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Dietary Carotenoids and the Risk of Invasive Breast Cancer

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Abstract

Certain classes of vitamins and nutrients found in fruits and vegetables have been of particular interest in relation to cancer prevention, owing to their potential anti-carcinogenic properties. We examined the association between certain fruits, vegetables, carotenoids, and vitamin A and breast cancer risk in a large population based case-control study of women residing in the states of Massachusetts, New Hampshire, and Wisconsin. The study was comprised of 5,707 women with incident invasive breast cancer (2,363 premenopausal women and 3,516 postmenopausal women) and 6,389 population controls (2,594 premenopausal women and 3,516 postmenopausal women). In an interview women were asked about their intake of carotenoid rich fruits and vegetables five years prior to a referent date. An inverse association was observed among premenopausal women was for high levels of vitamin A (OR: 0.82, 95%CI: 0.68–0.98, p for trend = 0.01), β-carotene (OR: 0.81, 95% CI 0.68–0.98, p for trend = 0.009), α-carotene (OR: 0.82, 95% CI: 0.68–0.98, p for trend = 0.07), and lutein/zeaxanthin (OR: 0.83, 95% CI 0.68 – 0.99, p for trend = 0.02). An inverse association was not observed among postmenopausal women. Among premenopausal women who reported ever smoking, these results were stronger than among never smokers, although tests for interaction were not statistically significant. Results from this study are comparable to previous prospective studies and suggest that a high consumption of carotenoids may reduce the risk of pre but not post menopausal breast cancer, particularly among smokers.

Keywords

breast cancer; nutrition; carotenoids; epidemiology

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Introduction

Several epidemiologic studies have suggested a protective role of fruits and vegetables in the etiology of various diseases, including both cancer and heart disease. 1 In a series of review articles, a consistent inverse association has been noted between the consumption of a wide variety of vegetables and fruits and the risk of cancer at most sites.2, 3 Raw forms of the fruits and vegetables have been most consistently associated with a lower risk.4 However, a relationship of fruit and vegetable consumption with breast cancer risk has not been seen in recent prospective studies. The Pooling Project of Prospective Studies of Diet and Cancer and the European Prospective Investigation into Cancer and Nutrition (EPIC) both examined the relationship between fruit and vegetable consumption in relation to breast cancer incidence and did not find an association.5, 6 However, a significant inverse association has been noted for total vegetables and breast cancer risk in case-control studies.7 Fewer studies have considered associations with specific phytochemicals in individual vegetable groups that may confer protection 8 or within strata of women based on menopausal status or exposures that may modify dietary associations.

Carotenoids have been protective for certain cancers in animals, and they may also have a protective influence in humans. Carotenoids are present in yellow and orange vegetables and fruits and in dark green leafy vegetables.9 Two major mechanisms have been proposed through which carotenoids may act to protect against cancer: through their potential antiproliferative and antioxidant properties. 10, 11 A subgroup of carotenoids, β-carotene, α-carotene, and B-cryptoxanthin, possess retinoic acid activity and are able to influence cell differentiation.12 Although lutein and zeaxanthin do not have retinoic acid activity they are able to reduce cell proliferation.13 Dietary carotenoids have also been shown to inhibit estrogen signaling of 17β-estradiol which may attenuate the effects of hormone-dependent malignancies.14

Many studies have investigated the relation of breast cancer with dietary 15–25, or serum levels of carotenoids 26–33, an inverse association was seen in 3 case-control studies15, 22, 24 and 7 prospective cohort studies.16, 17, 26, 27, 31–33 In a 14-year follow-up of the Nurses' Health Study 17, an inverse association limited to premenopausal women was found with intakes of β-carotene, lutein/zeaxanthin, and vitamin A. β-carotene's association was stronger among women consuming higher levels of alcohol.17 In a subsequent analysis of the Nurses' Health Study based mainly on premenopausal women16, inverse associations were observed with higher intake of α-carotene and β-carotene among current smokers. This finding is consistent with a protective influence of a carotenoid-rich diet on ROS-induced damage from tobacco smoke.

We investigated the relation of carotenoid intake, to the risk of invasive breast cancer in a US population-based case-control study. Based on approximately 5,700 women with breast cancer and 6,400 community controls, this large study provided the opportunity to explore these associations, as well as, how the association may be modified by smoking and alcohol.

Methods

Study Population

A detailed description of the Collaborative Breast Cancer Study (CBCS) has been previously reported.34–36 Briefly, CBCS was a population based case-control study conducted between 1996 and 2001. The study was conducted in New Hampshire, Massachusetts, and Wisconsin to explore risk factors for breast cancer. Women between the ages of 20 and 69 were eligible to participate. Women recently diagnosed with incident invasive breast cancer were identified through state cancer registries. Community controls

under the age of 65 were selected at random (within age strata) from lists of licensed drivers. Controls over the age of 65 were selected from lists of Medicare beneficiaries. Because of the manner in which controls were identified breast cancer cases less than 65 years of age had to have a driver's license while those 65 years and older had to be beneficiaries of Medicare. Controls had no history of breast cancer. Of the women eligible to participate in the study, approximately 81% of cases and 78% of controls completed the telephone interview. The mean time between case diagnosis and interview was 17.8 months (range 4.6 – 54.5 months). The present analysis is based on women (5,707 invasive breast cancer cases and 6,389 community controls) who provided complete information regarding intake of the fruits and vegetables included in the food survey.

Data Collection

Cases and controls completed a structured 30–40 minute telephone interview that included questions on known and suspected breast cancer risk factors. All exposures were assessed prior to a reference date corresponding to the date of diagnosis in the cases and a corresponding date in the controls.

The interview contained information on consumption of foods contributing importantly to intake of specific nutrient and nonnutrient components of diet and total carotenoids. Foods selected for inclusion were those that made the largest contribution to between-person variation in the consumption of individual dietary components in the Nurses' Health Study. Carotenoid-rich foods contained in the interview included oranges, orange juice, peaches, broccoli, Brussels sprouts, carrots, green beans, kale, romaine or leaf lettuce (not iceberg or head lettuce), spinach, sweet potatoes, and tomato sauces. Information was also collected on the usual intake of apples, cabbage, cauliflower, kohlrabi, onions, and turnips to evaluate the contribution of brassica vegetables and isoflavones to breast cancer risk. A few of the carotenoid-rich vegetables were also cruciferous vegetables (i.e. broccoli and Brussels sprouts). Women were asked to report their usual daily or weekly consumption of each food five years preceding the reference date. Multivitamin use was assessed for the same time period as the diet questions. The sequence of questions used to assess fruit and vegetable intake has been validated in another study.37

Nutrient data were calculated by multiplying the frequency of intake for the individual food by the nutrient content for a standard serving size. The carotenoid content (α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene) of each food was estimated based on the U.S. Department of Agriculture (USDA)-National Cancer Institute database that includes information on carotenoid content of foods. 38–40 Vitamin A from carotenoids was analyzed as retinol activity equivalents (RAE). The RAE measure assumes less efficient conversion of provitamin A carotenoids to retinol than what was previously thought.41 In the USDA –NCI carotenoid database, lutein and zeaxanthin are presented as one variable as they are indistinguishable in high performance liquid chromatography. 42

Analysis

Unconditional logistic regression was used to calculate odds ratios for the association between carotenoid consumption and breast cancer risk. Individual carotenoids were analyzed using both quantiles and servings per week or day. Trends in food and nutrient intake were evaluated using ordinal values for each level of intake with the term included as a continuous variable in the logistic regression model. Age as a continuous variable and state of residence were included in all models. Multivariate models also included terms for age at first birth, family history of breast cancer, education, history of benign breast disease, postmenopausal hormone use, age at menarche, parity, body mass index (BMI) calculated by dividing the woman's weight in kilograms by her height in meters squared, smoking

status and pack-years of smoking, recent alcohol consumption in drinks per week, use of multivitamins and inferred menopausal status as previously described.43 All analyses were conducted among all women and then separately for premenopausal and postmenopausal women.

To test whether the relationship between each food/nutrient and breast cancer varied across strata of other factors we included a cross product term for food/nutrient and the possible modifier in the multivariate model. Model log likelihoods were then compared to assess improvements in goodness of fit of the models. Modification was assessed for family history of breast cancer (yes/no), estimated lifetime ovulatory cycles (tertiles) 44, alcohol consumption (<2 drinks/wk, 2 or more drinks /wk), and smoking (never, current and past). Women with missing information on any of these variables were excluded from the analysis.

Results

The analysis included 5,707 women with invasive breast cancer and 6,389 community controls. A large majority of the population (97%) was comprised of women of European descent. Table 1 presents the distribution of known breast cancer risk factors and odds ratios and 95% confidence intervals associated with each factor. As seen in many previous studies, an increased risk of breast cancer was observed with greater education, a family history of breast cancer, a history of benign breast disease, nulliparity, and increased alcohol consumption. Factors inversely associated with breast cancer included increasing age at menarche and body mass in premenopausal women, and menopausal status in all women. Ever smoking was not associated with breast cancer risk. The relationship for ever smoking was similar in premenopausal and postmenopausal women (p for interaction by menopausal status = 0.94). Multivitamin use was not associated with breast cancer risk in these data.

Table 2 presents the results for total fruit and vegetable intake, and separately for different classes of vegetables. For all fruits and vegetables combined, no significant association was observed with breast cancer, either in premenopausal or postmenopausal women. Servings per day of fruit were unrelated to breast cancer even at high levels of consumption (2+ servings/day). Servings per day of cruciferous vegetables were unrelated to breast cancer (p trend=0.99), although a nonsignificantly lower risk was observed among the relatively few women that consumed large quantities of these vegetables (OR = 0.84, 95% CI = 0.56 – 1.28 for 2 or more servings per day versus less than 4 servings per week, based on 40 cases and 53 controls). Servings of carotenoid-rich vegetables had no relationship with postmenopausal breast cancer (p trend = 0.78). In contrast, intake of these vegetables was inversely associated with premenopausal breast cancer (p trend = 0.03): women consuming two or more servings per day of carotenoid-rich vegetables had a significant 17% reduction in risk when compared to women consuming less than 4 servings per week (OR = 0.83; 95% CI 0.73 – 0.96).

To further explore these relationships, we examined risk of breast cancer associated with intake of individual carotenoids and vitamin A (Table 3). For all women combined there was a decrease in breast cancer risk among women in the highest quintile of α-carotene (OR=0.87, 95% CI = 0.77 – 0.98) and β-carotene (OR=0.85, 95% CI = 0.76 – 0.96), and an increase in risk in the highest quintile of β-cryptoxanthin (OR=1.19, 95% CI = 1.06 – 1.34). Association of individual carotenoids with breast cancer differed according to menopausal status. Menopausal status modified the association between β-carotene and breast cancer (p for interaction= 0.03) and lutein/zeaxanthin and breast cancer (p for interaction= 0.003). In premenopausal women, inverse associations were observed for α-carotene, β-carotene, and lutein/zeaxanthin, as well as vitamin A, with evidence of significant dose response for β-carotene (p trend = 0.009), lutein/zeaxanthin (p trend = 0.02) and vitamin A (p trend = 0.01).

In contrast, none of these carotenoids were significantly related to the risk of postmenopausal breast cancer. A modest positive association of β-cryptoxanthin with breast cancer risk was observed only in postmenopausal women (p trend = 0.03). Lycopene was unrelated to breast cancer risk regardless of menopausal status. Inverse associations for premenopausal women were essentially unchanged when we limited the analysis to women aged 40 or younger at the reference date (570 cases and 598 controls) (data not shown).

Because of the large sample size we were able to examine associations by menopausal status according to deciles of carotenoid intake (data not shown). Comparing the highest to lowest decile in premenopausal women, odds ratios were lower for β-carotene (OR=0.72, 95%CI = 0.56 – 0.93; p trend = 0.02), lutein/zeaxanthin (OR=0.80, 95%CI = 0.61 – 1.04; p trend = 0.03), and vitamin A (OR=0.79, 95%CI = 0.51 – 1.23; p trend = 0.07), whereas deciles of α-carotene (p trend = 0.12), β-cryptoxanthin (p trend = 0.62) and lycopene (p trend = 0.14) had no associations with risk. Among postmenopausal women, β-cryptoxanthin was associated with a marginally significant increase in risk (p trend = 0.04), whereas the remaining carotenoids were unrelated to breast cancer even at extreme levels of intake.

We evaluated carotenoid associations with premenopausal breast cancer according to the potential modifying influences of other breast cancer risk factors. Inverse associations were consistent regardless of education, body mass, family history of breast cancer and estrogen exposure measured as lifetime ovulatory cycles (data not shown). Although tests for interaction did not reach statistical significance for any of the factors evaluated, associations appeared stronger among women who drank less or avoided alcohol, and among smokers (Table 4). For alcohol, the inverse associations with α-carotene, β-carotene, vitamin A, and lutein/zeaxanthin tended to be stronger, and were statistically significant in women consuming lower levels of alcohol. For smoking, inverse associations noted for the carotenoids associated with premenopausal breast cancer (α-carotene, β-carotene, and lutein/zeaxanthin) were stronger and were associated with a significant dose response only in ever smokers. For example, among smokers, those in the highest quintile of total vitamin A intake had a significant 25% lower risk (OR=0.75; 95% CI = 0.58 – 0.97) when compared to those in the lowest quintile (p trend = 0.02) whereas vitamin A had no significant association with premenopausal breast cancer among never smokers (P trend 0.21). With the exception of alcohol and lycopene, tests for interaction did not reach statistical significance for any of the factors evaluated. Among postmenopausal women, associations with carotenoids and vitamin A were nonsignificant, regardless of smoking and the other factors (data not shown).

Discussion

In this large population-based case-control study including more than 5,700 incident cases of invasive breast cancer we observed an inverse association for carotenoid-rich vegetables intake as well as specific carotenoids in the diet with risk of premenopausal though not postmenopausal breast cancer. Higher intake of α-carotene, β-carotene, lutein/zeaxanthin and vitamin A from food was associated with a statistically significant lower risk among premenopausal women. In contrast, consistent inverse associations with vegetable-derived carotenoids were not observed for post-menopausal women. β-cryptoxanthin from vegetables had no relation to premenopausal breast cancer but was associated with a modest increase in risk of postmenopausal breast cancer. Differences noted according to menopausal status were statistically significant for β-carotene and lutein/zeaxanthin. Results also suggested potential interactions of individual carotenoids with alcohol and smoking among premenopausal women: stronger inverse associations were observed in women consuming lower levels of alcohol and among ever smokers, though the tests for interaction according to these factors were not significant.

Vitamin A, a fat soluble vitamin, is active in the body as retinal, retinoic acid, and retinol. Retinal is active in vision; retinoic acid regulates cell differentiation, growth and embryonic development; and retinol plays a role in reproduction and is the major transport and storage form of vitamin A.45 Retinoic acids have been shown to induce differentiation and/or apoptosis of tumor cells, and inhibit tumor promotion in chemically induced cancers.46 Previous epidemiologic studies of vitamin A and breast cancer have shown mixed results. 16–19, 21, 25, 47–49 Results in the current study suggest that vitamin A from fruits and vegetables have a inverse association with breast cancer, most evident in premenopausal women.

Beta-carotene is a vitamin A precursor. In addition to its associations with vitamin A, β-carotene has other potential anticarcinogenic properties including its ability to act as an antioxidant and free radical scavenger, as well as its ability to modulate immune function, induce differentiation, contribute to chromosome stability, inhibit chromosome damage and cell proliferation, and promote apoptosis.13 In relation to breast cancer the results have been mixed.24, 30, 50, 51 Similar to the current results, a few case-control 22, 52 and cohort 17 studies have found a decreased risk of premenopausal breast cancer associated with increased β-carotene intake; however, not all studies have shown this benefit. 15, 21 It is unclear why the inverse association would be observed among premenopausal and not among postmenopausal women, it may be related to the carotenoid's ability to inhibit estrogen induced cell proliferation.14

Similar to β-carotene, α-carotene can also be cleaved to form retinol. As a precursor to vitamin A, α-carotene is only half as effective as β-carotene. Studies have shown that α-carotene can act as an antioxidant, free radical /reactive species scavenger. It induces differentiation and inhibits biochemical changes that are associated with proliferation.13 Similar to β-carotene, previous studies of α-carotene and breast cancer have also found mixed results.16, 17, 21

The carotenoids lutein and zeaxanthin have no vitamin A activity. 45 Similar to the other carotenoids lutein and zeaxanthin have been shown to have antioxidant properties and play a role in cell differentiation.13 The inverse association we observed for lutein/zeaxanthin intake among premenopausal women has also been observed in some 17 but not all 16, 21 prospective studies. We have previously reported an inverse association for increased lutein/zeaxanthin intake with ovarian cancer risk 53 based on a case-control study conducted in the same population as the current study.

Alcohol is a known risk factor for breast cancer. One mechanism proposed to explain the positive association of alcohol with breast cancer relates to the ability of alcohol to interfere with retinoid metabolism.54 Alcohol has the ability to act as a competitive inhibitor of the oxidation of vitamin A to the biologically active retinoic acid and it induces cytochrome P450 enzymes which enhance the metabolic breakdown of vitamin A.54 A study that examined the relationship between carotenoids and breast cancer found a strong inverse association for premenopausal breast cancer among women in the highest quintile of β-carotene intake who consumed 15 grams/day or more of alcohol (equivalent to >1 alcoholic beverage per day).17 The women who participated in our study had a relatively low intake of alcohol. In the present analysis, despite large numbers, relatively few premenopausal women consumed large amounts of alcohol and results at that level were unstable. Contrasting women in lower levels of alcohol consumption to those in higher levels (less than 2 versus 2 or more drinks per week) showed similar degrees of association with beta carotene but no substantial differences according to level of vitamin A. The test for trend for vitamin A was statistically significant only in women consuming lower levels of alcohol. No clear interaction of alcohol with vitamin A was observed in postmenopausal women. It was

possible that the results observed among women who consumed low levels of alcohol were due to chance.

An interaction of smoking and carotenoids in cancer is plausible given the antioxidant properties of the carotenoids and the known oxidative stress induced by tobacco smoke. In the current data, a high intake of α-carotene, β-carotene or lutein/zeaxanthin appeared to confer the greatest protection among smokers, consistent with a role for these carotenoids in breast cancer related to their ability to quench ROS induced by tobacco carcinogens. Similar results have been reported in the Nurses' Health Study.16, 17 As in the current data, a report from the Nurses' Health Study17 indicated that dietary carotenoids are more strongly protective for premenopausal than postmenopausal breast cancer. A more recent report based on the younger cohort of women (Nurses' Health Study II) 16 found that associations of individual carotenoids with breast cancer varied according to smoking status.. Both studies found similar protective associations among current smokers for the highest quintile of α-carotene and β-carotene compared to the lowest. In the CBCS data only, lutein/zeaxanthin was associated with a lower risk of breast cancer regardless of smoking category; however, a nonsignificant inverse association was observed in current smokers in both the NHSII (OR=0.79) and the CBCS (OR=0.81), with evidence of a significant dose response only in the current study. In both studies, lycopene and β-cryptoxanthin were unassociated with breast cancer regardless of smoking status. Thus, two studies yielded similar inferences regarding interactions of smoking with specific carotenoids, despite some differences in the magnitude of associations and the significance of results related in part to the larger size of the current study. It is unclear why the association of carotenoids in breast cancer is limited to premenopausal women, although it may be related to the increasing cell turnover in breast epithelium under the influence of cyclic ovarian estrogen exposure,55, 56 and the greater susceptibility to breast carcinogens, and protection afforded by intervening exposures including dietary antioxidants. Taken together, the studies add support to the idea that carotenoids are protective agents in breast cancer under conditions of increased oxidative stress particularly in women exposed to higher levels of estrogen.

The current study had several strengths but also some important limitations that should be considered when interpreting the results. A strength of the study was the large sample size which enabled a more powerful analysis of diet main effects and higher-order interactions than in most previous studies. In particular, we were able to examine interactions of diet with smoking and alcohol consumption specifically in premenopausal women in whom these interactions are most plausible. However, as in all case-control studies, selection and recall bias are concerns. Response rates were reasonably high in cases and controls, and associations for other factors (Table 1) are consistent with the literature. Nevertheless, preferential enrollment of more health conscious younger women could have contributed to inverse associations observed with carotenoid vegetables. Women were asked to report their usual consumption of fruits and vegetables five years prior to their diagnosis in the cases or a comparable time referent in controls. Recall bias might have occurred if cases differentially recalled their fruit and vegetable consumption. The fruits and vegetables that were ascertained in this study were not established cancer protection factors at the time of the study, though these foods have long been suspected to confer health, and some bias in reporting may have occurred. However, as noted the overall results showing stronger associations in premenopausal women, and interactions by smoking have also been observed in the prospective Nurses' Health Study, which is not vulnerable to selection or recall bias. Random error in reporting diet would have biased associations towards the null.

The USDA database that we used to calculate individual carotenoids is the best currently available. Nevertheless, carotenoid content in food is influenced by a number of factors including, geographic location, season and harvesting methods. 39 Cooking method can also

influence carotenoid levels in foods. Earlier studies have shown that the bioavailability of carotenoids depends on the method in which the food was prepared. 57, 58 In some food products heating has been shown to improve the bioavailability of carotenoids. 57, 58 The lack of information on cooking methods may have contributed to non-differential error, attenuating associations. Another limitation of this study is that we did not have information on total energy intake, dietary fiber, or animal fat intake, both dietary fiber and animal fat may play a role in the body's ability to absorb carotenoids. We also lacked information on carotenoids and vitamin A from supplements. Women reported use of multivitamins; however, we did not inquire whether multivitamins contained β-carotene, which would have been a fairly common component of multivitamins in the era of the study. We also did not inquire about the use of other nutritional supplements including vitamin A. Use of multivitamins was similar in cases and controls (Table 1); misclassification on carotenoids and vitamin A from supplement use would most likely have biased the present results to the null. When analyses were limited to women who were non-supplement users the odds ratios for the individual carotenoids were similar in magnitude to the results in table 3 (data not shown). In this analysis we examined vitamin A intake from carotenoid rich fruits and vegetables and did not include foods that are fortified with vitamin A (i.e. dairy products and fortified cereals).

Breast cancer is a major public health concern, and few modifiable risk factors have been identified. The results of this analysis suggest that consumption of specific carotenoids and vitamin A may reduce the risk of breast cancer in premenopausal women, especially among smokers. Because of the high prevalence of smoking in younger women, further studies should be undertaken to better understand the biological mechanism through which the carotenoids are acting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Descriptive characteristics of invasive breast cancer cases (N= 5,707) and controls (N= 6,389)

	Cases		Controls		
	N[1]	%	N[1]	%	OR[2] (95% CI)
Age					
<50	2044	35.8	2238	35.0	1.0 (ref)
50–59	1955	34.3	2304	36.1	0.92 (0.84 – 1.00)
>59	1708	29.9	1847	28.9	1.00 (0.91 – 1.09)
Race					
Caucasian	5512	96.6	6110	95.6	1.0 (ref)
Not Caucasian	163	2.9	242	3.8	0.75 (0.62 – 0.90)
Education					
≥ 12 years	2566	45.1	2915	45.9	1.0 (ref)
1–3 years college	1496	26.3	1717	26.9	1.01 (0.93 – 1.11)
College graduate	1631	28.6	1742	27.3	1.12 (1.03 – 1.23)
Body mass index (kg/m^2)					
Premenopausal					
<24	1102	46.8	1131	43.9	1.0 (ref)
24–27	669	28.4	737	28.6	0.94 (0.81 – 1.07)
>27	584	24.8	707	27.5	0.82 (0.71 – 0.95)
Postmenopausal					
<24	973	31.5	1158	33.2	1.0 (ref)
24–27	1044	33.8	1142	32.7	1.07 (0.95 – 1.21)
>27	1069	34.6	1192	34.1	1.04 (0.92 – 1.17)
Age at menarche					
<12	1227	21.5	1284	20.1	1.0 (ref)
12–14	3827	67.1	4261	66.7	0.93 (0.85 – 1.02)
>14	595	10.4	785	12.3	0.78 (0.67 – 0.89)
Parity					

	Cases		Controls		
	N[1]	%	N[1]	%	OR[2] (95% CI)
Nulliparous	812	14.2	769	12.0	1.0 (ref)
1–2	2508	43.9	2567	40.2	0.92 (0.82 – 1.03)
>2	2381	41.7	3047	47.7	0.69 (0.61 – 0.77)
Menopausal status					
Premenopausal	2363	43.2	2594	42.0	1.0 (ref)
Postmenopausal	3110	56.8	3516	57.5	0.87 (0.77 – 0.97)
Family history of breast cancer					
No	4525	79.2	5536	86.7	1.0 (ref)
Yes	1150	20.1	817	12.8	1.58 (1.41 – 1.78)
History of benign breast disease					
No	3899	68.3	4885	76.5	1.0 (ref)
Yes	1752	30.7	1445	22.6	1.10 (1.06 – 1.15)
Recent alcohol consumption (drinks/week)					
0	983	17.2	1119	17.5	1.0 (ref)
<2	2526	44.3	3012	47.2	0.95 (0.86 – 1.05)
2 – <4	786	13.8	862	13.5	1.04 (0.91 – 1.18)
4+	1407	24.7	1391	21.8	1.18 (1.05 – 1.32)
Smoking					
Never smokers	2667	46.8	2945	46.3	1.0 (ref)
Ever smokers	3034	53.2	3437	53.8	1.00 (0.93 – 1.08)
Multivitamin use					
No	3166	56.9	3462	55.5	1.0 (ref)
Yes	2403	43.1	2782	44.5	0.94 (0.87 – 1.01)

[1]Column totals are unequal due to missing data

[2]Odds ratios are adjusted for age and state of residence

Table 2

Odds ratios and 95% confidence intervals for breast cancer according to servings of vegetables (5,707 cases and 6,389 controls)

	All women				Premenopausal			Postmenopausal		
	Cases 5707	**Controls 6389**	**OR[1]**	**OR[2]**	**Cases 2363**	**Controls 2594**	**OR[2]**	**Cases 3110**	**Controls 3516**	**OR[2]**
All fruits and vegetables										
<1 serving/day	269	306	1.0 (ref)	1.0 (ref)	141	152	1.0 (ref)	115	143	1.0 (ref)
1–<2 servings/day	1088	1222	1.00 (0.83 – 1.20)	1.01 (0.84 – 1.21)	527	546	1.07 (0.82 – 1.39)	507	616	0.98 (0.74 – 1.30)
2–<3 servings/day	1646	1815	1.01 (0.84 – 1.21)	1.01 (0.84 – 1.21)	685	733	1.03 (0.79 – 1.33)	901	1006	1.05 (0.80 – 1.37)
3–<4 servings/day	1346	1524	0.98 (0.82 – 1.18)	0.99 (0.82 – 1.19)	517	586	0.99 (0.76 – 1.29)	772	868	1.04 (0.79 – 1.36)
4–<5 servings/day	785	824	1.05 (0.87 – 1.27)	1.05 (0.87 – 1.28)	284	317	1.00 (0.75 – 1.34)	472	465	1.16 (0.87 – 1.55)
5 + servings/day	573	698	0.93 (0.76 – 1.13)	0.94 (0.76 – 1.15)	209	260	0.95 (0.70 – 1.28)	343	418	0.97 (0.72 – 1.30)
P for trend			0.60	0.24			0.14			0.88
All fruits										
< 4 servings/week	1384	1606	1.0 (ref)	1.0 (ref)	662	721	1.0 (ref)	653	806	1.0 (ref)
4 –<5 servings/week	359	404	1.01 (0.86 – 1.19)	1.03 (0.88 – 1.21)	163	156	1.13 (0.88 – 1.45)	184	225	1.00 (0.80 – 1.25)
5–<6 servings/week	319	365	0.99 (0.84 – 1.17)	0.99 (0.84 – 1.18)	137	161	0.95 (0.73 – 1.22)	165	192	1.01 (0.79 – 1.28)
6–<7 servings/week	312	287	1.21 (1.01 – 1.45)	1.24 (1.03 – 1.48)	141	132	1.15 (0.88 – 1.50)	149	139	1.30 (0.99 – 1.67)
1–<2 servings/day	2477	2785	1.02 (0.93 – 1.11)	1.03 (0.93 – 1.13)	987	1107	1.01 (0.88 – 1.17)	1403	1552	1.07 (0.93 – 1.22)
2+ servings/day	856	942	1.05 (0.93 – 1.18)	1.08 (0.95 – 1.22)	273	317	1.00 (0.82 – 1.22)	556	602	1.13 (0.96 – 1.32)
P for trend			0.47	0.82			0.44			0.27
Carotenoid rich vegetables										
< 4 servings/week	1027	1086	1.0 (ref)	1.0 (ref)	417	399	1.0 (ref)	572	644	1.0 (ref)
4–<5 servings/week	599	660	0.97 (0.84 – 1.11)	0.97 (0.84 – 1.11)	242	260	0.90 (0.72 – 1.13)	328	369	1.01 (0.83 – 1.22)
5–<6 servings/week	593	643	1.01 (0.87 – 1.16)	1.01 (0.88 – 1.17)	250	234	1.06 (0.84 – 1.33)	315	377	0.99 (0.81 – 1.19)
6–<7 servings/week	561	664	0.92 (0.80 – 1.06)	0.92 (0.80 – 1.07)	218	272	0.80 (0.64 – 1.01)	321	364	1.03 (0.85 – 1.25)
1–<2 servings/day	2285	2483	1.02 (0.92 – 1.13)	1.00 (0.90 – 1.12)	949	1065	0.89 (0.75 – 1.05)	1247	1306	1.11 (0.96 – 1.28)
2+ servings/day	642	653	0.86 (0.75 – 0.99)	0.83 (0.73 – 0.96)	287	364	0.83 (0.67 – 1.03)	327	456	0.84 (0.69 – 1.01)
P for trend			0.41	0.07			0.03			0.78
Cruciferous vegetables										

	All women				Premenopausal			Postmenopausal		
	Cases 5707	**Controls 6389**	**OR[1]**	**OR[2]**	**Cases 2363**	**Controls 2594**	**OR[2]**	**Cases 3110**	**Controls 3516**	**OR[2]**
<1 servings/week	1179	1298	1.0 (ref)	1.0 (ref)	569	579	1.0 (ref)	559	668	1.0 (ref)
1–<2 servings/week	1346	1548	0.96 (0.86 – 1.07)	0.95 (0.85 – 1.06)	555	646	0.88 (0.75 – 1.04)	743	835	1.03 (0.89 – 1.20)
2–<3 servings/week	1133	1327	0.93 (0.83 – 1.04)	0.91 (0.81 – 1.02)	466	545	0.86 (0.72 – 1.02)	627	719	0.99 (0.84 – 1.15)
3–<4 servings/week	729	762	1.04 (0.91 – 1.18)	1.04 (0.91 – 1.19)	275	281	1.01 (0.82 – 1.24)	421	451	1.07 (0.90 – 1.28)
4–<5 servings/week	471	519	0.98 (0.84 – 1.13)	0.96 (0.83 – 1.12)	173	191	0.91 (0.72 – 1.16)	280	305	1.05 (0.86 – 1.28)
5+ servings/week	849	935	0.97 (0.86 – 1.10)	0.97 (0.85 – 1.09)	325	352	0.96 (0.79 – 1.17)	480	538	1.00 (0.84 – 1.19)
P for trend			0.94	0.99			0.75			0.81

[1] Age and state adjusted

[2] Adjusted for age, state, family history of breast cancer, age at first birth, alcohol intake, education, age at menarche, benign breast disease, multivitamin use, body mass index, smoking (status and packyears), hormone replacement therapy, parity, menopausal status

Table 3

Odds ratio and 95% confidence interval for risk of breast cancer and quintiles of nutrients from carotenoid rich foods (5,707 cases and 6,389 controls)

	All women				Premenopausal (2,363 cases, 2,594 controls)			Postmenopausal (3,110 cases, 3,516 controls)		
	Cases	Controls	OR[1]	OR[2]	Cases	Controls	OR[2]	Cases	Controls	OR[2]
α-carotene										
Quintile 1	1134	1233	1.0 (ref)	1.0 (ref)	511	508	1.0 (ref)	569	662	1.0 (ref)
Quintile 2	1129	1306	0.93 (0.83 – 1.04)	0.94 (0.84 – 1.06)	494	556	0.90 (0.75 – 1.06)	585	684	0.99 (0.84 – 1.16)
Quintile 3	1158	1273	0.96 (0.86 – 1.08)	0.98 (0.88 – 1.09)	445	474	0.94 (0.79 – 1.13)	679	749	1.04 (0.89 – 1.21)
Quintile 4	1182	1246	1.01 (0.90 – 1.13)	1.00 (0.89 – 1.13)	466	508	0.92 (0.77 – 1.10)	657	690	1.06 (0.90 – 1.24)
Quintile 5	1104	1331	0.88 (0.78 – 0.98)	0.87 (0.77 – 0.98)	447	548	0.82 (0.68 – 0.98)	620	731	0.93 (0.79 – 1.09)
P for trend			0.17	0.11			0.07			0.62
β-carotene										
Quintile 1	1187	1193	1.0 (ref)	1.0 (ref)	544	492	1.0 (ref)	598	646	1.0 (ref)
Quintile 2	1122	1313	0.89 (0.79 – 0.99)	0.89 (0.79 – 1.00)	481	512	0.89 (0.74 – 1.06)	588	734	0.89 (0.76 – 1.04)
Quintile 3	1163	1285	0.95 (0.85 – 1.06)	0.95 (0.84 – 1.06)	464	531	0.84 (0.69 – 1.00)	657	703	1.03 (0.88 – 1.21)
Quintile 4	1158	1269	0.96 (0.86 – 1.08)	0.94 (0.84 – 1.06)	442	538	0.77 (0.64 – 0.92)	655	674	1.07 (0.91 – 1.25)
Quintile 5	1077	1329	0.88 (0.78 – 0.99)	0.85 (0.76 – 0.96)	432	521	0.81 (0.68 – 0.98)	612	759	0.87 (0.75 – 1.04)
P for trend			0.18	0.03			0.009			0.73
β-cryptoxanthin										
Quintile 1	1061	1297	1.0 (ref)	1.0 (ref)	489	548	1.0 (ref)	523	678	1.0 (ref)
Quintile 2	1161	1287	1.07 (0.95 – 1.20)	1.09 (0.97 – 1.22)	524	573	1.03 (0.86 – 1.23)	580	656	1.14 (0.97 – 1.35)
Quintile 3	1161	1249	1.11 (0.99 – 1.24)	1.11 (0.99 – 1.25)	514	534	1.11 (0.93 – 1.32)	599	657	1.14 (0.97 – 1.34)
Quintile 4	1117	1310	1.03 (0.92 – 1.16)	1.04 (0.93 – 1.17)	426	501	1.00 (0.83 – 1.20)	651	755	1.10 (0.93 – 1.29)
Quintile 5	1207	1246	1.17 (1.05 – 1.31)	1.19 (1.06 – 1.34)	410	438	1.11 (0.92 – 1.34)	757	770	1.25 (1.06 – 1.46)
P for trend			0.03	0.02			0.42			0.03
Vitamin A										
Quintile 1	1180	1197	1.0 (ref)	1.0 (ref)	542	500	1.0 (ref)	589	642	1.0 (ref)
Quintile 2	1130	1305	0.90 (0.80 – 1.01)	0.90 (0.80 – 1.01)	484	513	0.90 (0.75 – 1.08)	601	726	0.92 (0.78 – 1.07)
Quintile 3	1157	1284	0.95 (0.85 – 1.06)	0.94 (0.84 – 1.06)	451	513	0.87 (0.72 – 1.04)	656	718	1.01 (0.86 – 1.19)
Quintile 4	1166	1270	0.97 (0.86 – 1.08)	0.94 (0.84 – 1.06)	455	542	0.80 (0.67 – 0.96)	659	676	1.06 (0.90 – 1.24)

	All women				Premenopausal (2,363 cases, 2,594 controls)			Postmenopausal (3,110 cases, 3,516 controls)		
	Cases	Controls	OR[1]	OR[2]	Cases	Controls	OR[2]	Cases	Controls	OR[2]
Quintile 5	1074	1333	0.87 (0.78 – 0.98)	0.84 (0.74 – 0.94)	431	526	0.82 (0.68 – 0.98)	605	754	0.87 (0.74 – 1.03)
P for trend			0.13	0.02			0.01			0.48
Lutein/zeaxanthin										
Quintile 1	1153	1202	1.0 (ref)	1.0 (ref)	557	524	1.0 (ref)	550	618	1.0 (ref)
Quintile 2	1166	1280	0.97 (0.87 – 1.09)	0.97 (0.86 – 1.09)	495	483	1.01 (0.84 – 1.21)	622	741	0.96 (0.81 – 1.12)
Quintile 3	1160	1282	0.99 (0.88 – 1.11)	0.99 (0.88 – 1.11)	441	533	0.84 (0.70 – 1.00)	670	702	1.11 (0.95 – 1.30)
Quintile 4	1155	1296	1.02 (0.91 – 1.14)	1.00 (0.89 – 1.13)	459	519	0.91 (0.75 – 1.09)	649	724	1.09 (0.92 – 1.28)
Quintile 5	1073	1329	0.94 (0.84 – 1.06)	0.93 (0.82 – 1.05)	411	535	0.83 (0.68 – 0.99)	619	731	1.04 (0.88 – 1.23)
P for trend			0.61	0.39			0.02			0.26
Lycopene										
Quintile 1	1077	1257	1.0 (ref)	1.0 (ref)	281	344	1.0 (ref)	750	861	1.0 (ref)
Quintile 2	804	841	1.15 (1.01 – 1.31)	1.15 (1.01 – 1.31)	306	329	1.16 (0.93 – 1.46)	460	474	1.16 (0.99 – 1.37)
Quintile 3	1486	1715	1.04 (0.93 – 1.16)	1.05 (0.94 – 1.17)	592	682	1.07 (0.89 – 1.33)	842	967	1.05 (0.92 – 1.21)
Quintile 4	1178	1216	1.17 (1.04 – 1.32)	1.20 (1.06 – 1.35)	573	556	1.28 (1.07 – 1.61)	558	610	1.13 (0.97 – 1.33)
Quintile 5	1162	1360	1.02 (0.91 – 1.15)	1.03 (0.91 – 1.16)	611	683	1.10 (0.93 – 1.38)	500	604	1.00 (0.86 – 1.18)
P for trend			0.56	0.41			0.17			0.77

[1] Age and state adjusted

[2] Adjusted for age, state, family history of breast cancer, age at first birth, alcohol intake, education, age at menarche, benign breast disease, multivitamin use, body mass index, smoking (status and pack years), hormone replacement therapy, parity, menopausal status

[3] Ranges for quintiles of each carotenoid in mcg:
α-carotene: quintile1:< 1030.6, quintile2:1030.9 – 1927.2, quintile 3: 1927.3 – 3789.0, quintile 4: 3789.1 – 5685.8, quintile 5: > 5686.0
B-carotene: quintile1: < 6880.2, quintile 2: 6880.8 – 11227.6, quintile 3: 11231.5 – 16424.2, quintile 4: 16425.1 – 25013.7, quintile 5: >25022.9
Vitamin A: quintile 1:< 673.0, quintile 2: 673.4 – 1076.5, quintile 3: 1077 – 1550.9, quintile 4: 1551.1 – 2309.3, quintile 5: >2309.6
B-cryptoxanthin: quintile1: < 375.8, quintile2: 376.2 – 793.4, quintile3: 793.6 – 1310.9, quintile 4:1311.0 – 1652.9, quintile 5: > 1653.0
Lutein/zeaxanthin: quintile1: <3795.1, quintile 2: 3795.9 – 6432.7, quintile 3: 6434.3 – 10330.4, quintile 4: 10330.6 – 16453.3 quintile 5: > 16454.4
Lycopene: quintile 1: < 9996.0, quintile 2: 9996.6 – 19988.0, quintile 3: 19988.1 – 19990.9, quintile 4: 19991.5 – 39976.6, quintile 5: > 39976.7

Table 4

Multivariate adjusted odds ratios and 95% confidence interval for premenopausal breast cancer according to alcohol intake and smoking status for dietary carotenoids and vitamin A

	Alcohol[1]		Smoking[1]	
	< 2 drinks/wk	2 or more drinks/wk	Never	Ever
	1460 cases, 1643 controls	903 cases, 951 controls	1221 cases, 1313 controls	1137 cases, 1266 controls
α-carotene				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quintile 2	0.85 (0.68 – 1.06)	0.96 (0.71 – 1.29)	0.93 (0.72 – 1.21)	0.81 (0.64 – 1.04)
Quintile 3	1.00 (0.79 – 1.25)	0.84 (0.62 – 1.15)	1.07 (0.82 – 1.38)	0.81 (0.62 – 1.05)
Quintile 4	0.81 (0.65 – 1.02)	1.07 (0.79 – 1.45)	1.02 (0.79 – 1.31)	0.83 (0.64 – 1.07)
Quintile 5	0.76 (0.61 – 0.96)	0.91 (0.67 – 1.22)	0.90 (0.70 – 1.16)	0.72 (0.55 – 0.93)
P for trend	0.009	0.80	0.64	0.03
	P for interaction = 0.19		P for interaction = 0.14	
β-carotene				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quintile 2	0.86 (0.69 – 1.07)	0.95 (0.69 – 1.31)	0.86 (0.67 – 1.11)	0.92 (0.71 – 1.18)
Quintile 3	0.81 (0.65 – 1.01)	0.87 (0.64 – 1.19)	0.90 (0.70 – 1.15)	0.78 (0.60 – 1.02)
Quintile 4	0.74 (0.59 – 0.92)	0.84 (0.61 – 1.15)	0.81 (0.63 – 1.04)	0.73 (0.56 – 0.95)
Quintile 5	0.81 (0.64 – 1.02)	0.85 (0.62 – 1.16)	0.83 (0.64 – 1.08)	0.79 (0.61 – 1.03)
P for trend	0.007	0.21	0.14	0.02
	P for interaction = 0.40		P for interaction = 0.32	
β-cryptoxanthin				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quintile 2	1.09 (0.87 – 1.35)	0.92 (0.69 – 1.23)	1.10 (0.85 – 1.43)	0.95 (0.75 – 1.21)
Quintile 3	1.16 (0.93 – 1.45)	1.03 (0.77 – 1.39)	1.24 (0.96 – 1.61)	1.02 (0.79 – 1.31)
Quintile 4	1.02 (0.81 – 1.29)	0.93 (0.69 – 1.26)	1.18 (0.90 – 1.54)	0.85 (0.65 – 1.10)
Quintile 5	1.15 (0.91 – 1.46)	1.04 (0.76 – 1.43)	1.15 (0.88 – 1.51)	1.12 (0.85 – 1.47)
P for trend	0.80	0.78	0.29	0.85
	P for interaction = 0.72		P for interaction = 0.38	
Vitamin A				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quintile 2	0.94 (0.76 – 1.17)	0.85 (0.62 – 1.16)	0.91 (0.71 – 1.17)	0.89 (0.69 – 1.15)
Quintile 3	0.83 (0.67 – 1.04)	0.90 (0.66 – 1.23)	0.90 (0.70 – 1.16)	0.84 (0.65 – 1.09)
Quintile 4	0.76 (0.61 – 0.95)	0.87 (0.64 – 1.19)	0.81 (0.64 – 1.05)	0.80 (0.61 – 1.03)
Quintile 5	0.86 (0.67 – 1.07)	0.79 (0.57 – 1.07)	0.88 (0.68 – 1.15)	0.75 (0.58 – 0.97)
P for trend	0.009	0.21	0.21	0.02
	P for interaction = 0.73		P for interaction = 0.16	
Lutein/zeaxanthin				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

	Alcohol[1]		Smoking[1]	
	< 2 drinks/wk	**2 or more drinks/wk**	**Never**	**Ever**
	1460 cases, 1643 controls	**903 cases, 951 controls**	**1221 cases, 1313 controls**	**1137 cases, 1266 controls**
Quintile 2	1.04 (0.84 – 1.29)	0.94 (0.68 – 1.29)	1.04 (0.81 – 1.33)	0.96 (0.72 – 1.25)
Quintile 3	0.79 (0.63 – 0.98)	0.86 (0.63 – 1.18)	0.77 (0.60 – 0.99)	0.88 (0.67 – 1.14)
Quintile 4	0.91 (0.73 – 1.13)	0.85 (0.62 – 1.17)	0.94 (0.73 – 1.22)	0.83 (0.64 – 1.07)
Quintile 5	0.82 (0.65 – 1.04)	0.78 (0.57 – 1.07)	0.80 (0.61 – 1.05)	0.80 (0.62 – 1.05)
P for trend	0.02	0.11	0.07	0.06
	P for interaction = 0.33		P for interaction = 0.61	
Lycopene				
Quintile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quintile 2	1.30 (0.99 – 1.72)	0.91 (0.61 – 1.36)	1.14 (0.83 – 1.58)	1.16 (0.85 – 1.60)
Quintile 3	1.20 (0.94 – 1.53)	0.87 (0.61 – 1.23)	1.08 (0.81 – 1.44)	1.10 (0.83 – 1.45)
Quintile 4	1.39 (1.08 – 1.78)	1.14 (0.79 – 1.63)	1.39 (1.03 – 1.86)	1.23 (0.92 – 1.63)
Quintile 5	1.35 (1.05 – 1.72)	0.81 (0.58 – 1.15)	1.22 (0.92 – 1.62)	1.04 (0.78 – 1.37)
P for trend	0.04	0.51	0.08	0.81
	P for interaction = 0.01		P for interaction = 0.22	

[1]Odds ratios are adjusted for age, state, family history of breast cancer, age at first birth, alcohol intake, education, age at menarche, benign breast disease, multivitamin use, body mass index, smoking (status and pack years), and parity