Premenopausal Intakes of Vitamins A, C, and E, Folate, and Carotenoids, and Risk of Breast Cancer[1]

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Abstract

Intakes of vitamins A, C, and E, folate, and carotenoids have been hypothesized to reduce the risk of breast cancer. However, previous epidemiological studies on these nutrients and breast cancer risk have been inconclusive, and have included primarily postmenopausal women.

We examined the intake of these nutrients in relation to breast cancer risk among 90,655 premenopausal women ages 26–46 years in 1991 in the Nurses' Health Study II. Nutrient intake was assessed with a validated food-frequency questionnaire at baseline in 1991 and in 1995.

During 8 years of follow-up from 1991 to 1999, we documented 714 incident cases of invasive breast cancer. Overall, none of the vitamins and carotenoids was strongly related to a reduced risk of breast cancer. However, intake of vitamin A, including preformed vitamin A and carotenoids, was associated with a reduced risk of breast cancer among smokers; participants in the highest quintile of total vitamin A intake had a multivariate relative risk of 0.28 (95% confidence interval 0.12–0.62; *P*, test for trend <0.001; *P*, test for interaction <0.001) compared with those in the lowest quintile of intake.

We found no evidence that higher intakes of vitamins C and E, and folate in early adult life reduce risk of breast cancer. However, intake of vitamin A may be related to a reduced risk of breast cancer among smokers.

Introduction

Vitamins A, C, and E, folate, and carotenoids have been hypothesized to reduce the risk of breast cancer by their roles as an antioxidant (vitamins C and E, and carotenoids; Ref. 1), a regulator of cell differentiation (vitamin A; Ref. 2), and a modulator of DNA synthesis and methylation (folate; Ref. 3). However, previous studies of these nutrients and breast cancer have been inconclusive, and have included primarily postmenopausal women with diet measured after 40 years of age (4). Because some risk factors for breast cancer have different associations among pre- and postmenopausal women (5), the relations between these nutrients and breast cancer risk may differ by menopausal status. In addition, some risk factors for breast cancer, such as ionizing radiation, are most important in early adult life (6), and this also may be true for aspects of diet that protect against genotoxic damage. Therefore, we evaluated the associations of intakes of these vitamins and carotenoids with risk of breast cancer in premenopausal women in the Nurses' Health Study II.

Materials and Methods

Study Population. The Nurses' Health Study II is a prospective cohort study of 116,671 female registered nurses who were 25–42 years of age and living in 1 of 14 states in the United States when they responded to a questionnaire about their medical histories and lifestyles in 1989. Follow-up questionnaires were sent biennially to update information on risk factors and medical events.

For the current analysis, we started follow-up from 1991 when diet was first measured. From the 97,807 women who returned the 1991 dietary questionnaire, we excluded women who had an implausible total energy intake (<800 or >4,200 kcal/day) or who left >70 food items blank in the 1991 FFQ ($n = 2,361$). We also excluded women who reported a diagnosis of cancer, except nonmelanoma skin cancer, before the return of 1991 questionnaire ($n = 1,325$). Because the proportion of postmenopausal women at baseline was small ($n = 3,466$), we excluded them from this analysis, leaving a total of 90,655 premenopausal women. Among those who answered the FFQ in 1991, 85% completed the 1995 FFQ, and the response rate to the 8-year follow-up questionnaire was 93%.

To confirm the consistency of some findings in this cohort, we also examined data from the Nurses' Health Study, a prospective study of nurses 34–59 years of age when they first provided dietary data in 1980. Intakes of antioxidant vitamins and carotenoids in relation to breast cancer risk in the Nurses' Health Study has been reported previously (7); we used the same follow-up from 1980 to 1994 and examined the associations by smoking status.

The study was approved by the human research committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

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[3] The abbreviations used are: FFQ, food-frequency questionnaire; USDA, United States Department of Agriculture; RR, relative risk; CI, confidence interval.

Table 1 Age-standardized distribution of potential risk factors for breast cancer according to total vitamin A intake in 1991 in women 26–46 years of age at baseline[a]

	Total vitamin A intake quintile				
	1	2	3	4	5
No. of women	18,128	18,131	18,129	18,131	18,128
Percentage of group					
Smokers	16	13	11	10	10
Oral contraceptive use	13	11	11	10	9
History of benign breast disease	32	33	33	33	34
Family history of breast cancer in mother and sisters	9	9	9	9	9
Parity ≥3	21	22	21	20	17
Age at menarche <12 years	24	24	24	25	26
Multivitamin use	14	31	47	59	69
Mean					
Age (yr)	36	36	36	36	36
Alcohol (g/day)	3.3	3.2	3.2	3.1	2.8
Body mass index (kg/m^2)	25	25	25	24	24
Age at first birth (yr)	25	26	26	26	26
Animal fat intake (% of energy)	19	18	18	17	16

[a] Except for the data on mean age, all data shown are standardized to the age distributions of the cohort in 1991.

Dietary Assessment. A semiquantitative FFQ with ~130 food items listed was sent to women in 1991 and 1995 to assess usual dietary intake in the past year. Participants were asked how often, on average, they had consumed each type of food or beverage during the past year. The questionnaire had nine possible responses, ranging from never or less than once per month to six or more times per day. Participants also reported their current use, and dose of multivitamins and vitamins A, C, and E supplements biennially. Nutrient intake per individual was calculated as the sum of the contributions from foods based on USDA food-composition data (8) and supplemented with information from manufacturers. Food-composition data for specific types of carotenoids were based on the USDA-National Cancer Institute carotenoid database developed by Chung-Ahuja *et al.* (9) and Mangels *et al.* (10). Values for lutein and zeaxanthin were reported as combined. The carotenoid contents of tomato-based food products were updated with values from the USDA (11).

We used the regression-residual method to adjust nutrient intakes for total energy intake (12), and calculated cumulative averaged intake of nutrients using the 1991 and 1995 dietary data. Specifically, 1991 intake was used for the 1991–1995 follow-up period, and the average of 1991 and 1995 intake was used for 1995–1999 follow-up period.

The reproducibility and validity of vitamin and carotenoid intake have been assessed in the Nurses' Health Study. The Pearson correlation coefficients between estimates from the FFQ and the average of two 1-week diet records were 0.79 for energy-adjusted total vitamin A (including contribution from food and supplements) and 0.76 for energy-adjusted total vitamin C after correction for attenuation because of random error in diet records (13). Vitamin E intake was positively correlated with its plasma concentrations ($r = 0.41$; Ref. 14). Folate intake was positively related to erythrocyte levels ($r = 0.55$; Ref. 15). The Pearson correlation coefficients between estimates of specific dietary carotenoids and respective plasma concentrations among nonsmoking women ranged from 0.18 to 0.47 (16).

Identification of Cases. Biennial questionnaires mailed between 1991 and 1999 were used to identify newly diagnosed cases of breast cancer. Deaths were documented by responses to follow-up questionnaires by family members or the postal service and by a search of the National Death Index. The National Death Index has been shown to have a sensitivity of at least 96.5% in the Nurses' Health Study (17). When a case of breast cancer was reported, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and for permission to seek relevant hospital records and pathology reports. Pathology reports confirmed 98% of the self-reports. Because the accuracy of self-reporting was high, we included the few self-reported cases from whom records could not be obtained.

Statistical Analysis. Participants contributed person-time from the date of return of the 1991 questionnaire until the date of breast cancer diagnosis, death, or June 1999, whichever came first. Participants were divided into quintiles according to their nutrient intakes. RRs of breast cancer were calculated as the incidence rate for a given quintile of nutrient as compared with the rate for the lowest quintile. We used Cox proportional hazards regression to account for potential effects of other risk factors for breast cancer (18). To control as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. Multivariate models also adjusted simultaneously for smoking status, body mass index, height, age at menarche, oral contraceptive use, family history of breast cancer, history of benign breast disease, parity and age at first birth, menopausal status, and intakes of calories, animal fat, and alcohol. All of the covariates except height, age at menarche, and family history of breast cancer were updated in each questionnaire cycle. SAS PROC PHREG (19) was used for all of the analysis, and the Anderson-Gill data structure (20) was used to handle time-varying covariates efficiently (*i.e.,* a new data record was created for every questionnaire cycle at which a participant was at risk, with covariates set to their values at the time that the questionnaire was returned). For all of the RRs, 95% CIs were calculated. Tests for trend were conducted using the median value for each category of nutrient as a continuous variable. To test whether the association between vitamin A and breast cancer risk was modified by smoking status (never, past, and current), cross-product terms for the level of smoking and vitamin A intake expressed as a continuous variable were included in multivariate model. The *P*

Table 2 RR and 95% CI of breast cancer according to quintile of cumulative averaged vitamin intake in women 26–46 years of age at baseline

Nutrient	Quintile of intake					*P*, test for trend
	1	2	3	4	5	
Total vitamin A						
Median intake (IU/day)	5,639	8,724	11,466	14,884	21,916	
Age-adjusted RR (95% CI)	1.00	1.05 (0.83–1.32)	0.82 (0.64–1.05)	1.06 (0.84–1.33)	0.98 (0.78–1.23)	0.96
Multivariate[a] RR (95% CI)	1.00	1.02 (0.81–1.29)	0.79 (0.62–1.02)	1.02 (0.81–1.30)	0.97 (0.76–1.23)	0.97
Vitamin A from food only						
Median intake (IU/day)	4,895	7,354	9,525	12,281	17,801	
Age-adjusted RR (95% CI)	1.00	0.95 (0.75–1.20)	0.89 (0.70–1.13)	0.99 (0.79–1.24)	0.92 (0.73–1.16)	0.66
Multivariate[a] RR (95% CI)	1.00	0.92 (0.72–1.16)	0.86 (0.68–1.10)	0.96 (0.76–1.21)	0.92 (0.72–1.17)	0.74
Total preformed vitamin A						
Median intake (IU/day)	964	1,645	2,529	4,160	7,366	
Age-adjusted RR (95% CI)	1.00	0.98 (0.79–1.23)	0.84 (0.67–1.06)	0.95 (0.76–1.20)	0.82 (0.65–1.04)	0.12
Multivariate[a] RR (95% CI)	1.00	0.95 (0.76–1.19)	0.81 (0.64–1.02)	0.92 (0.73–1.16)	0.80 (0.63–1.02)	0.10
Preformed vitamin A from food only						
Median intake (IU/day)	799	1,213	1,604	2,101	3,339	
Age-adjusted RR (95% CI)	1.00	1.11 (0.88–1.39)	1.03 (0.82–1.30)	1.00 (0.79–1.26)	0.90 (0.70–1.14)	0.17
Multivariate[a] RR (95% CI)	1.00	1.08 (0.86–1.35)	1.00 (0.79–1.26)	0.97 (0.77–1.23)	0.88 (0.69–1.12)	0.15
Total vitamin C						
Median intake (mg/day)	80	122	164	234	572	
Age-adjusted RR (95% CI)	1.00	0.99 (0.79–1.26)	1.03 (0.81–1.30)	0.98 (0.77–1.25)	0.98 (0.78–1.24)	0.83
Multivariate[a] RR (95% CI)	1.00	0.97 (0.77–1.23)	1.00 (0.79–1.27)	0.96 (0.75–1.23)	0.96 (0.75–1.21)	0.72
Vitamin C from food only						
Median intake (mg/day)	69	97	122	150	200	
Age-adjusted RR (95% CI)	1.00	1.28 (1.00–1.65)	1.47 (1.15–1.88)	1.23 (0.96–1.58)	1.24 (0.96–1.59)	0.34
Multivariate[a] RR (95% CI)	1.00	1.25 (0.97–1.61)	1.46 (1.14–1.87)	1.24 (0.96–1.60)	1.30 (1.00–1.69)	0.16
Total vitamin E						
Median intake (mg/day)	7	8	10	15	59	
Age-adjusted RR (95% CI)	1.00	1.12 (0.88–1.43)	1.21 (0.95–1.53)	0.99 (0.77–1.27)	1.20 (0.95–1.51)	0.29
Multivariate[a] RR (95% CI)	1.00	1.09 (0.85–1.39)	1.16 (0.91–1.48)	0.95 (0.73–1.22)	1.13 (0.89–1.43)	0.49
Vitamin E from food only						
Median intake (mg/day)	6	7	8	9	10	
Age-adjusted RR (95% CI)	1.00	1.19 (0.93–1.52)	1.20 (0.94–1.53)	1.14 (0.90–1.46)	1.18 (0.93–1.51)	0.34
Multivariate[a] RR (95% CI)	1.00	1.15 (0.90–1.48)	1.17 (0.91–1.49)	1.12 (0.87–1.43)	1.17 (0.92–1.50)	0.34
Total folate						
Median intake (μg/day)	228	301	386	547	826	
Age-adjusted RR (95% CI)	1.00	1.09 (0.87–1.37)	0.92 (0.73–1.16)	0.90 (0.71–1.14)	1.05 (0.83–1.32)	0.94
Multivariate[a] RR (95% CI)	1.00	1.06 (0.84–1.33)	0.89 (0.70–1.13)	0.87 (0.68–1.11)	1.03 (0.81–1.32)	0.96
Folate from food only						
Median intake (μg/day)	210	260	300	345	429	
Age-adjusted RR (95% CI)	1.00	1.21 (0.95–1.53)	1.13 (0.89–1.44)	1.10 (0.87–1.40)	1.03 (0.81–1.32)	0.81
Multivariate[a] RR (95% CI)	1.00	1.18 (0.93–1.50)	1.11 (0.87–1.42)	1.09 (0.86–1.40)	1.07 (0.82–1.38)	0.94

[a] Multivariate model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past <25, past 25+, current <25, and current 25+ cigarettes/day), height (<62, 62–<65, 65–<68, 68+ inches), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth 30+ years, parity 3+ and age at first birth <25 years, parity 3+ and age at first birth 25+ years), body mass index (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, 30.0+ kg/m^2), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past <4 years, past 4+ years, current <8 years, current 8+ years), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (nondrinkers, <5, 5–<10, 10–<20, 20+ g/d), energy (quintiles), and animal fat (quintiles).

for the tests for interaction was obtained from a likelihood ratio test with 2 degrees of freedom. All of the *P*s were two-sided.

Results

During 711,651 person-years of follow-up of 90,655 women, we documented 714 cases of invasive breast carcinoma. The age range of the participants at baseline was 26–46 years (mean = 36; SD ±5). The age range of cases at the time of diagnosis of breast cancer was 26–52 (mean = 43, SD ± 5). Table 1 presents the distribution of risk factors for breast cancer by quintiles of total vitamin A intake. Women with higher intake of total vitamin A were less likely to be smokers, to use oral contraceptives, to have more than three children, and to consume alcohol, and were more likely to be <12 years old at menarche and to use multivitamins.

Intakes of vitamins A, C, and E, and folate were not appreciably associated with breast cancer risk (Table 2). The multivariate RRs for the highest quintile of intake compared with the lowest were 0.97 (95% CI, 0.76–1.23) for total vitamin A, 0.96 (95% CI, 0.75–1.21) for total vitamin C, 1.13 (95% CI, 0.89–1.43) for total vitamin E, and 1.03 (95% CI, 0.81–1.32) for total folate. Although not statistically significant, there was a suggestion of an inverse relationship between total preformed vitamin A intake and breast cancer risk; the multivariate RR for the highest quintile of intake compared with the lowest was 0.80 (95% CI, 0.63–1.02; *P*, test for trend = 0.10). For vitamin intakes from food only, the results were similar after excluding participants taking multivitamins and/or any of the vitamin supplements.

Similarly, none of the carotenoids were clearly related to

Table 3 RR and 95% CI of breast cancer according to quintile of cumulative averaged carotenoid intake in women 26–46 years of age at baseline

Nutrient	Quintile of intake					P, test for trend
	1	2	3	4	5	
Total carotenoids						
Median intake (IU/day)	3,414	5,795	7,960	10,832	16,963	
Age-adjusted RR (95% CI)	1.0	0.95 (0.75–1.21)	0.84 (0.66–1.07)	1.01 (0.81–1.28)	0.92 (0.73–1.16)	0.74
Multivariate[a] RR (95% CI)	1.0	0.92 (0.73–1.17)	0.81 (0.63–1.03)	0.98 (0.78–1.24)	0.91 (0.71–1.16)	0.76
α-Carotene						
Median intake (μg/day)	183	405	606	883	1,537	
Age-adjusted RR (95% CI)	1.0	0.86 (0.68–1.08)	0.91 (0.73–1.15)	0.86 (0.69–1.09)	0.85 (0.68–1.07)	0.28
Multivariate[a] RR (95% CI)	1.0	0.83 (0.65–1.05)	0.90 (0.71–1.13)	0.85 (0.67–1.07)	0.85 (0.67–1.08)	0.35
β-Carotene						
Median intake (μg/day)	1,675	2,769	3,739	4,993	7,701	
Age-adjusted RR (95% CI)	1.0	1.03 (0.81–1.31)	0.87 (0.68–1.11)	1.08 (0.85–1.36)	0.97 (0.77–1.23)	0.96
Multivariate[a] RR (95% CI)	1.0	1.00 (0.79–1.27)	0.83 (0.65–1.06)	1.04 (0.82–1.32)	0.96 (0.75–1.22)	0.97
β-Cryptoxanthin						
Median intake (μg/day)	8	23	37	58	104	
Age-adjusted RR (95% CI)	1.0	1.07 (0.83–1.37)	1.11 (0.87–1.42)	1.24 (0.98–1.56)	1.12 (0.88–1.42)	0.35
Multivariate[a] RR (95% CI)	1.0	1.07 (0.83–1.37)	1.11 (0.87–1.43)	1.26 (0.99–1.60)	1.20 (0.94–1.54)	0.11
Lycopene						
Median intake (μg/day)	3,570	5,527	7,637	10,494	15,745	
Age-adjusted RR (95% CI)	1.0	1.01 (0.79–1.30)	0.92 (0.71–1.18)	1.19 (0.94–1.51)	1.14 (0.90–1.45)	0.09
Multivariate[a] RR (95% CI)	1.0	1.01 (0.79–1.30)	0.91 (0.71–1.18)	1.19 (0.94–1.50)	1.17 (0.92–1.49)	0.06
Lutein/zeaxanthin						
Median intake (μg/day)	1,006	1,811	2,630	3,680	5,939	
Age-adjusted RR (95% CI)	1.0	0.93 (0.73–1.18)	0.97 (0.77–1.24)	1.08 (0.85–1.36)	0.99 (0.78–1.25)	0.70
Multivariate[a] RR (95% CI)	1.0	0.89 (0.69–1.13)	0.93 (0.73–1.18)	1.02 (0.80–1.29)	0.96 (0.75–1.22)	0.82

[a] The model was adjusted for the same covariates as multivariate model on Table 2.

breast cancer risk (Table 3). However, there was a nonsignificant inverse association between α-carotene and breast cancer risk; participants in the highest quintile of intake had a multivariate RR of 0.85 (95% CI, 0.67–1.08) compared with the lowest. The results for the vitamins and carotenoids were similar when we used baseline intake.

We also examined whether the association between these nutrients and breast cancer risk differed by different levels of other breast cancer risk factors such as family history (yes or no), body mass index ($<$25 or $\geq$25 kg/m^2), oral contraceptive use (yes or no), alcohol intake ($<$5 or $\geq$5 g/day), and smoking habits (never, past, or current). The overall associations did not vary by different levels of these risk factors except for smoking habits at baseline. Among smokers, there were strong inverse associations for all of the forms of vitamin A (total vitamin A, vitamin A from food only, total preformed vitamin A, preformed vitamin A from food only, and total carotenoids), as well as for some carotenoids with vitamin A activity (α- and β-carotene; Tables 4 and 5). The multivariate RR for the highest quintile of total vitamin A intake compared with the lowest was 0.28 (95% CI, 0.12–0.62; P, test for trend $<$ 0.001). In contrast, there was a weak positive association between total vitamin A and breast cancer risk among never-smokers (Table 4). The test for interaction for total vitamin A intake was highly significant ($P <$ 0.001).

Intakes of total vitamin E and total folate were weakly associated with risk of breast cancer among smokers also (Table 4). Because intakes of vitamins A and E, and folate may be correlated, we conducted analyses including two of the nutrients at a time among smokers to identify the nutrient(s) responsible for the inverse association. When we included both total vitamin A and total folate (r = 0.61) in a multivariate model, the inverse association for total folate disappeared but the inverse association for total vitamin A remained (data not shown). In a similar analysis for total vitamin A and total vitamin E (r = 0.55), the association for total vitamin E was greatly attenuated, and the association for total vitamin A remained (data not shown). Therefore, these results suggest that vitamin A was more likely to be the nutrient responsible for the apparent inverse association. The observed effect modification by smoking status was similar when we used either updated smoking status or baseline nutrient intake.

Some of the participants who were premenopausal at baseline became postmenopausal during the follow-up period. Thus, ~10% of the women with breast cancer were postmenopausal at the time of diagnosis. Restricting analyses to those who remained premenopausal throughout follow-up (n = 641 breast cancer cases) resulted in similar associations; the RR for the highest quintile of total vitamin A among current smokers was 0.32 (95% CI, 0.14–0.74).

To confirm the vitamin A findings, we examined multivitamins and total vitamin A from supplemental sources (including the contribution from multivitamins and vitamin A supplements) by smoking status. The inverse associations were consistent for multivitamins and total supplemental vitamin A among smokers, but the results were stronger for baseline intake than for updated intake. Among smokers, users of multivitamins at baseline had a multivariate RR of 0.55 (95% CI, 0.35–0.88) compared to nonusers. For supplemental vitamin A, multivariate RRs were 0.47 (95% CI, 0.24–0.93) for intake of $<$5000 IU/day and 0.62 (95% CI, 0.35–1.10) for $\geq$5000 IU/day compared with nonusers of supplemental vitamin A.

An inverse association between vitamin A and breast cancer risk among smokers has not been reported previously. To address the possibility that this is a chance finding, we examined the association between vitamin A-related nutrients and breast cancer in the Nurses' Health Study, a cohort of older female nurses (7). When we stratified by menopausal status, there was a statistically significant inverse association for α-carotene only among premenopausal smokers (169 cases of

Table 4 Multivariate RR and 95% CI of breast cancer according to quintile of cumulative averaged vitamin intake by smoking status at baseline in women 26–46 years of age at baseline[a]

Nutrient	Quintile of intake					P, test for trend
	1	2	3	4	5	
Total vitamin A						
Never	1.00	1.09 (0.79–1.50)	0.97 (0.70–1.35)	1.21 (0.89–1.66)	1.35 (0.99–1.84)	0.03
Past	1.00	1.05 (0.64–1.72)	0.92 (0.55–1.52)	1.02 (0.62–1.67)	0.91 (0.55–1.49)	0.65
Current	1.00	1.04 (0.62–1.75)	0.36 (0.18–0.73)	0.76 (0.42–1.36)	0.28 (0.12–0.62)	<0.001
Vitamin A from food only						
Never	1.00	1.05 (0.76–1.45)	0.97 (0.70–1.35)	1.22 (0.89–1.67)	1.26 (0.92–1.73)	0.07
Past	1.00	0.83 (0.51–1.36)	0.76 (0.46–1.26)	0.94 (0.59–1.51)	0.75 (0.46–1.23)	0.42
Current	1.00	0.69 (0.39–1.20)	0.85 (0.49–1.46)	0.41 (0.21–0.79)	0.33 (0.16–0.70)	0.001
Total preformed vitamin A						
Never	1.00	1.06 (0.79–1.43)	0.89 (0.66–1.22)	0.94 (0.69–1.28)	0.98 (0.72–1.34)	0.80
Past	1.00	0.70 (0.44–1.12)	0.64 (0.40–1.02)	0.94 (0.60–1.46)	0.72 (0.45–1.15)	0.62
Current	1.00	0.98 (0.57–1.67)	0.76 (0.42–1.39)	0.82 (0.45–1.50)	0.45 (0.22–0.91)	0.02
Preformed vitamin A from food only						
Never	1.00	1.00 (0.73–1.35)	1.06 (0.78–1.43)	1.06 (0.78–1.43)	0.94 (0.69–1.29)	0.70
Past	1.00	1.27 (0.82–1.97)	0.83 (0.51–1.35)	0.87 (0.53–1.42)	0.92 (0.56–1.51)	0.37
Current	1.00	0.89 (0.51–1.57)	0.96 (0.54–1.69)	0.70 (0.37–1.33)	0.54 (0.28–1.05)	0.05
Total vitamin C						
Never	1.00	1.01 (0.73–1.40)	1.14 (0.83–1.57)	1.02 (0.73–1.41)	1.13 (0.82–1.55)	0.50
Past	1.00	0.87 (0.54–1.41)	0.86 (0.52–1.41)	1.19 (0.74–1.90)	0.81 (0.50–1.32)	0.47
Current	1.00	1.03 (0.59–1.79)	0.90 (0.49–1.64)	0.53 (0.26–1.11)	0.78 (0.43–1.39)	0.37
Vitamin C from food only						
Never	1.00	1.39 (0.99–1.96)	1.44 (1.03–2.02)	1.39 (0.99–1.95)	1.47 (1.04–2.07)	0.10
Past	1.00	1.07 (0.64–1.80)	1.49 (0.91–2.44)	1.17 (0.70–1.97)	1.33 (0.79–2.25)	0.32
Current	1.00	1.07 (0.59–1.92)	1.61 (0.91–2.87)	1.04 (0.55–1.97)	0.78 (0.38–1.59)	0.55
Total vitamin E						
Never	1.00	1.35 (0.98–1.87)	1.28 (0.92–1.79)	1.08 (0.76–1.52)	1.42 (1.03–1.95)	0.12
Past	1.00	0.99 (0.59–1.68)	1.25 (0.76–2.06)	1.02 (0.60–1.72)	1.19 (0.73–1.94)	0.56
Current	1.00	0.64 (0.35–1.18)	0.93 (0.52–1.66)	0.73 (0.38–1.37)	0.53 (0.27–1.01)	0.10
Vitamin E from food only						
Never	1.00	1.35 (0.97–1.88)	1.38 (0.99–1.91)	1.30 (0.93–1.81)	1.40 (1.00–1.94)	0.13
Past	1.00	0.72 (0.42–1.24)	1.04 (0.64–1.69)	0.90 (0.55–1.46)	1.03 (0.64–1.66)	0.57
Current	1.00	1.38 (0.77–2.47)	0.80 (0.42–1.53)	0.95 (0.51–1.79)	0.86 (0.44–1.67)	0.40
Total folate						
Never	1.00	1.13 (0.83–1.54)	0.91 (0.66–1.26)	0.94 (0.68–1.30)	1.22 (0.88–1.67)	0.31
Past	1.00	1.05 (0.64–1.70)	0.96 (0.59–1.58)	0.99 (0.60–1.63)	1.18 (0.72–1.94)	0.50
Current	1.00	0.92 (0.55–1.57)	0.95 (0.53–1.70)	0.63 (0.33–1.21)	0.46 (0.21–1.00)	0.03
Folate from food only						
Never	1.00	1.27 (0.92–1.75)	1.11 (0.80–1.54)	1.13 (0.82–1.57)	1.30 (0.93–1.81)	0.25
Past	1.00	0.98 (0.60–1.61)	1.10 (0.68–1.80)	0.99 (0.60–1.64)	0.99 (0.59–1.65)	0.94
Current	1.00	1.15 (0.66–1.99)	1.18 (0.67–2.10)	1.26 (0.69–2.30)	0.31 (0.10–0.91)	0.17

[a] The model was adjusted for the same covariates as multivariate model on Table 2 except smoking. For current smokers, the model was adjusted for categories of number of cigarettes/day (1–4, 5–14, 15–24, 25–34, 35+, unknown). Number of cases (person-years); never smokers = 424 (468,091), past smokers = 181 (157,457), current smokers = 109 (85,224).

breast cancer), and no association was found among premenopausal nonsmokers (571 cases) or postmenopausal women (1915 cases). To best simulate the population of Nurses' Health Study II, we restricted the analyses to premenopausal women and cases of breast cancer diagnosed at <50 years of age (506 cases), because age at diagnosis of breast cancer in the Nurses' Health Study II was substantially lower than the Nurses' Health Study. Consistent with the Nurses' Health Study II findings, vitamin A-related nutrients were inversely related to breast cancer risk only among smokers (Table 6). However, contrary to the Nurses' Health Study II results, there was no suggestion of positive association between total vitamin A and breast cancer risk among women who had never smoked, and the test for interaction was not statistically significant ($P = 0.38$).

Discussion

In this prospective study among women who were premenopausal at baseline, we did not find any strong overall associations between intakes of vitamins A, C, and E, folate, and carotenoids, and risk of breast cancer. However, intake of vitamin A was strongly related to a substantially lower risk of breast cancer among smokers. We also confirmed this finding with vitamin A among premenopausal women with breast cancer diagnosed before <50 years of age in another prospective study of women.

Vitamin A includes preformed vitamin A (retinol and retinyl esters) and carotenoids with provitamin A activity. Vitamin A is an essential nutrient for proper function of several organs, such as the skin, liver, and eye, and immune system. Vitamin A has been hypothesized to reduce the risk of breast cancer through different mechanisms; first, that metabolites of vitamin A regulate cell growth, differentiation, and death (2); and second, that some carotenoids (α- and β-carotene, and β-cryptoxanthin) that can be converted to retinol also have antioxidant activity. We found consistent inverse associations for preformed vitamin A [which comes primarily from supple-

Table 5 Multivariate RR and 95% CI of breast cancer according to quintile of cumulative averaged carotenoid intake by smoking status at baseline in women 26–46 years of age at baseline[a]

Nutrient	Quintile of intake					P, test for trend
	1	2	3	4	5	
Total carotenoids						
Never	1.00	0.93 (0.67–1.28)	0.87 (0.63–1.22)	1.18 (0.86–1.60)	1.22 (0.89–1.67)	0.04
Past	1.00	1.04 (0.63–1.72)	0.84 (0.50–1.40)	1.03 (0.63–1.67)	0.81 (0.49–1.35)	0.39
Current	1.00	0.77 (0.45–1.34)	0.70 (0.40–1.23)	0.48 (0.26–0.91)	0.28 (0.13–0.62)	<0.001
α-Carotene						
Never	1.00	0.84 (0.61–1.16)	0.90 (0.66–1.23)	0.90 (0.66–1.23)	1.10 (0.81–1.48)	0.23
Past	1.00	0.71 (0.44–1.15)	0.91 (0.57–1.43)	0.86 (0.55–1.36)	0.62 (0.38–1.02)	0.12
Current	1.00	0.90 (0.52–1.57)	1.00 (0.57–1.75)	0.59 (0.31–1.12)	0.33 (0.14–0.75)	0.003
β-Carotene						
Never	1.00	0.91 (0.65–1.26)	0.89 (0.64–1.24)	1.28 (0.94–1.73)	1.24 (0.90–1.70)	0.02
Past	1.00	1.42 (0.85–2.38)	1.09 (0.64–1.85)	1.08 (0.64–1.82)	1.04 (0.61–1.75)	0.56
Current	1.00	0.86 (0.50–1.47)	0.60 (0.33–1.10)	0.48 (0.25–0.89)	0.34 (0.17–0.69)	<0.001
β-Cryptoxanthin						
Never	1.00	1.04 (0.75–1.46)	1.33 (0.97–1.83)	1.06 (0.76–1.47)	1.24 (0.90–1.72)	0.29
Past	1.00	0.79 (0.48–1.30)	0.77 (0.46–1.28)	1.28 (0.81–2.02)	1.20 (0.74–1.93)	0.10
Current	1.00	1.68 (0.92–3.08)	0.76 (0.38–1.56)	2.08 (1.16–3.74)	0.97 (0.48–1.96)	0.93
Lycopene						
Never	1.00	0.90 (0.65–1.24)	0.93 (0.68–1.28)	1.11 (0.82–1.50)	1.15 (0.85–1.57)	0.11
Past	1.00	1.02 (0.60–1.73)	1.00 (0.59–1.68)	1.24 (0.76–2.03)	1.19 (0.72–1.95)	0.35
Current	1.00	1.49 (0.77–2.89)	0.83 (0.39–1.78)	1.57 (0.82–3.02)	1.37 (0.70–2.71)	0.39
Lutein/zeaxanthin						
Never	1.00	0.84 (0.61–1.15)	0.94 (0.69–1.27)	0.99 (0.73–1.35)	1.05 (0.77–1.43)	0.38
Past	1.00	0.82 (0.47–1.42)	1.00 (0.60–1.69)	1.11 (0.68–1.83)	0.95 (0.57–1.57)	0.88
Current	1.00	1.39 (0.75–2.56)	0.79 (0.41–1.53)	1.01 (0.54–1.91)	0.79 (0.41–1.54)	0.26

[a] The model was adjusted for the same covariates as multivariate model on Table 2 except smoking. For current smokers, the model was adjusted for categories of number of cigarettes/d (1–4, 5–14, 15–24, 25–34, 35+, unknown). Number of cases (person-years); never smokers = 424 (468,091), past smokers = 181 (157,457), current smokers = 109 (85,224).

mental sources, animal-based foods (*e.g.*, milk and liver), and breakfast cereal in this cohort] and for carotenoids (mainly from fruits and vegetables). Thus, our findings are supportive of a specific vitamin A effect rather than a general antioxidant effect.

A combined analysis of 12 case-control studies reported a significant inverse association between β-carotene, but not preformed vitamin A, and breast cancer risk among postmenopausal women but not among premenopausal women (21). Among the few case-control studies that examined intakes of vitamin A or carotenoids in relation to premenopausal breast cancer, some (22, 23), but not others (24, 25), found inverse associations. Most prospective studies of vitamin A (or preformed vitamin A and carototenoids) intake and breast cancer have not found overall inverse associations (26–30). In one prospective study, a modest inverse association was observed with total vitamin A intake but not with carotenoid intake (31, 32), and the results did not differ by menopausal status. In the Nurses' Health Study, an inverse association with both preformed vitamin A and carotenoids was observed among premenopausal women only (7). In these studies, the number of premenopausal cancer cases was small, and their diet usually was measured after 40 years of age. In the two prospective studies we examined, the inverse association between vitamin A and breast cancer was seen only among premenopausal smokers with breast cancer diagnosed relatively early in life. Thus, an inverse association might have been missed in the previous studies. In an analysis by smoking status, one prospective study with 1589 cases of breast cancer found nonsignificant inverse associations between α- and β-carotene, and breast cancer only among smokers (32).

We are not aware of any potential mechanism to explain the apparent inverse relationship between vitamin A intake and breast cancer risk among smokers only. Although it is well known that smoking causes an oxidative stress and that smokers have lower plasma levels of some vitamins and carotenoids, including β-carotene, even after accounting for dietary intake, plasma retinol level is tightly regulated by the liver and is not affected by smoking (33, 34). Vitamin A deficiency is rare in developed countries because adequate amounts are contained in the diet, and the liver can store any excess. However, one *in vitro* study found that exposure to cigarette smoke lowered plasma retinol levels (35). Therefore, even if smoking does not lower plasma levels of retinol, it may increase retinol turnover and decrease stores in breast tissues. Thus, lower intake of vitamin A might be harmful in this condition. Alternatively, vitamin A may block a pathway by which smoking induces breast cancer. Although smoking has not been known as an important risk factor for breast cancer, the association between smoking and breast cancer may be different among younger women (36–38).

This study had several strengths. The prospective nature of the study avoided biases of case-control studies. Our study provided a unique opportunity to evaluate intake of vitamins and carotenoids, and breast cancer in younger women. Because pre- and postmenopausal breast cancers have distinctly different etiologies (39, 40), and for some risk factors, such as adiposity (5), the direction of associations is reversed, the relationships between nutrients and breast cancer in premenopausal women could be different from those in postmenopausal women. Several known risk factors, such as a variety of reproductive factors and radiation, operate primarily before middle age (6, 41). Our results also suggest that dietary intake in early adult life combined with other conditions (*e.g.*, smoking) may have a strong impact on the development of breast cancer.

Some limitations need to be considered. First, the inverse

Table 6 Multivariate RR and 95% CI of breast cancer (with age of diagnosis <50) according to quintile of cumulative averaged intake of vitamin A-related nutrients by current smoking status in premenopausal women in the Nurses' Health Study (1980–1994)[a]

Nutrient	Quintile of intake					P, test for trend
	1	2	3	4	5	
Total vitamin A						
Never	1.00	0.71 (0.47–1.07)	0.78 (0.52–1.17)	0.77 (0.51–1.18)	0.94 (0.61–1.43)	0.96
Past	1.00	1.53 (0.95–2.47)	1.41 (0.86–2.29)	1.02 (0.60–1.76)	1.40 (0.84–2.34)	0.65
Current	1.00	0.73 (0.46–1.18)	0.55 (0.32–0.95)	0.31 (0.15–0.65)	0.63 (0.34–1.14)	0.02
Vitamin A from food only						
Never	1.00	0.93 (0.62–1.39)	0.73 (0.47–1.12)	1.02 (0.68–1.53)	0.89 (0.57–1.40)	0.79
Past	1.00	1.35 (0.82–2.21)	1.89 (1.18–3.03)	1.14 (0.67–1.94)	1.39 (0.83–2.34)	0.48
Current	1.00	0.53 (0.31–0.89)	0.75 (0.46–1.23)	0.39 (0.20–0.74)	0.44 (0.22–0.89)	0.005
Total preformed vitamin A						
Never	1.00	0.66 (0.43–1.01)	0.78 (0.52–1.17)	0.73 (0.47–1.11)	0.93 (0.61–1.41)	0.84
Past	1.00	0.98 (0.62–1.55)	0.88 (0.55–1.41)	1.09 (0.69–1.72)	0.90 (0.55–1.47)	0.85
Current	1.00	0.62 (0.37–1.04)	0.60 (0.34–1.06)	0.73 (0.43–1.23)	0.59 (0.32–1.08)	0.17
Total carotenoids						
Never	1.00	0.95 (0.63–1.45)	1.07 (0.71–1.61)	0.85 (0.55–1.33)	1.12 (0.73–1.72)	0.72
Past	1.00	1.01 (0.63–1.63)	1.08 (0.67–1.73)	1.01 (0.62–1.63)	1.09 (0.67–1.78)	0.75
Current	1.00	0.68 (0.41–1.12)	0.87 (0.53–1.43)	0.51 (0.27–0.94)	0.55 (0.28–1.08)	0.04
α-Carotene						
Never	1.00	1.00 (0.65–1.55)	1.22 (0.80–1.85)	0.90 (0.57–1.41)	1.06 (0.68–1.64)	0.95
Past	1.00	0.85 (0.53–1.37)	0.85 (0.53–1.37)	0.85 (0.53–1.39)	1.03 (0.64–1.65)	0.68
Current	1.00	0.76 (0.47–1.22)	0.29 (0.15–0.57)	0.74 (0.45–1.23)	0.23 (0.10–0.55)	0.002
β-Carotene						
Never	1.00	0.88 (0.58–1.33)	0.97 (0.65–1.46)	0.87 (0.57–1.34)	0.89 (0.57–1.39)	0.65
Past	1.00	1.11 (0.68–1.82)	1.35 (0.84–2.16)	1.05 (0.64–1.72)	1.15 (0.69–1.90)	0.79
Current	1.00	0.63 (0.38–1.05)	0.70 (0.43–1.15)	0.47 (0.25–0.87)	0.53 (0.28–1.02)	0.03

[a] Multivariate model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for height (inches), parity (0, 1, 2, 3 or 4, ≥5) and age at first birth (<25, 25–<30, 30+ years), body mass index (<20, 20–<22, 22–<24, 24–<27, ≥27 kg/m^2) 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, gain >25 kg), age at menarche (≤12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol intake (nondrinkers, <5, 5–<15, 15+ g/day), energy (quintiles). For current smokers, the model was also adjusted for categories of number of cigarettes/day (1–4, 5–14, 15–24, 25–34, 35+, unknown). Number of cases (person-years); never smokers = 210 (192,753), past smokers = 174 (132,691), current smokers = 122 (93,797).

association we observed among smokers might be because of chance, because we examined many nutrients and interactions. However, the association was consistent across different sources of vitamin A and was found in another population. Thus, our finding is unlikely to be the result of chance only. Second, the number of cases was limited, especially when we examined associations by smoking strata (109 and 122 current smokers in the Nurses' Health Study II and the Nurses' Health Study, respectively). Third, there were few alcohol drinkers and intake was very low in this cohort. Therefore, we did not have enough power to examine the association between vitamins and carotenoids, and breast cancer risk among moderate to high alcohol drinkers. Previous studies have found inverse associations between some of these nutrients and breast cancer among regular alcohol consumers (7, 42, 43).

In conclusion, in this cohort of women who were premenopausal at baseline, we found no evidence that higher intakes of vitamins C and E, and folate reduce risk of breast cancer. Vitamin A intake was related to a reduced risk of breast cancer among smokers but not among nonsmokers. Although we are not aware of any previous studies reporting similar findings, we confirmed the results in another large cohort of women. Additional studies are needed to examine this finding and to identify relevant biological mechanisms.

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