or a sister (yes or no), history of benign breast disease (yes or no), body mass index (weight in kg/height in m^2) (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to <27, or ⩾27) at age 18 years, weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), and height in inches.

cancer, but they had inverse relationships among postmenopausal women currently taking hormones. In addition, the use of supplements of vitamins A, C, and E and multivitamins was not associated with overall risk of breast cancer.

The results of this 14-year follow-up study largely corroborate and extend the findings from a previous analysis in this cohort with 8 years of follow-up *(7)*. At that time, no associations were seen between vitamin C or E intake and breast cancer risk. However, there were modest inverse associations between preformed vitamin A and carotenoid vitamin A intakes and breast cancer risk, which were stronger among premenopausal women *(7)*. Our updated analyses, which used food composition data for specific carotenoids, suggest that apparent beneficial effects of carotenoid intakes might be attributable to α-carotene, β-carotene, or lutein/zeaxanthin, but not to β-cryptoxanthin and lycopene. This is consistent with

Table 3. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for breast cancer* according to the categories for cumulative updated average intake of fruits and vegetables by menopausal status†,‡ in a cohort of 83 234 women, for the period from 1980 through 1994

	Servings/day					
	<2 (referent)	2.0–2.9	3.0–3.9	4.0–4.9	⩾5.0	*P* for trend§
Fruits						
Premenopausal†	1.00	0.94 (0.79–1.11)	0.99 (0.79–1.26)	0.70 (0.45–1.08)	0.74 (0.45–1.24)	.13
Postmenopausal†,‡	1.00	0.97 (0.87–1.08)	0.94 (0.82–1.08)	0.89 (0.72–1.09)	0.84 (0.64–1.09)	.10
Vegetables						
Premenopausal†	1.00	0.83 (0.69–0.99)	0.95 (0.77–1.18)	0.92 (0.68–1.24)	0.64 (0.43–0.95)	.10
Postmenopausal†,‡	1.00	1.08 (0.95–1.22)	1.01 (0.88–1.17)	1.13 (0.95–1.33)	1.02 (0.85–1.24)	.61
Fruits and vegetables						
Premenopausal†	1.00	0.89 (0.67–1.18)	0.90 (0.68–1.19)	0.83 (0.62–1.11)	0.77 (0.58–1.02)	.05
Postmenopausal†,‡	1.00	0.98 (0.75–1.27)	1.05 (0.82–1.35)	1.05 (0.82–1.35)	1.03 (0.81–1.31)	.73
	Servings/day					
	<0.25 (referent)	0.25–0.49	0.50–0.74	0.75–0.90	⩾1.00	*P* for trend§
Cruciferous vegetables						
Premenopausal†	1.00	0.79 (0.67–0.92)	0.90 (0.71–1.14)	0.92 (0.69–1.24)	0.83 (0.52–1.32)	.19
Postmenopausal†,‡	1.00	0.96 (0.86–1.07)	1.06 (0.93–1.22)	0.98 (0.82–1.18)	0.98 (0.77–1.25)	.83

*A total of 784 incident cases of invasive breast cancer were diagnosed in premenopausal women, and 1913 cases were diagnosed in postmenopausal women.

†The model included indicator variables for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0, 1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of breast cancer in mother or a sister (yes or no), history of benign breast disease (yes or no), alcohol intake (0, 0.1–4.9, 5–14.9, or ⩾15 g/day), body mass index (weight in kg/height in m^2) (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to <27, or ⩾27) at age 18 years, weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), and height in inches.

‡The model also included indicator variables for age at menopause (<45, 45–49, 50–54, or ⩾55 years) and for postmenopausal hormone use (never, past <5 years, past ⩾5 years, current <5 years, or current ⩾5 years).

§*P* values are two-sided (Wald's test).

a population-based case–control study among premenopausal women *(16).* In our study, total vitamin E from food and supplements was related to a weak increased risk of premenopausal breast cancer; however, no dose or duration relation was seen. We speculated that it might be due to use of vitamin E supplements for the treatment of more severe benign breast disease. Notably, it was seen only among premenopausal women (who have more symptoms of benign breast disease). Consistent with the findings from three other prospective cohorts of postmenopausal women *(9–11),* there were no significant overall relationships between dietary intakes of vitamins A, C, and E and fruit and vegetable consumption and breast cancer risk among postmenopausal women.

Few studies have addressed the hypothesis that family history of breast cancer might modify the associations of diet and breast cancer. In a case–control study, the risk of breast cancer was inversely related to higher intake of α-tocopherol from foods among premenopausal women who had a positive family history *(33).* We observed that inverse associations for dietary intakes of specific carotenoids, vitamins A and C, and possibly for total vitamin E from foods were strongest among premenopausal women with a positive family history of breast cancer, supporting the hypothesis that the cause of breast cancer differs among women according to their family history of breast cancer *(34).*

In vitro studies have shown that retinoic acid strongly inhibits proliferation of estrogen receptor (ER)-positive human breast cancer cells through retinoic acid receptors (RARs), but does not inhibit the growth of ER-negative cells *(35).* However, estrogens were found to increase expression of RARα gene in ER-positive breast cancer cells *(35),* which suggests that the anticarcinogenic effects of retinoic acid might require estrogens to induce its nuclear receptor (RAR). Consistent with the findings from *in vitro* studies, we observed the inverse associations between vitamin A and provitamin A carotenoids and breast cancer risk only among premenopausal women and among postmenopausal women currently taking hormones. A previous study *(25)* reported that hormones may affect metabolism of the carotenoids. Premenopausal women and postmenopausal women taking estrogens had higher plasma levels of carotenoids than did postmenopausal women not taking estrogens, even controlling for intake *(25).* This may also partly explain our findings that inverse associations between carotenoids and breast cancer risk were present among premenopausal women and among postmenopausal women currently taking hormones.

Consumption of alcohol increases risk of breast cancer, even among young premenopausal women *(36,37).* Metabolic studies *(38,39)* among baboons and among premenopausal women suggest that alcohol may interfere with conversion of β-carotene to vitamin A. This may explain why the inverse associations of dietary β-carotene and total vitamin A and risk of breast cancer were stronger among women who consumed greater than or equal to 15 g/day of alcohol compared with those who consumed less. Forman et al. *(39)* also reported a decreased plasma concentration of lutein/zeaxanthin but a slightly increased concentration of anhydrolutein, an oxidative byproduct of lutein/zeaxanthin, after 30 g/day of alcohol for 3 months. Lutein/zeaxanthin may function as an antioxidant to neutralize the oxidative stress induced by alcohol

Table 4. Multivariate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for breast cancer* according to duration and dose of vitamin supplements in a cohort of 77 925 women, for the period from 1980 through 1994

			Current user			
	Never user	Past user	<2 y	2–4 y	5–9 y	⩾10 y
			Duration, y			
Vitamin A						
No. of cases	2107	146	44	16	19	15
RR (95% CI)†	1.00 (referent)	1.10 (0.93–1.31)	1.17 (0.86–1.58)	1.04 (0.63–1.70)	0.95 (0.60–1.49)	0.97 (0.59–1.62)
Vitamin C						
No. of cases	1420	341	167	93	157	169
RR (95% CI)†	1.00 (referent)	1.05 (0.93–1.19)	0.99 (0.84–1.16)	1.02 (0.82–1.26)	1.01 (0.85–1.19)	0.98 (0.83–1.15)
Vitamin E						
No. of cases	1696	246	101	63	127	114
RR (95% CI)†	1.00 (referent)	0.96 (0.84–1.10)	1.19 (0.97–1.45)	1.07 (0.83–1.38)	1.14 (0.95–1.36)	1.11 (0.92–1.35)
Multivitamin						
No. of cases	1058	455	145	134	232	323
RR (95% CI)†	1.00 (referent)	0.97 (0.86–1.09)	0.89 (0.75–1.06)	1.01 (0.84–1.21)	0.88 (0.76–1.02)	0.96 (0.85–1.09)
			Dose			
Vitamin A, IU/day	Never user	<8000	8000–12 000	13 000–22 000	⩾23 000	
No. of cases	2107	22	31	5	5	
RR (95% CI)†	1.00 (referent)	0.93 (0.61–1.42)	1.21 (0.84–1.72)	1.11 (0.46–2.67)	0.49 (0.20–1.18)	
Vitamin C, mg/day	Never user	<400	400–700	750–1250	⩾1300	
No. of cases	1420	55	182	125	42	
RR (95% CI)†	1.00 (referent)	0.96 (0.73–1.25)	1.08 (0.93–1.27)	1.02 (0.85–1.23)	1.04 (0.77–1.42)	
Vitamin E, IU/day	Never user	<100	100–250	300–500	⩾600	
No. of cases	1696	22	64	244	55	
RR (95% CI)†	1.00 (referent)	0.98 (0.64–1.49)	1.07 (0.83–1.37)	1.19 (1.04–1.37)	0.92 (0.70–1.21)	

*A total of 2523 incident cases of invasive breast cancer were included in this analysis. Information on only 77 925 women was available regarding use of vitamin supplements. The number reported for each vitamin category is varied because of missing information on dose of vitamin supplements.

†The model included indicator variables for age (5-year categories), length of follow-up, total energy intake (quintiles), parity (0, 1 or 2, 3 or 4, or ⩾5), age at first birth (⩽24, 25–29, or ⩾30 years), age at menarche (⩽12, 13, or ⩾14 years), history of breast cancer in mother or a sister (yes or no), history of benign breast disease (yes or no), alcohol intake (0, 0.1–4.9, 5–14.9, or ⩾15 g/day), body mass index (weight in kg/height in m^2) (<20, ⩾20 to <22, ⩾22 to <24, ⩾24 to <27, or ⩾27) at age 18 years, weight change from age 18 years (loss >2, loss or gain of 2, gain >2 to ⩽5, gain >5 to ⩽10, gain >10 to ⩽20, gain >20 to ⩽25, or gain >25 kg), height in inches, menopausal status (premenopausal, postmenopausal), age at menopause (premenopausal, <45, 45–49, 50–54, or ⩾55 years), and postmenopausal hormone use (premenopausal, never, past <5 years, past ⩾5 years, current <5 years, or current ⩾5 years).

(40); women who consume alcohol may thus have a higher requirement. These authors observed no change in preformed vitamin A levels with 30 g/day of alcohol drinking for 3 months *(39).* Consistent with these findings, we observed a strong inverse association between dietary intake of lutein/zeaxanthin and breast cancer risk among premenopausal women who consumed greater than or equal to 15 g/day of alcohol and saw no difference in association between preformed vitamin A and breast cancer risk according to alcohol consumption. The inverse associations between dietary carotenoids and breast cancer risk among premenopausal women who consumed greater than or equal to 15 g/day of alcohol were also independent of total folate intake but they were attenuated after additional controlling for total vitamin C from food and supplements.

In this prospective cohort, biased reporting is unlikely to explain these findings. High follow-up rates minimize the concern that results were due to differential loss to follow-up. The estimates of vitamin intakes derived from the food-frequency questionnaires are reasonably valid and reflect long-term intakes of study participants *(18,19).* Nonetheless, some misclassification of individual long-term intake exists but is likely to be random and underestimates true associations. Our use of repeated measures of dietary intake partially accounts for within-person variation due to changes in dietary habits during the follow-up period. After controlling for recognized risk factors for breast cancer, the results were virtually identical to the age-adjusted relative risks, suggesting that residual confounding by nondietary factors is unlikely to explain the observed findings. We cannot exclude unknown nondietary lifestyle factors partially explaining the findings, but the unknown risk factors would need to be strong predictors of breast cancer and also closely associated with intakes of these micronutrients.

The values for individual carotenoids in the USDA–NCI database are the best available; however, the database has limitations due to limited analytic data on carotenoid content of specific foods with implications for the reliability of the carotenoid data *(15).* Also, the carotenoid content of foods is influenced by factors, such as geographic location, season, varieties, growth and harvesting conditions, and food preparation methods *(15).* In the food-frequency questionnaires, certain foods with similar nutrient contents are grouped together; for example, in the 1980 food-frequency questionnaire, tomatoes were grouped with tomato juices, while use of tomato sauces was not asked until 1984. These factors result in measurement error, which is likely to be nondifferential and could attenuate associations for some carotenoids.

The results from this study and three of four cohort studies that examined vitamin A supplements *(7–9,12)* suggest a possible weak inverse association with breast cancer risk at high doses *(7–9);* however,

the number of cases in the greater than or equal to 23 000-IU/day category was limited. The findings from this study including others did not support a reduction in risk with supplemental vitamin C *(7,8,10,12,16)* and vitamin E *(7–9,12,16).* Besides vitamins and carotenoids, fruits and vegetables contain many other phytochemicals, including indoles, dithiolthiones, isothiocyanates, selenium, flavonoids, and protease inhibitors *(41).* Many of these substances are protective against cancer in animals or *in vitro* models *(41,42).* Therefore, the possibility remains that other constituents in fruits and vegetables account for the inverse associations in this study.

Consumption of fruits and vegetables high in specific carotenoids may reduce breast cancer risk among premenopausal women, particularly among those who are at elevated risk because of a positive family history of breast cancer or consumption of alcohol. Whether these apparent protective effects are due to these specific compounds or to other constituents of fruits and vegetables remains unclear.

REFERENCES

(1) Frei B. Reactive oxygen species and antioxidant vitamins: mechanisms of action. Am J Med 1994;97(3A):5S–13S.

(2) Kelley DS, Bendich A. Essential nutrients and immunologic functions. Am J Clin Nutr 1996; 63:994S–996S.

(3) Blomhoff R. Introduction: overview of vitamin A metabolism and function. In: Blomhoff R, editor. Vitamin A in health and disease. New York (NY): Marcel Dekker; 1994. p. 1–35.

(4) Blomhoff R. Transport and metabolism of vitamin A. Nutr Rev 1994;52(2 Pt 2):S13–23.

(5) Wang XD, Krinsky NI, Benotti PN, Russell RM. Biosynthesis of 9-*cis*-retinoic acid from 9-*cis*-β-carotene in human intestinal mucosa *in vitro.* Arch Biochem Biophys 1994;313:150–5.

(6) Garland M, Willett WC, Manson JE, Hunter DJ. Antioxidant micronutrients and breast cancer. J Am Coll Nutr 1993;12:400–11.

(7) Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Rosner B, Hennekens CH, 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;329:234–40.

(8) 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 Causes Control 1993;4:29–37.

(9) 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; 144:165–74.

(10) Verhoeven DT, Assen N, Goldbohm RA, Dorant E, van't Veet P, Sturmans F, 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: 149–55.

(11) Graham S, Zielezny M, Marshall J, Priore R, Freudenheim J, Brasure J, et al. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. Am J Epidemiol 1992;136:1327–37.

(12) Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992;66:673–9.

(13) Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case–control studies. J Natl Cancer Inst 1990;82:561–9.

(14) Chug-Ahuja JK, Holden JM, Forman MR, Mangels AR, Beecher GR, Lanza E. The development and application of a carotenoid database for fruits, vegetables, and selected multicomponent foods. J Am Diet Assoc 1993;93: 318–23.

(15) Mangels AR, Holden JM, Beecher GR, Forman MR, Lanza E. Carotenoid content of fruits and vegetables: an evaluation of analytic data [published erratum appears in J Am Diet Assoc 1993;93:527]. J Am Diet Assoc 1993;93: 284–96.

(16) 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;88:340–8.

(17) Zhang S, Tang G, Russell RM, Mayzel KA, Stampfer MJ, Willett WC, et al. Measurement of retinoids and carotenoids in breast adipose tissue and a comparison of concentrations in breast cancer cases and control subjects. Am J Clin Nutr 1997;66:626–32.

(18) Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food-frequency questionnaire. Am J Epidemiol 1985;122: 51–65.

(19) Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988; 127:188–99.

(20) Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.

(21) U. S. Department of Agriculture. Composition of foods—raw, processed, and prepared, 1963–1991 Agricultural Handbook No. 8 Series. Washington (DC): Department of Agriculture, Govt Print Off; 1992.

(22) Tonucci LH, Holden JM, Beecher GR, Khachik F, Davis CS, Mulokozi G. Carotenoid content of thermally processed tomato-based food products. J Agric Food Chem 1995;43: 579–86.

(23) Willett WC, Stampfer MJ, Underwood BA, Speizer FE, Rosner B, Hennekens CH. Validation of a dietary questionnaire with plasma carotenoid and alpha-tocopherol levels. Am J Clin Nutr 1983;38:631–9.

(24) Stryker WS, Kaplan LA, Stein EA, Stampfer MJ, Sober A, Willett WC. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. Am J Epidemiol 1988;127: 283–96.

(25) Michaud DS, Giovannucci EL, Ascherio A, Rimm EB, Forman MR, Sampson L, et al. Associations of plasma carotenoid concentrations and dietary intake of specific carotenoids in samples of two prospective cohort studies using a new carotenoid database. Cancer Epidemiol Biomarkers Prev 1998;7: 283–90.

(26) Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. Am J Epidemiol 1984; 119:837–9.

(27) Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.

(28) Rothman KJ. Modern epidemiology. Boston (MA): Little, Brown; 1986.

(29) Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. Stat Med 1988;7: 205–22.

(30) D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9: 1501–15.

(31) Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.

(32) Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407–11.

(33) Ambrosone CB, Marshall JR, Vena JE, Laughlin R, Graham S, Nemoto T, et al. Interaction of family history of breast cancer and dietary antioxidants with breast cancer risk (New York, United States). Cancer Causes Control 1995;6:407–15.

(34) Colditz GA, Rosner BA, Speizer FE. For the Nurses' Health Study Research Group. Risk factors for breast cancer according to family history of breast cancer. J Natl Cancer Inst 1996;88:365–71.

(35) van der Leede BJ, Folkers GE, van den Brink CE, van der Saag PT, van der Burg B. Retinoic acid receptor α1 isoform is induced by estradiol and confers retinoic acid sensitivity in human breast cancer cells. Mol Cell Endocrinol 1995;109:77–86.

(36) Schatzkin A, Longnecker MP. Alcohol and breast cancer. Where are we now and where do we go from here? Cancer 1994;74(3 Suppl): 1101–10.

(37) Swanson CA, Coates RJ, Malone KE, Gammon MD, Schoenberg JB, Brogan DJ, et al. Alcohol consumption and breast cancer risk among women under age 45 years. Epidemiology 1997;8:231–7.

(38) Leo MA, Kim C, Lowe N, Lieber CS. Interaction of ethanol with β-carotene: delayed blood clearance and enhanced hepatotoxicity. Hepatology 1992;15:883–91.

(39) Forman MR, Beecher GR, Lanza E, Reichman ME, Graubard BI, Campbell WS, et al. Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women: a controlled dietary study. Am J Clin Nutr 1995;62: 131–5.

(40) Garro AJ, Lieber CS. Alcohol and cancer. Annu Rev Pharmacol Toxicol 1990;30:219–49.

(41) Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. Cancer Causes Control 1991;2:427–42.

(42) So FV, Guthrie N, Chambers AF, Moussa M, Carroll KK. Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices. Nutr Cancer 1996;26:167–81.

NOTES

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