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Premenopausal Breast Cancer Risk and Intake of Vegetables, Fruits, and Related Nutrients

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Background: **Given the international variations in breast cancer incidence rates and the changes in breast cancer incidence among migrant populations, it has been hypothesized that diet is a factor influencing risk of this disease. Many studies indicate that a diet high in vegetables and fruits may protect against breast cancer.** ***Purpose:*** **We conducted a case–control study of diet, including the intake of non-food supplements, and premenopausal breast cancer risk. We evaluated in detail usual intake of vegetables and fruits (each measured as the total reported grams consumed for all queried vegetables and fruit), vitamins C and E, folic acid, individual carotenoids, and dietary fiber with its components.** ***Methods:*** **Case patients (n = 297) were identified through pathology records from hospitals in Erie and Niagara counties in western New York. They consisted of premenopausal women 40 years of age or older who were diagnosed with breast cancer from November 1986 through April 1991. Control subjects (n = 311), frequency-matched to case patients on the basis of age and county of residence, were randomly selected from New York State Department of Motor Vehicles records. In-person interviews included detailed reports of usual diet in the period 2 years before the interview. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).** ***Results:*** **There was a reduction in risk associated with high intake of several nutrients. With the lowest quartile of intake as the referent, adjusted ORs for the highest quartile of intake for specific nutrients were as follows: vitamin C (OR = 0.53; 95% CI - 0.33-0.86), α-tocopherol (OR = 0.55; 95% CI = 0.34-0.88), folic acid (OR = 0.50; 95% CI = 0.31-0.82), α-carotene (OR = 0.67; 95% CI = 0.42-1.08) and β-carotene (OR = 0.46; 95% CI = 0.28-0.74), lutein + zeaxanthin (OR = 0.47; 95% CI = 0.28-0.77), and dietary fiber from vegetables and fruits (OR = 0.48; 95% CI = 0.30-0.78). No association with risk was found for β-cryptoxanthin, lycopene, or grain fiber. Fruits were weakly associated with a reduction in risk (fourth quartile OR = 0.67; 95% CI = 0.42-1.09). No association was found between breast cancer risk and intake of vitamins C and E and folic acid taken as supplements. A strong inverse association between total vegetable intake and risk was observed (fourth quartile OR = 0.46; 95% CI = 0.28-0.74). This inverse association was found to be independent of vitamin C, α-tocopherol, folic acid, dietary fiber, and α-carotene. Adjusting for β-carotene or lutein + zeaxanthin somewhat attenuated the inverse association with vegetable intake.** ***Conclusions:*** **In this population, intake of vegetables appears to decrease premenopausal breast cancer risk. This effect may be related, in part, to β-carotene and lutein + zeaxanthin in vegetables. It appears, however, that, of the nutrients and food components examined, no single dietary factor explains the effect. Evaluated components found together in vegetables may have a synergistic effect on breast cancer risk; alternatively, other unmeasured factors in these foods may also influence risk. [J Natl Cancer Inst 1996;88:340-8]**

Given the international variation in breast cancer incidence rates and the changes in incidence among migrant populations (*1*), it has been hypothesized that diet is a factor influencing risk of this disease. There has been considerable attention paid to the hypothesis that fat intake is related to increased risk of breast cancer (*2*). While less research has focused on other dietary constituents, a number of studies (*3-9*) would appear to indicate that a diet high in vegetables and fruits may protect against breast cancer. While a few studies (*10-12*) have failed to find a relation, the finding of a protective effect of fruits and vegetables is relatively consistent and, therefore, provocative in terms of breast cancer prevention. The role of vegetables, fruits, and the nutrients and other dietary components found in these foods re-

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quires further attention. In particular, while there is evidence that the carotenoids are associated with a reduced risk of breast cancer (*8,9,13-18*), the relation of individual carotenoids to risk has not been examined. Furthermore, the extent to which risk is explained by individual nutrients and food components and the extent to which any protective effect of vegetables and fruits is not explained by those nutrients require further attention. We conducted a case–control study of diet, including the intake of non-food supplements, and premenopausal breast cancer risk; we evaluated in detail usual intake of vegetables, fruits, vitamins C and E, folic acid, individual carotenoids, and dietary fiber with its components.

Subjects and Methods

This study was conducted as part of a series of case–control studies, all using the same Western New York Diet Study Questionnaire that had diet as the main topic discussed during the interview, examining factors related to risk of premenopausal and postmenopausal breast cancer, endometrial cancer, and ovarian cancer. Included in this study as case patients were both premenopausal and postmenopausal women who lived in Erie and Niagara counties, were 40-85 years old, and were diagnosed with primary, histologically confirmed breast cancer during the period from November 1986 through April 1991. Women were considered to be premenopausal if they were currently menstruating or, if they were not menstruating because of a hysterectomy or other medical intervention, if they had at least one ovary and were under age 50. Because there is evidence that premenopausal and postmenopausal breast cancer etiologies may differ, the study was designed to examine the two groups separately. This article is limited to premenopausal women; findings regarding postmenopausal women have been reported elsewhere (*14*).

Identification of Case Patients and Control Subjects

All case patients and control subjects were white; at the time of the study design, black women were not included because they constituted 10% of incident cases and the numbers of cases accrued within the time frame of the study would not have been sufficient for analysis of risk. All participants provided written, informed consent; procedures for protection of human subjects in this study were approved by the Human Subjects Review Board of the State University of New York at Buffalo (School of Medicine and Biomedical Sciences) and all the participating hospitals. This approval was in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Cases were identified from pathology records of all the major hospitals in the two counties. When a case was identified, the patient's physician was notified and was asked permission to interview the patient. Of eligible case patients, we were able to interview 66%. In most instances (74%), failure to secure an interview resulted from physician refusal to allow contact with the patient. The average time between diagnosis and interview was about 2 months. A total of 301 women with premenopausal breast cancer were included in the study; for the adjusted analyses, there were 297 cases with complete data for all the variables.

Control subjects were selected from residents of the two counties and were frequency matched to the case patients on age and county of residence. Control subjects were randomly selected from the New York State Department of Motor Vehicles records. (Approximately 94% of the eligible case patients in this study held a driver's license.) Of control subjects contacted, we were able to interview 62%, for a total of 316 control subjects (311 included in the adjusted analyses). The lack of response among control subjects has potential for bias. To determine the extent of that bias, we conducted a short interview at the time of initial telephone contact with a subset of control subjects, both those agreeing and those not agreeing to participate in the study. Results of that short interview are shown in Table 1. Because this very brief interview was done at the initial contact, and the intent was to quickly characterize participants and nonparticipants, we did not ascertain menopausal status. Among women below the age of 50 years, 184 participants answered this interview, and 11 refused. Fifty-two nonparticipants answered the brief questions; 41 refused to answer even these few questions. Participants and nonparticipants gave virtually identical responses to questions regarding diet. Smokers tended to be somewhat less likely to participate.

Table 1. Assessment of response bias: comparison of telephone responses at time of contact for selected characteristics of participating and nonparticipating control subjects*

	Mean (standard deviation)	
	Participants	Nonparticipants
Coffee, cups/day	3.7 (3.4)	3.8 (4.1)
Meat, times/wk	4.7 (2.2)	4.8 (2.2)
Vegetables, times/wk	5.2 (2.3)	5.3 (3.5)
Fruit, times/wk	4.8 (2.5)	5.1 (2.9)
Current smokers, %	27.6	39.2

*Based on a sample of participating and nonparticipating eligible control subjects younger than 50 years. Of participants queried, 184 answered the questions and 11 refused; of nonparticipants queried, 52 answered and 41 refused.

Because control subjects were all holders of a driver's license, we asked the case patients whether they held a driver's license. Nine case patients did not have a license. They did not differ from the other case patients in terms of diet (e.g., mean intake of kilocalories, vegetables, or fruit) or age at first birth. They were significantly less educated and slightly, though not statistically significantly, older (data not shown). Those women without licenses were included in these analyses.

Personal Interviews

Interviews were limited to women who were alert, able to speak English, and well enough to be interviewed. All participants were interviewed in their homes by trained interviewers. The interview lasted, on average, 2 hours. Included in the interview were questions relating to diet, family history of cancer, medical and reproductive histories, and other factors relating to lifestyle and occupation. Body mass index (BMI) was by self-report and was expressed as weight in kilograms/height (in meters)^2 for the time point 2 years prior to interview. Family history of breast cancer was defined as having at least one first-degree relative (mother, sister, or daughter) with breast cancer.

Diet was assessed by a detailed series of questions regarding frequency and quantity of usual intake of 172 foods in the year 2 years before the interview. Questions included information on portion size relative to food models, food preparation, and seasonality of intake. Details regarding interviewing quality control, the questionnaire, and its reliability have been reported elsewhere (*19-21*). The focus of this article is on the effect of vegetables and fruits and related nutrients and food components; not included in this discussion is any association with macronutrients, although macronutrients were examined for their role as potential confounders.

Nutrient Composition Data

Nutrient composition of foods was calculated by use of data from the U.S. Department of Agriculture data tapes and published food composition tables (*22,23*), as well as other published food composition data (*22-27*). For missing values, composition values were imputed from similar foods. Food composition data for individual carotenoids were based on data for more than 2300 fruits, vegetables, and multi-ingredient foods from the U.S. Department of Agriculture (*28,29*). These values were limited to carotenoids in vegetables and fruits and did not include those in animal products. Composition values for lutein and zeaxanthin were reported as a combined total. Intakes of individual carotenoids calculated using this food composition database were compared with concurrent plasma carotenoid measures. Correlations for intake measures based on either a food-frequency questionnaire or a 7-day food record compared with blood measures were relatively high, on the order of .3 to .5 (*30*).

An index of total vegetable intake, in grams, was calculated from each participant's interview based on queries regarding usual intake of 31 vegetables. The index of vegetables did not include mixed foods that contain vegetables (e.g., spaghetti, lasagna, or pizza), and it did not contain white potatoes. When potatoes were included in the vegetable index, results were similar, although the overall intake in each category was higher. Total fruit intake was based on a question regarding usual intake of 21 fruits.

Statistical Analysis

Risk of breast cancer in each category relative to the indicated referent category was estimated with odds ratios (ORs) and 95% confidence intervals (CIs), calculated with unconditional logistic regression (*31*). Crude ORs and ORs adjusting for other potential confounders were examined for quartiles of intake with the low-intake group as the referent. Adjusted analyses included control for age, education, age at menarche, and BMI as continuous variables; categorical variables were used for adjustment for first-degree relative with breast cancer (yes/no), previous benign breast disease (yes/no), and age at first birth (four dummy variables: never, age 20-21 years, age 22-25 years, and age 26-39 years). For categorical analyses, cutoffs for quartiles were determined, to the extent possible, by even distribution of the control subjects to four categories. Tests for trend for each nutritional variable were computed from the *P* value of the logistic regression of the continuous variable with appropriate covariates (*32*). Such a test allows for examination of the trend in the entire range of intakes with control for potential confounders. All reported *P* values for trend are for two-tailed statistical tests. Kilocalorie-adjusted nutrients were calculated by the method of regression residuals described by Willett and Stampfer (*33*).

Results

The risk patterns associated with total intake of vegetables and of fruit in grams are shown in Table 2. Because all intakes were calculated from a food-frequency questionnaire, caution should be exercised in the interpretation of the quantities presented. While food-frequency questionnaires have been shown to be valid and reliable for the ranking of individuals in terms of consumption, they are less valid for the quantification of intake (*34*). Risk in the upper quartile of vegetable intake (intake of more than approximately five servings per day) was less than half that for the referent group (intake of less than approximately three servings per day) (adjusted OR = 0.46; 95% CI = 0.28-0.74). There was a weaker reduction in risk associated with the fourth quartile of fruit intake (adjusted OR = 0.67; 95% CI = 0.42-1.09).

We also examined risk associated with each of the food items in the questionnaire. With adjustment for nondietary risk factors, among vegetables and fruits queried, we observed decreases in risk associated with intakes of tomatoes, spinach, greens, corn, carrots, summer squash, cucumbers, melons (other than cantaloupe), berries, apples, pears, raisins, lemon, and lime.

To identify if particular nutrients explained the associations seen for vegetables and fruits, we examined several nutrients and food components for their relation to risk. Adjusted risks associated with intake of vitamin C, α-tocopherol, folic acid, and dietary fiber were calculated (Table 3). There was a similar decrease in risk associated with increasing intakes of all of these dietary components, an adjusted OR on the order of 0.50 for the fourth quartile.

We examined risk of premenopausal breast cancer associated with the components of dietary fiber (i.e., risk associated with intake of neutral detergent residue, hemicellulose, cellulose, and lignin). These components were highly statistically correlated with total dietary fiber and with each other; correlations ranged from $r = .80$ to $r = .95$. ORs were similar for each of these components, on the order of 0.60 (data not shown). However, when we examined the food source of the fiber, the decrease in risk associated with dietary fiber was explained by intake of fiber from vegetables and fruit and not by grain fiber intake (Table 3).

ORs associated with intake of specific carotenoids are shown in Table 4. There was a strong protective effect associated with higher intakes of α-carotene and β-carotene and of lutein + zeaxanthin. There was little evidence of any association of risk with intake of β-cryptoxanthin or lycopene.

In Table 5, risks associated with intake of some of these nutrients as supplements are shown. Very few participants (five case patients and six control subjects) took supplemental β-carotene, so that nutrient is not included. There was no relation apparent for intake of vitamin C, α-tocopherol, or folic acid as supplements with risk of breast cancer. When total intakes of these three nutrients were calculated by combining diet and supplement intakes, observed risks were somewhat attenuated compared with the risks associated with dietary intake alone (data not shown).

Next, we investigated the extent to which risk reductions seen for these nutrients were independent of total vegetable intake. In Table 6, the risk associated with each dietary component adjusted for total vegetable intake is shown. The associations were

Table 2. Risk of premenopausal breast cancer associated with total intake of vegetables and fruit: western New York, November 1986 through April 1991

Quartile	No. of case patients	No. of control subjects	Crude odds ratio	Adjusted*	
				Odds ratio	95% confidence interval
Vegetables (g/day)					
1 (≤276)	107	78	1.00†	1.00†	
2 (277-382)	74	79	0.68	0.80	0.51-1.24
3 (383-522)	71	77	0.67	0.65	0.41-1.03
4 (≥523)	45	77	0.43	0.46	0.28-0.74
Trend‡				*P*<.001	
Fruit (g/day)					
1 (≤204)	83	79	1.00†	1.00†	
2 (205-332)	75	77	0.93	0.96	0.61-1.50
3 (333-483)	84	79	1.01	0.82	0.51-1.31
4 (≥484)	55	76	0.69	0.67	0.42-1.09
Trend‡				*P* = .05	

*Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, and kilocalories by residuals (*33*); quartile cutoffs shown are without adjustment for kilocalories.

†Referent group.

‡*P* value for trend calculated from coefficient from logistic regression adjusted as above with nutrient as a continuous variable; values are negative unless otherwise indicated.

Table 3. Risk of premenopausal breast cancer associated with intake of selected nutrients: western New York, November 1986 through April 1991

Quartile	No. of case patients	No. of control subjects	Crude odds ratio	Adjusted*	
				Odds ratio	95% confidence interval
Vitamin C (mg/day)					
1 (≤131)	91	79	1.00†	1.00†	
2 (132-176)	84	77	0.95	0.87	0.56-1.36
3 (177-223)	64	76	0.73	0.70	0.44-1.12
4 (≥224)	58	79	0.64	0.53	0.33-0.86
Trend‡				*P* = .03	
α-Tocopherol (mg/day)					
1 (≤6)	104	75	1.00†	1.00†	
2 (7-8)	70	88	0.57	0.69	0.44-1.09
3 (9-10)	54	65	0.60	0.84	0.54-1.32
4 (≥11)	69	83	0.60	0.55	0.34-0.88
Trend‡				*P* = .03	
Folic acid (μg/day)					
1 (≤304)	100	79	1.00†	1.00†	
2 (305-367)	73	74	0.78	0.91	0.58-1.42
3 (368-459)	69	78	0.70	0.76	0.48-1.21
4 (≥460)	55	80	0.54	0.50	0.31-0.82
Trend‡				*P* = .009	
Dietary fiber (g/day)					
1 (≤21)	96	77	1.00†	1.00†	
2 (22-27)	85	84	0.81	0.87	0.56-1.36
3 (28-32)	54	68	0.64	0.58	0.36-0.92
4 (≥33)	62	82	0.61	0.52	0.32-0.85
Trend‡				*P* = .001	
Fruit and vegetable fiber (g/day)					
1 (≤15)	113	83	1.00†	1.00†	
2 (16-19)	76	78	0.72	0.74	0.48-1.15
3 (20-24)	56	76	0.54	0.51	0.32-0.81
4 (≥25)	52	74	0.52	0.48	0.30-0.78
Trend‡				*P*<.001	
Grain fiber (g/day)					
1 (≤5)	85	89	1.00†	1.00†	
2 (6)	34	54	0.66	0.91	0.56-1.47
3 (7-9)	103	87	1.24	1.16	0.73-1.84
4 (≥10)	75	81	0.97	1.03	0.64-1.65
Trend‡				*P* = .55 (+)	

*Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, and kilocalories by residuals (*33*); quartile cutoffs shown are without adjustment for kilocalories.

†Referent group.

‡*P* value for trend calculated from coefficient from logistic regression adjusted as above with nutrient as a continuous variable; values are negative unless otherwise indicated; (+) = positive.

weaker, with all fourth quartile CIs including the null value. For β-carotene and for lutein + zeaxanthin, there remained evidence of a statistically significant negative trend after adjusting for total vegetable intake, although CIs for fourth quartile ORs included the null.

In Table 7 are shown estimates of risk associated with vegetable intake after adjusting for the other dietary components. Adjusting for vitamin C, α-tocopherol, folic acid, dietary fiber, or α-carotene did not substantially alter the relation of intake of vegetables to risk; trends remained strong. However, adjusting for β-carotene or lutein + zeaxanthin resulted in less strong risk estimates for vegetable intake. Fourth quartile ORs (95% CIs) were 0.84 (0.43-1.63) and 0.76 (0.41-1.44), and *P*-values for trend were .24 and. 15, respectively.

Discussion

In this case–control study of premenopausal breast cancer, we found a strong protective effect associated with usual intake of vegetables and a less strong association with fruit intake. Among individual nutrients and other food components found in vegetables and fruits, we observed reductions in risk associated with vitamin C, α-tocopherol, folic acid, α-carotene, β-carotene, lutein + zeaxanthin, and fiber from vegetables and fruits. The effect of increased intake appeared similar for most of these, although there was some indication that β-carotene and lutein + zeaxanthin were more independently related to risk than were the other factors. No association with risk was observed for β-cryptoxanthin, lycopene, or grain fiber.

A number of other researchers (*3-9*) have found protective effects of vegetable intake for premenopausal and postmenopausal breast cancer, although a few (*10-12*) have not. The results of studies of individual nutrients associated with fruit and vegetable intake have been mixed. Some studies have found protective effects for vitamin A (*12,13,35*), carotenoids (*8,9,13-18*), vitamin E (*36*), vitamin C (*14,37*), and fiber (*7,8,14,15,37-39*). Other studies report no effect for dietary vitamin A (*16,40*),

Table 4. Risk of premenopausal breast cancer associated with intake of carotenoids from fruits and vegetables: western New York, November 1986 through April 1991

Quartile	No. of case patients	No. of control subjects	Crude odds ratio	Adjusted*	
				Odds radio	95% confidence interval
α-Carotene (μg/day)					
1 (≤625)	108	78	1.00†	1.00†	
2 (626-959)	68	78	0.63	0.82	0.52-1.28
3 (960-1554)	62	77	0.58	0.77	0.48-1.22
4 (≥1555)	59	78	0.55	0.67	0.42-1.08
Trend‡				*P* = .002	
β-Carotene (μg/day)					
1 (≤3965)	99	79	1.00†	1.00†	
2 (3966-5624)	77	77	0.80	0.78	0.50-1.21
3 (5625-7945)	68	77	0.70	0.65	0.41-1.03
4 (≥7946)	53	78	0.54	0.46	0.28-0.74
Trend‡				*P*<.001	
β-Cryptoxanthin (μg/day)					
1 (≤47)	81	78	1.00†	1.00†	
2 (48-102)	71	78	0.88	0.87	0.54-1.39
3 (103-185)	69	78	0.85	1.02	0.64-1.62
4 (≥186)	76	77	0.95	1.05	0.65-1.67
Trend‡				*P* = .89 (+)	
Lycopene(μg/day)					
1 (≤3775)	98	80	1.00†	1.00†	
2 (3776-5171)	62	78	0.65	1.01	0.64-1.57
3 (5172-7122)	58	76	0.62	0.64	0.40-1.04
4 (≥7123)	79	77	0.84	0.87	0.55-1.39
Trend‡				*P* = .24	
Lutein + zeaxanthin (μg/day)					
1 (≤3652)	103	79	1.00†	1.00†	
2 (3653-5036)	75	79	0.73	1.01	0.65-1.56
3 (5037-7161)	71	76	0.72	0.79	0.50-1.25
4 (≥7162)	48	77	0.48	0.47	0.28-0.77
Trend‡				*P*<.001	

*Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, and kilocalories by residuals (*33*); quartile cutoffs shown are without adjustment for kilocalories.

†Referent group.

‡*P* value for trend calculated from coefficient from logistic regression adjusted as above with nutrient as a continuous variable; values are negative unless otherwise indicated; (+) = positive.

Table 5. Risk of premenopausal breast cancer associated with vitamin supplement intake: western New York, November 1986 through April 1991

Quartile	No. of case patients*	No. of control subjects*	Crude odds ratio	Adjusted†	
				Odds ratio	95% confidence interval
Vitamin C daily (mg)					
1 (0)	134	139	1.00‡	1.00‡	
2 (1-47)	37	43	0.89	0.87	0.52-1.48
3 (48-263)	59	66	0.93	0.89	0.57-1.39
4 (≥264)	60	60	1.04	0.98	0.62-1.54
Trend§				*P* = .81	
α-Tocopherol daily (mg)					
1 (0)	141	153	1.00‡	1.00‡	
2 (1-29)	36	49	0.80	0.76	0.46-1.27
3 (30)	64	59	1.18	1.04	0.67-1.62
4 (≥31)	50	48	1.13	0.95	0.58-1.55
Trend§				*P* = .99	
Folic acid daily (μg)					
1 (0)	154	159	1.00‡	1.00‡	
2 (1-399)	42	55	0.79	0.81	0.50-1.30
3 (≥400)	96	96	1.03	0.97	0.67-1.42
Trend§				*P* = .98	

*Total numbers of case patients and of control subjects differ from the rest of the study because of missing values for supplement use for some participants.

†Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, and dietary intake of that nutrient.

‡Referent group.

§*P* value for trend calculated from coefficient from logistic regression adjusted as above with nutrient as a continuous variable; values are negative unless otherwise indicated.

Table 6. Risk of premenopausal breast cancer associated with several dietary components, adjusting for total vegetable intake: western New York, November 1986 through April 1991

Dietary component	Odds ratios (95% confidence interval)*			Trend†
	Second quartile	Third quartile	Fourth quartile	
Vitamin C	1.01 (0.64-1.59)	0.90 (0.54-1.48)	0.85 (0.47-1.55)	.46 (+)
α-Tocopherol	0.71 (0.45-1.13)	0.94 (0.60-1.49)	0.71 (0.43-1.17)	.34
Folic acid	1.05 (0.66-1.67)	0.94 (0.58-1.52)	0.76 (0.43-1.37)	.50
Dietary fiber	0.97 (0.62-1.53)	0.71 (0.43-1.16)	0.81 (0.45-1.46)	.09
α-Carotene	0.87 (0.55-1.38)	0.96 (0.59-1.57)	1.06 (0.62-1.81)	.18
β-Carotene	0.86 (0.55-1.35)	0.80 (0.48-1.33)	0.71 (0.38-1.34)	.02‡
Lutein + zeaxanthin	1.14 (0.72-1.80)	1.01 (0.61-1.67)	0.74 (0.39-1.42)	.04‡

*Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, kilocalories by residuals (*33*), and total vegetable intake.

†*P* value for trend calculated from the coefficient from logistic regression adjusted as above with the dietary component as a continuous variable; values are negative unless otherwise indicated; (+) = positive.

‡Cautious interpretation of this trend is in order, since confidence intervals for fourth quartile ORs included the null.

carotenoids (*11,36,40*), vitamin E (*7,11,13*), vitamin C (*12,13*), or fiber (*41*).

Plausible mechanisms of action can be proposed for each of the observed associations. The action of vitamin C may be related to its function as an antioxidant and to its action on the immune system. In a meta-analysis of breast cancer case–control studies, Howe et al. (*42*) found the most consistent decrease in risk associated with vitamin C intake, although the effect was more pronounced for postmenopausal women than for premenopausal women. In the Nurses' Health Study (*13*), no effect of vitamin C was found. While we found a decreased risk associated with vitamin C from foods, no such effect was seen for vitamin C supplements. Rohan et al. (*7*) also found no effect of vitamin C supplementation. These results suggest that the observed effect may be the result of other factors associated with vitamin C, that the vitamin C has an effect only in combination with other food components, or that intake at the level of supplementation does not affect risk.

Vitamin E could have a role in inhibiting cancer via its action as an antioxidant, as well as its potential effects on selenium, nitrosamine formation, and expression of certain oncogenes (*43*). We found a drop in risk associated with food sources of vitamin E but again not with supplements. Vitamin E is found concentrated in foods such as oils and grains, which were not included in the vegetable index. When vitamin E was adjusted for that vegetable index, the risk associated with vitamin E was attenuated. It appeared that the apparent protective effect was explained for the most part by vegetable intake.

Folic acid may diminish neoplastic changes. Folate is important in methylation of thymidylate for DNA synthesis, the biosynthesis of purines, and for DNA methylation. The latter may affect gene regulation. There is some evidence of differences in methylation status of the estrogen receptor gene in normal breast tissue compared with breast tumor tissue (*44*). Also of potential relevance to breast cancer is the relation between folate and alcohol intake. High levels of alcohol intake have been shown to decrease folate utilization (*45*). In that there is evidence suggesting that alcohol increases breast cancer risk (*46*), it may be that the observed effect involves folic acid. Folic acid has not been well studied for an effect related to breast cancer. We found evidence of a reduced risk associated with folic acid; there was no effect observed for folate supplement intake.

Dietary fiber may affect breast cancer risk by decreasing reabsorption in the gut of estrogen excreted in the biliary system (*47,48*). While other studies (*6,7,14,15,37-39*) have found a protective effect associated with dietary fiber for breast cancer, none of these studies has examined fiber by food source. While a short-term intervention with increased wheat bran resulted in lower serum estrogen levels (*49*), we found the association of risk with fiber to be confined to fiber from fruits and vegetables

Table 7. Risk of premenopausal breast cancer associated with vegetable intake, adjusting for other dietary components: western New York, November 1986 through April 1991

Adjusting component	Odds ratios for vegetable intake (95% confidence interval)*			Trend†
	Second quartile	Third quartile	Fourth quartile	
Vitamin C	0.80 (0.51-1.26)	0.65 (0.40-1.07)	0.46 (0.25-0.85)	.001
α-Tocopherol	0.81 (0.52-1.27)	0.66 (0.42-1.05)	0.47 (0.29-0.78)	<.001
Folic acid	0.82 (0.52-1.29)	0.69 (0.43-1.10)	0.50 (0.29-0.87)	.002
Dietary fiber	0.83 (0.53-1.30)	0.70 (0.44-1.12)	0.53 (0.31-0.91)	.003
α-Carotene	0.86 (0.55-1.36)	0.72 (0.45-1.16)	0.60 (0.34-1.06)	.01
β-Carotene	0.93 (0.59-1.48)	0.85 (0.52-1.41)	0.84 (0.43-1.63)	.24
Lutein + zeaxanthin	0.89 (0.57-1.40)	0.84 (0.51-1.38)	0.76 (0.41-1.44)	.15

*Adjusted for age, education, age at first birth, age at menarche, first-degree relative with breast cancer, previous benign breast disease, body mass index, kilocalories by residuals (*33*), and each listed dietary component.

†*P* value for trend calculated from the coefficient from logistic regression adjusted as above with the dietary component as a continuous variable; values are negative unless otherwise indicated.

and no protective effect associated with grain fiber intake. Fruit and vegetable fiber differs from grain fiber in its chemistry as well as in its association of intake with other vegetable components.

There has been considerable discussion of carotenoids as potential chemopreventive agents (*50*). To our knowledge, no one has examined individual carotenoids in diet other than β-carotene in relation to breast cancer epidemiology. While dietary intake of the carotenoids tends to be associated, the carotenoids do differ in their antioxidant activities, in their provitamin A capacity, and in their food sources (*50*). In this population, we found the protective effect to be limited to α-carotene, β-carotene, and lutein + zeaxanthin; β-cryptoxanthin and lycopene were not associated with risk. While there was a weak protective effect associated with tomato intake for the query related to intake of tomatoes either raw or cooked, the lycopene index included a number of other foods that were not found to be related to risk. In an examination of risk in relation to blood carotenoids, Potischman et al. (*16*) also found a protective effect associated with β-carotene levels but not with acarotene or lycopene levels. The major sources of β-carotene in U.S. diets are carrots, cantaloupe, and broccoli; spinach, other greens, and broccoli are major contributors of lutein + zeaxanthin (*29*). This finding of a lack of an effect of lycopene might argue against the mechanism of action of carotenoids being an antioxidant effect; the singlet oxygen quenching by lycopene appears to be substantially higher than that of β-carotene (*51*). It may also be that the other dietary contributors to lycopene, items including pizza, lasagna, and spaghetti (items which were not associated with risk in this study), may be related in some other way, either in terms of the other ingredients or in terms of associated behaviors, to factors that are not protective. While the lack of an effect associated with β-cryptoxanthin intake may have been because of low variation in intake, it would also argue against the action being a vitamin A effect in that our data showed that β-cryptoxanthin, which also has provitamin activity, did not appear to decrease risk. Furthermore, we did not see any effect of preformed retinol. Other investigators (*8*) have found retinol intakes both from diet and from supplements to be related to a reduced risk. Carotenoids may also act via effects on mutagenicity, tumor formation, and immune function (*52*).

It appears that vegetables exert a protective effect independent of vitamin C, α-tocopherol, folic acid, and fiber. After adjustment for the carotenoids β-carotene and lutein + zeaxanthin, the effect of vegetables was less strong, with fourth quartile ORs on the order of 0.80 rather than 0.50. When these same dietary components were entered in a model in turn adjusting for total vegetable intake, estimates of associated risks were considerably less strong (all fourth quartile ORs including the null), although there was evidence of a trend associated with both β-carotene intake and lutein + zeaxanthin intake. It appears that, while each of the examined components may affect risk, there probably remains some unexplained protection attributable to total intake of vegetables. Intake of the carotenoids β-carotene and lutein + zeaxanthin may explain that protective effect, at least in part. Other unmeasured factors in these foods may also affect risk. Some effect specific to combinations of components found in foods, perhaps a synergistic effect, may be important. For example, there is evidence of synergistic effects of α-tocopherol and β-carotene (*50*). Certainly, the lack of association with supplements seems to indicate that, at least for vitamin C, α-tocopherol, and folic acid, ingestion of these nutrients alone, at the level of supplementation, does not have an effect. Numerous other substances in vegetables and fruits may affect risk (*43*). These substances could include indoles, sterols, isoprenoids, and isoflavonoids. Several of these may affect estrogen metabolism, availability, and excretion (*53-57*) as well as immune function (*58*), and they may have other effects on tumorigenesis (*59*). These substances have not been studied in relation to human breast cancer epidemiology; food composition data for these substances are generally limited or nonexistent, preventing the evaluation of their relation to risk.

In the evaluation of our results, the issues of bias common to case–control studies must be recognized. This study was designed to be population based, with ascertainment of virtually all the cases in the two counties in the time period of the study. There was, however, an issue of nonparticipation among both case patients and control subjects. For case patients, failure to participate was primarily related to refusal of the physicians to allow us to contact their patients. Such refusals were most probably related more to characteristics of the physicians than to those of the patients. Nonetheless, it may be that individuals with more advanced disease were not included; these results would not then generalize to that group. Control subjects were also selected to be representative of the two counties of the study. While there was considerable nonparticipation among control subjects, our study of nonparticipants would seem to indicate that diet was not related to failure to participate. There were, however, individuals who refused to participate in both the case–control study and the study of nonparticipants. It may be that these individuals differed from the participants and that there was bias which we were unable to detect.

Differences among case patients and control subjects in their ability to accurately recall past dietary practices is of concern in any case–control study. In studies examining this issue, there is evidence that recall bias may not affect results. Friedenreich et al. (*60*) found virtually no difference in prospective and retrospective assessments of intakes of β-carotene, vitamin C, and vitamin E with regard to evaluation of breast cancer risk. In addition, there was no difference in reliability of case patients compared with control subjects for recall of supplement use. In a second similar study by Giovannucci et al. (*61*), there was little difference in estimates of risk based on prospective as opposed to retrospective assessments of intake for vitamin C and β-carotene; however, the two assessments were substantially different for fiber.

Random measurement error in estimation of usual intake is also of concern. Such error would tend to attenuate the estimate of the true risk (*62,63*). The questionnaire used in this study has been evaluated extensively; while there may be an error in estimation of intake, there is evidence that we are able to rank individuals with some accuracy (*21*). The questionnaire was extremely detailed in nature, eliciting far more information than is common in most epidemiologic studies of diet and cancer; data were collected with regard to food portion size, food preparation, use of food in and out of season, and use of canned,

frozen, and fresh fruits and vegetables. The detail involved provides some credence to the resulting data. Nonetheless, some caution should be observed in interpretation of the quantities reported by the participants; food-frequency questionnaires are less accurate in terms of quantitative assessment of intake.

While there has been considerable focus on the role of fat in the etiology of breast cancer, less attention has been paid to evidence that vegetables and fruits and related nutrients and food components may be associated with decreased risk of this disease. The ecologic evidence relating fat to breast cancer could in fact be explained by associated differences in consumption of fruits and vegetables. Our study would suggest that, while any of several nutrients and dietary components may be related to decreased risk, total vegetable consumption may be the active protective agent. These results are interesting in light of the recent failure of supplementation trials of individual nutrients (*64-66*). Given the results of those trials, the findings regarding the individual carotenoids β-carotene and lutein + zeaxanthin need to be considered cautiously. Our findings suggest that further research is needed to address the effects of non-nutritive substances in vegetables and fruits, such as isoflavonoids, indoles, and isoprenoids. Nonetheless, if evidence continues to accumulate indicating that intake of vegetables and fruits, particularly vegetables, is protective against breast cancer, a public health message encouraging consumption of these would be appropriate even without a complete understanding of the underlying mechanism of action. Such a result could have considerable relevance to prevention of a disease affecting large numbers of women.

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Notes

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