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Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study

Thomas E. Rohan, Geoffrey R. Howe, Christine M. Friedenreich, Meera Jain, and Anthony B. Miller

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Risk of breast cancer was examined in relation to intake of dietary fiber and vitamins A, C, and E, and food groups which are sources of these dietary constituents, in a cohort of 56,837 women enrolled in the Canadian National Breast Screening Study. Between 1982 and 1987, 519 incident, histologically confirmed cases of breast cancer were identified among women who previously had completed self-administered dietary questionnaires. Their nutrient and food intake was compared with that of 1,182 women who had not developed breast cancer during the follow-up period. Women at the uppermost quintile level of dietary fiber intake had a 30 percent reduction in risk of breast cancer relative to that for women at the lowest quintile level (adjusted odds ratio = 0.68, 95 percent confidence interval = 0.46-1.00), and the reduction in risk persisted after adjustment (separately) for total vitamin A, β-carotene, vitamin C, and α-tocopherol. Inverse associations of similar magnitude were observed in association with consumption of pasta, cereals (the trend for which was statistically significant), and vegetables rich in vitamins A and C. Smaller, statistically nonsignificant reductions in risk were observed with increasing intake of dietary retinol, β-carotene, and vitamin C, but the magnitude of these associations was reduced after adjustment for other dietary factors. Vitamin E intake was not associated with altered risk of breast cancer.

Key words: Canada, cancer etiology, case-control study, cohort study, dietary fiber, vitamin A, vitamin C, vitamin E.

Introduction

Much of the emphasis in research on the dietary etiology of breast cancer has been on the possible roles of fat and energy intake.[1] Less attention has been paid to other factors such as dietary fiber and vitamins A, C, and E. Each of these factors has been postulated to have anti-cancer effects for which plausible biologic mechanisms have been proposed.[2-5] Furthermore, there is a limited amount of epidemiologic evidence to suggest that they have inverse associations with risk of breast cancer.[2-7] However, much of this evidence derives from case-control studies, which are more susceptible to selection and information biases than cohort studies. Therefore, we investigated these associations prospectively in the cohort of women who were enrolled in the Canadian National Breast Screening Study (NBSS) and who completed dietary questionnaires prior to breast cancer diagnosis.

Materials and methods

The study methods have been described in detail elsewhere.[8] Briefly, the investigation was conducted as a

Drs Rohan, Howe, and Jain are with the NCIC Epidemiology Unit, University of Toronto, Toronto, Canada. The authors are also affiliated with the Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Canada (Drs Rohan, Howe, Jain, and Miller), and with the Department of Community Health Sciences, University of Calgary, Calgary, Canada (Dr Friedenreich). Address correspondence to Dr Rohan, NCIC Epidemiology Unit, University of Toronto, McMurrich Building, 3rd Floor, 12 Queen's Park Crescent West, Toronto, Ontario, M5S 1A8, Canada.

case-control study nested within the NBSS dietary cohort. The NBSS is a multi-center, randomized, controlled trial of screening for breast cancer in Canadian women aged 40 to 59.[9] The study involves 89,835 women who were recruited at 15 screening centers across Canada. Women were eligible to participate in the study if they had no history of breast cancer, were not currently pregnant, and had not had a mammogram in the preceding 12 months. Women aged 40-49 years were randomized either to have annual mammography plus physical examination, or to have an initial physical examination only, and women in both the intervention and the control group were taught breast self-examination. Randomization in the 50-59 year age-group was either to annual mammography plus physical examination, or to annual physical examination alone. The NBSS is now in the follow-up phase to determine cancer incidence and mortality.

At the time of their enrollment, all participants in the NBSS completed a lifestyle questionnaire which sought identifying information, and also data on factors such as demographic characteristics, family history of breast cancer, menstrual and reproductive history, use of oral contraceptives and replacement estrogens, and cigarette smoking. Additionally, 56,837 of the 89,835 women enrolled in the NBSS completed self-administered, diet-history questionnaires. (Women aged 40 to 49 years who were enrolled in the study before 1982 and assigned to the control group did not return to the screening center and therefore did not receive a diet-history questionnaire.) The diet-history questionnaire elicits information on the usual frequency of consumption, and usual amount consumed, of 86 food items, which include the great majority of those found in the Canadian diet. Quantification is assisted by means of photographs and standard serving sizes. The questionnaire also seeks information on methods of food preparation, and on the use of vitamin supplements (multivitamins and specific vitamin supplements).

Nutrient intake is estimated from the questionnaires by use of a database for Canadian foods that has been described elsewhere.[10] Briefly, development of the database entailed modification and extension of food composition tables from the United States Department of Agriculture (USDA)[11] to include typically Canadian items. Sources for these additions included food composition tables, commercial firms, cookbooks, and recipes obtained directly from participants in previous studies.[10] The values for dietary fiber were obtained principally from British sources,[12-14] which are based on the Southgate method of fiber measurement.[15] For food items not contained in these sources, dietary fiber values were derived by means of extrapolation based on crude fiber estimates,[11] or by summing the dietary fiber content of the various fractions of food items (*e.g.*, apple peel and pulp). (Estimates of the fractional composition of foods have been published by the USDA.[16]) A comparison between an early version of the self-administered questionnaire used here and a full interviewer-administered questionnaire which has been subjected to validity and reliability testing[17] and used in a number of epidemiologic studies[10] revealed that the two methods gave estimates of dietary fiber and vitamin C intake which were moderately strongly correlated with each other (correlation coefficient for dietary fiber = 0.70 and for vitamin C = 0.64) and which resulted in the majority of subjects being placed in the same or an adjacent tertile upon categorization of intake.[18] A separate study[19] showed that foods which make a substantial contribution to total vitamin C and vitamin E intake, and which are included in the self-administered questionnaire used in the present study, gave estimates of intake which were strongly correlated (coefficients = 0.94 and 0.93, respectively) with those derived from the full interviewer-administered questionnaire.

Between 1982 and 1987, active follow-up, supplemented by passive follow-up involving record linkage to provincial cancer registries, identified a total of 519 newly incident, histologically confirmed breast-cancer cases among women who previously had returned completed dietary questionnaires. Of these cases, 322 (62 percent) were identified at screening, and 197 (38 percent) were not detected at screening but were identified through the NBSS follow-up procedures.

For each breast cancer case, two controls were selected randomly from women who had not developed breast cancer by the end of the follow-up period, and were matched individually to cases on age (± one year), screening center, and date of enrollment (± two months). Although it would have been preferable to select controls from the entire cohort at risk at the time each case was diagnosed, this approach was not adopted for logistic reasons. However, any bias introduced as a result of this is likely to be negligible, since breast cancer occurred relatively infrequently during the follow-up period. Originally, a total of 1,184 controls were selected, since two controls were also selected for each of the 73 cases whose dietary questionnaires were received after their breast cancers were diagnosed. Because these 73 cases were excluded from the analysis, as were two controls whose dietary data were considered to be inadequate, the study included 519 cases and 1,182 controls. Characteristics of the study population have been described elsewhere.[8]

In order to maximize utilization of the available data (*e.g.*, for the subgroup analyses), unconditional logistic regression was used to estimate relative risks (RR), 95 percent confidence intervals (CI), and (two-sided) *P* values. This enabled data to be included for the 146 controls who were matched to the 73 cases who had returned their dietary questionnaires after diagnosis. Conditional logistic regression analyses yielded point estimates which were very similar to those of the corresponding unconditional logistic regression analyses, thereby justifying breaking of the matching and confirming that the original matching variables were uncorrelated with dietary factors among the study participants. For the logistic regression analyses, intakes of nutrients and foods were categorized (mostly) by quintiles according to their distribution in the controls; however, since α-tocopherol is contained in relatively few dietary items, it had a limited number of values for

Table 1. Risk of breast cancer by levels of intake of dietary fiber and vitamins A, C, and E

Dietary factor	Level[a]					*P* (trend)
	1 (low)[b]	2	3	4	5 (high)	
Dietary fiber						
No. of cases	116	87	118	102	96	
No. of controls	220	200	285	236	241	
Unadjusted OR (CI)	1.0	0.83 (0.59-1.16)	0.79 (0.58-1.07)	0.82 (0.59-1.13)	0.76 (0.55-1.05)	0.099
Adjusted OR (CI)[c]	1.0	0.78 (0.55-1.11)	0.72 (0.51-1.02)	0.76 (0.52-1.09)	0.68 (0.46-1.00)	0.093
Vitamin A						
No. of cases	111	131	92	92	93	
No. of controls	235	237	236	237	237	
Unadjusted OR (CI)	1.0	1.17 (0.86-1.60)	0.82 (0.59-1.15)	0.82 (0.59-1.14)	0.83 (0.60-1.15)	0.039
Adjusted OR (CI)[c]	1.0	1.22 (0.88-1.70)	0.85 (0.59-1.21)	0.77 (0.54-1.11)	0.80 (0.55-1.17)	0.034
Retinol						
No. of cases	117	112	97	86	107	
No. of controls	234	237	237	237	237	
Unadjusted OR (CI)	1.0	0.95 (0.69-1.30)	0.82 (0.59-1.13)	0.73 (0.52-1.01)	0.90 (0.66-1.24)	0.172
Adjusted OR (CI)[c]	1.0	0.92 (0.66-1.29)	0.80 (0.56-1.13)	0.73 (0.51-1.04)	0.83 (0.58-1.18)	0.186
β-carotene						
No. of cases	116	116	94	98	95	
No. of controls	235	237	235	238	237	
Unadjusted OR (CI)	1.0	0.99 (0.72-1.36)	0.81 (0.59-1.12)	0.83 (0.60-1.15)	0.81 (0.59-1.12)	0.089
Adjusted OR (CI)[c]	1.0	0.96 (0.69-1.34)	0.82 (0.58-1.17)	0.82 (0.58-1.17)	0.77 (0.53-1.10)	0.123
Vitamin C						
No. of cases	118	99	92	106	104	
No. of controls	227	245	229	244	237	
Unadjusted OR (CI)	1.0	0.78 (0.56-1.07)	0.77 (0.56-1.07)	0.84 (0.61-1.15)	0.84 (0.61-1.16)	0.348
Adjusted OR (CI)[c]	1.0	0.78 (0.56-1.10)	0.80 (0.57-1.13)	0.89 (0.63-1.25)	0.88 (0.62-1.26)	0.597
Vitamin E						
No. of cases	99	80	96	130	114	
No. of controls	209	198	250	266	259	
Unadjusted OR (CI)	1.0	0.85 (0.60-1.21)	0.81 (0.58-1.13)	1.03 (0.75-1.42)	0.93 (0.67-1.29)	0.566
Adjusted OR (CI)[c]	1.0	0.91 (0.63-1.33)	0.83 (0.57-1.19)	1.15 (0.80-1.67)	0.96 (0.63-1.45)	0.597
α-tocopherol						
No. of cases	64	85	252	118	—	
No. of controls	136	197	595	254	—	
Unadjusted OR (CI)	1.0	0.92 (0.62-1.35)	0.90 (0.65-1.25)	0.99 (0.68-1.43)	—	0.578
Adjusted OR (CI)[c]	1.0	0.94 (0.62-1.41)	0.94 (0.64-1.39)	1.05 (0.65-1.70)		0.544

[a] Cut-points: dietary fiber (g/day), 13, 16, 20, 25; vitamin A (IU/day), 6133, 8545, 10793, 14136; retinol (IU/day), 1158, 1884, 2678, 4431; β-carotene (IU/day), 3446, 4625, 6115, 8441; vitamin C (mg/day), 101, 137, 172, 220; vitamin E (mg/day), 12, 15, 19, 25; α-tocopherol (mg/day), 3, 4, 7.

[b] Reference category.

[c] Adjusted for age, energy intake, age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, and history of benign breast disease.

OR = odds ratio; CI = 95% confidence interval.

intake, and therefore was categorized by quartiles. Data on the use of vitamin supplements were categorized by tertiles, since relatively few women reported having used them.

Results

Table 1 shows the distribution of cases and controls by levels of intake of dietary fiber and vitamin A, C, and E, and the associated unadjusted and adjusted odds ratios (OR) and CIs. For all of the dietary factors shown in the table, there was relatively little variation in risk with increasing intake. If anything, however, the predominant pattern was one of slightly reduced risk for most levels of intake above the baseline level. For vitamin A, the associated test for trend was statistically significant (adjusted two-sided P-value = 0.034), although this probably reflects the change in risk from the second level of intake, where risk was slightly increased (above the baseline risk), to that at the fifth level, where the risk of breast cancer was slightly less than one.

These results are summarized in Table 2, in which the dietary factors are treated as continuous variables. The table shows the change in risk per unit of intake of each of the dietary variables, where the units are defined as the difference between the respective upper and lower quintile cut-points. There was a 10-15 percent decrease in risk with each unit increase in consumption of dietary fiber, vitamin A, retinol, and β-carotene (all of borderline statistical significance), and essentially no change in risk with increasing consumption of vitamins C and E, and α-tocopherol.

As shown in Tables 1 and 2, adjustment for age, energy intake, and breast cancer risk factors (age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, and history of benign breast disease) had virtually no impact on the point estimates for dietary fiber and vitamins A, C, and E. Further adjustment for cigarette smoking and alcohol consumption also was without effect (data not shown). In contrast, adjustment of the dietary factors for each other and for other relevant dietary factors did have an effect on some of the point estimates of association, although the resulting patterns generally were not changed substantially. Since, to a varying extent, vitamins A, C, and E are contained in fiber-rich foods, their associations with risk of breast cancer were examined simultaneously with that for dietary fiber intake (retinol and total vitamin E were not examined since they were essentially uncorrelated with dietary fiber intake).

Table 3 shows that, after adjustment for dietary fiber intake, the point estimates for vitamin A, β-carotene, and vitamin C were generally closer to unity, and there was some evidence for an increase in risk of breast cancer with increasing α-tocopherol intake (although the trend in risk was not statistically significant). Also, after adjustment for vitamin C and (separately) α-tocopherol, there were statistically significant trends of decreasing risk of breast cancer with increasing dietary fiber intake. In other models, adjustment of vitamins C and E, and α-tocopherol, for vitamin A intake, and adjustment of dietary fiber and vitamins A, C, and E (and their constituents) for total fat intake (which was associated with increased risk of breast cancer in this cohort[8]) had little impact on the patterns described previously. There was no statistical evidence of effect modification of the associations for vitamins A, C, and E (and their constituents) by dietary fiber (dichotomized at the median level of intake) (data not shown).

Relatively few subjects reported use of any vitamin supplements. Table 4 shows that there was a 30 percent reduction in risk in association with supplementation with more than 5,000 IU of vitamin A per day, but the trend in risk with increasing levels of vitamin A supplementation was not statistically significant. In contrast, there was a statistically significant 40-50 percent

Table 2. Risk of breast cancer per unit intake[a] of dietary fiber and vitamins A, C, and E

Dietary factor	Unit	Unadjusted OR (CI)[c]	Adjusted OR (CI)[b,c]
Dietary fiber	12 g/day	0.87 (0.73-1.03)	0.85 (0.70-1.04)
Vitamin A	8,003 IU/day	0.85 (0.74-1.00)	0.83 (0.70-0.98)
Retinol	3,273 IU/day	0.90 (0.79-1.04)	0.89 (0.77-1.03)
β-carotene	4,995 IU/day	0.86 (0.74-1.01)	0.85 (0.72-1.00)
Vitamin C	119 mg/day	0.96 (0.82-1.13)	0.99 (0.83-1.17)
Vitamin E	13 mg/day	1.01 (0.89-1.15)	1.02 (0.87-1.19)
α-tocopherol	4 mg/day	0.97 (0.81-1.17)	0.96 (0.76-1.21)

[a] Unit = difference between upper and lower quintile cut-point.
[b] Adjusted for age, energy intake, age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, and history of benign breast disease.
[c] OR = odds ratio; CI = 95% confidence interval.

Table 3. Risk of breast cancer by levels of intake of dietary fiber and vitamins A, C, and E, for various pairs of these nutrients considered simultaneously[a]

Dietary factors	Partial correlation coefficient[c]	Level[b]								*P* (trend)
		1 (low)[d]	2		3		4		5 (high)		
			OR[e]	(CI)[f]	OR[e]	(CI)[f]	OR[e]	(CI)[f]	OR[e]	(CI)[f]	
Dietary fiber	0.40	1.0	0.77	(0.53-1.11)	0.75	(0.52-1.07)	0.83	(0.56-1.23)	0.76	(0.49-1.18)	0.317
Vitamin A		1.0	1.31	(0.93-1.84)	0.91	(0.63-1.31)	0.84	(0.57-1.25)	0.88	(0.58-1.33)	0.083
Dietary fiber	0.52	1.0	0.80	(0.55-1.15)	0.76	(0.52-1.10)	0.81	(0.54-1.23)	0.74	(0.47-1.17)	0.317
β-carotene		1.0	1.02	(0.73-1.44)	0.90	(0.62-1.32)	0.91	(0.62-1.35)	0.86	(0.57-1.31)	0.322
Dietary fiber	0.50	1.0	0.79	(0.55-1.13)	0.71	(0.50-1.02)	0.74	(0.49-1.10)	0.63	(0.41-0.99)	0.046
Vitamin C		1.0	0.83	(0.59-1.17)	0.88	(0.62-1.27)	1.02	(0.70-1.48)	1.05	(0.71-1.56)	0.410
Dietary fiber	0.35	1.0	0.75	(0.52-1.09)	0.69	(0.48-1.00)	0.71	(0.47-1.05)	0.60	(0.39-0.93)	0.046
α-tocopherol		1.0	1.06	(0.69-1.62)	1.15	(0.75-1.76)	1.37	(0.81-2.33)	—	—	0.157

[a] Adjusted for age, energy intake, age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, and history of benign breast disease.

[b] Cut-points: dietary fiber (g/day), 13, 16, 20, 25; vitamin A (IU/day), 6133, 8545, 10793, 14136; retinol (IU/day), 1158, 1884, 2678, 4431; β-carotene (IU/day), 3446, 4625, 6115, 8441; vitamin C (mg/day), 101, 137, 172, 220; vitamin E (mg/day), 12, 15, 19, 25; α-tocopherol (mg/day), 3, 4, 7.

[c] Adjusted for total caloric intake.

[d] Reference category.

[e] OR = odds ratio.

[f] CI = 95% confidence interval.

Table 4. Risk of breast cancer by levels of intake of vitamin supplements

Vitamin supplement	Level[a]			*P* (trend)
	1 (low)[b]	2	3 (high)	
Vitamin A				
No. of cases	430	64	25	
No. of controls	978	131	73	
Unadjusted OR (CI)	1.0	1.04 (0.75-1.45)	0.70 (0.43-1.15)	0.225
Adjusted OR (CI)[c]	1.0	1.10 (0.79-1.54)	0.70 (0.42-1.15)	0.420
Vitamin C				
No. of cases	351	91	77	
No. of controls	839	209	134	
Unadjusted OR (CI)	1.0	1.04 (0.79-1.37)	1.37 (1.01-1.87)	0.055
Adjusted OR (CI)[c]	1.0	1.04 (0.78-1.39)	1.46 (1.05-2.01)	0.051
Vitamin E				
No. of cases	439	44	36	
No. of controls	993	104	85	
Unadjusted OR (CI)	1.0	0.99 (0.68-1.45)	0.96 (0.63-1.46)	0.488
Adjusted OR (CI)[c]	1.0	1.01 (0.69-1.49)	1.00 (0.65-1.54)	0.708
α-tocopherol				
No. of cases	449	20	50	
No. of controls	1,015	61	106	
Unadjusted OR (CI)	1.0	0.80 (0.47-1.34)	1.12 (0.80-1.62)	0.454
Adjusted OR (CI)[c]	1.0	0.79 (0.47-1.35)	1.20 (0.83-1.75)	0.655

[a] For all vitamin supplements, level 1 represents zero intake. Cut-points between levels 2 and 3: vitamin A (IU/day), 5000; vitamin C (mg/day), 250; vitamin E (mg/day), 4; α-tocopherol (mg/day), 3.

[b] Reference category.

[c] Adjusted for age, energy intake, age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, and history of benign breast disease.

OR = odds ratio; CI = 95% confidence interval.

increase in the risk of breast cancer in association with intake of more than 250 mg/day of vitamin C supplements, and the trend in risk with increasing intake was of borderline statistical significance. There was little variation in risk across levels of intake of vitamin E and α-tocopherol supplements. The patterns for total vitamin A, E, and α-tocopherol intake, obtained by summing dietary and supplementary sources, differed little from those shown in Table 1 (data not shown); for vitamin C, any evidence of a protective effect disappeared.

Table 5 shows the risk of breast cancer associated with consumption of several food groups which represent some of the major sources of dietary fiber and vitamins A, C, and E. There was a statistically significant decrease in risk with increasing consumption of cereals, and a similar, albeit statistically nonsignificant trend for pasta consumption. For the other dietary factors shown in the table, the deviation from baseline risk was less pronounced. Using a method analogous to that which has been used to differentiate the effects of individual components of calories from an effect of calories themselves,[20] it was shown first, that there was no association between total food intake and risk of breast cancer (data not shown), and second, that the associations for cereal and pasta intake persisted after adjust-

Table 5. Risk of breast cancer by levels of intake of selected food groups[a]

Food group	Level[b]					*P* (trend)
	1 (low)[c]	2	3	4	5 (high)	
Cereals						
No. of cases	188	93	78	86	73	
No. of controls	372	193	178	236	203	
Unadjusted OR (CI)	1.0	0.95 (0.70-1.29)	0.87 (0.63-1.19)	0.72 (0.53-0.98)	0.71 (0.52-0.98)	0.010
Adjusted OR (CI)[d]	1.0	0.97 (0.71-1.33)	0.91 (0.65-1.27)	0.71 (0.52-0.98)	0.74 (0.53-1.04)	0.014
Bread						
No. of cases	112	91	106	97	112	
No. of controls	229	243	232	240	238	
Unadjusted OR (CI)	1.0	0.77 (0.55-1.06)	0.93 (0.68-1.29)	0.83 (0.60-1.14)	0.96 (0.70-1.32)	0.572
Adjusted OR (CI)[d]	1.0	0.76 (0.54-1.08)	0.93 (0.66-1.30)	0.79 (0.56-1.12)	0.95 (0.68-1.33)	0.471
Pasta						
No. of cases	126	103	90	96	103	
No. of controls	212	256	231	245	238	
Unadjusted OR (CI)	1.0	0.68 (0.49-0.93)	0.66 (0.47-0.91)	0.66 (0.48-0.91)	0.73 (0.53-1.00)	0.081
Adjusted OR (CI)[d]	1.0	0.67 (0.48-0.94)	0.66 (0.47-0.93)	0.67 (0.48-0.95)	0.75 (0.53-1.04)	0.125
Fruit						
No. of cases	115	105	115	89	94	
No. of controls	234	237	236	236	239	
Unadjusted OR (CI)	1.0	0.90 (0.65-1.24)	0.99 (0.72-1.36)	0.77 (0.55-1.07)	0.80 (0.58-1.11)	0.132
Adjusted OR (CI)[d]	1.0	0.84 (0.60-1.18)	1.01 (0.73-1.41)	0.76 (0.54-1.08)	0.81 (0.57-1.14)	0.174
Vegetables						
No. of cases	106	92	116	107	97	
No. of controls	233	238	237	237	237	
Unadjusted OR (CI)	1.0	0.85 (0.61-1.18)	1.08 (0.78-1.48)	0.99 (0.72-1.37)	0.90 (0.65-1.25)	0.590
Adjusted OR (CI)[d]	1.0	0.81 (0.57-1.15)	1.05 (0.75-1.47)	0.97 (0.69-1.37)	0.86 (0.61-1.23)	0.752
Vegetables rich in vitamins A and C						
No. of cases	114	98	124	91	91	
No. of controls	235	230	240	239	238	
Unadjusted OR (CI)	1.0	0.88 (0.63-1.22)	1.07 (0.78-1.45)	0.78 (0.57-1.09)	0.79 (0.57-1.09)	0.148
Adjusted OR (CI)[d]	1.0	0.85 (0.60-1.19)	1.03 (0.74-1.43)	0.81 (0.57-1.14)	0.74 (0.52-1.05)	0.086

[a] Food group data could not be calculated for 1 case.

[b] Cut points: cereals (g/day), 0, 5, 14, 23; bread (g/day), 38, 58, 75, 101; pasta (g/day), 12, 22, 34, 49; fruit (g/day), 189, 282, 373, 491; vegetables (g/day), 203, 269, 373, 433; vegetables rich in vitamins A and C (g/day), 45, 73, 108, 169.

[c] Reference category.

[d] Adjusted for age, age at menarche, surgical menopause, age at first livebirth, years of education, family history of breast cancer, history of benign breast disease, and other contributors to total food intake.

OR = odds ratio; CI = 95% confidence interval.

ment for the effects of other contributors to total food intake (and for breast-cancer risk factors).

The menopausal status of the study participants was documented at the time of their entry into the NBSS, but was not updated subsequently. Therefore, the only women whose menopausal status was known with certainty either at the time of diagnosis (for the cases) or at the end of the follow-up period (for the controls) were those who were postmenopausal at enrollment, the remainder consisting of women who either remained premenopausal or became peri- or postmenopausal. When the preceding analyses were repeated within menopausal strata (postmenopausal or other), the patterns were similar to those already described, and there were no statistically significant differences between the RR estimates for the two menopausal groups (data not shown).

Analyses also were conducted within strata defined by allocation in the NBSS (*i.e.*, to the screening or control arm of the trial), and by interval between completion of the dietary questionnaire and diagnosis of breast cancer. The results of these analyses did not differ substantially from those described above, and neither did those in which adjustment was made for the presence of breast symptoms at enrollment (data not shown).

Discussion

This study has provided some evidence to suggest that a relatively high dietary-fiber intake is associated with a small (30 percent) reduction in risk of breast cancer. The crude OR for the highest *cf* the lowest quintile level of intake was 0.76 (CI = 0.55-1.05), while after adjustment for several breast-cancer risk factors and for energy intake it was 0.68 (CI = 0.46-1.00). The reduction in risk persisted after adjustment (separately) for vitamin A, β-carotene, vitamin C, and α-tocopherol, and was not confined to any specific menopausal subgroup. An inverse and statistically significant association of similar magnitude was observed in association with consumption of cereals (a good source of fiber), and with intake of pasta and of vegetables rich in vitamins A and C. Smaller reductions in risk (of the order of 10-20 percent for the highest *cf* the lowest quintile level of intake) were also observed in association with relatively high dietary-intake of vitamin A, retinol, β-carotene, and vitamin C, but the magnitude of these associations was reduced somewhat when they were adjusted for other relevant dietary factors. There was no association between dietary vitamin-E intake and risk of breast cancer. Consideration of supplemental sources of vitamin intake did not change the findings for vitamins A and E, and α-tocopherol, but abolished any evidence of a protective effect for vitamin C.

Total vitamin A is a composite of preformed vitamin A (retinol) and the carotenoids (the most intensively studied of which has been β-carotene); retinol is involved in the regulation of cell differentiation and has been shown experimentally to inhibit carcinogenesis, while β-carotene might reduce cancer risk either as a result of its conversion to retinol or through its action as an antioxidant and free radical scavenger.[3] In this study, there were weak inverse associations with retinol and β-carotene intake, while total vitamin A intake had a statistically significant, inverse association with risk of breast cancer (although, as indicated earlier, this probably reflects the difference between the risks at the second and fifth quintile levels of intake). Previous studies of total vitamin A generally have shown it to be associated inversely with risk of breast cancer,[7,21-23] although in one recent small investigation,[24] there was no difference between cases and controls in dietary intake of vitamin A. When the constituents of vitamin A have been examined separately, retinol intake has been shown mostly to be unrelated to risk of breast cancer;[6,22,25,26] however, one study[27] showed some evidence of increasing risk with increasing consumption, while two[7,23] provided some suggestion of an inverse association. In contrast, studies of β-carotene intake generally have yielded inverse associations with breast cancer risk,[26,28-30] although some have shown no association.[25-27] The somewhat different results for dietary retinol and β-carotene might reflect the fact that only the latter is correlated with serum levels,[3] although it is conceivable that dietary retinol could influence cancer risk by a mechanism which is independent of the serum level of retinol.[31] Furthermore, the inconsistent results for individual nutrients might reflect (at least partly) varying degrees of uncontrolled confounding by other nutrients such as dietary fiber. Indeed, in the present study, adjustment for dietary fiber abolished the statistical significance of the trend in risk for vitamin A intake, and generally moved the point estimates for vitamin A and β-carotene closer to unity (retinol was uncorrelated with dietary fiber intake), which suggests that any protective effect associated with consumption of these items might be mediated by other constituents of fiber-containing foods. Very few of the earlier studies adjusted for dietary fiber intake (or other nutrients); in one,[22] adjustment for dietary fiber (and vitamin C) removed the inverse association for β-carotene, while in another,[29] the inverse association for β-carotene persisted after adjustment for soya protein (soya beans are a source of phyto-estrogens—see below). Clearly, there is a need for further studies in

which attempts are made to delineate the independent effects of vitamin A and its constituents.

Vitamins C and E both have antioxidant activity and have been shown to inhibit the formation of nitrosamines,[4,5,32] on the basis of which they are considered to be potential cancer-inhibiting agents. With respect to previous studies of breast cancer, a combined analysis of several case-control studies[22] showed a strong inverse association with dietary vitamin C intake, as did two recent case-control studies;[6,30] however, in two other case-control studies,[21,26] and in one cohort study,[7] there was no association between vitamin C intake and risk of breast cancer. In the present study, supplemental vitamin C intake was associated with an increase in risk of borderline statistical significance, while the combination of supplemental and dietary vitamin C intake was not associated with altered risk. Although some experimental studies have shown that supplementation with vitamin C might enhance the development of cancer at sites other than the breast,[33] the evidence is not consistent, and other epidemiologic studies of supplemental vitamin C have not shown an association with risk of breast cancer.[6,7] The association between vitamin E intake and breast cancer has been examined previously in only two case-control studies, of which one[6] showed a strong inverse association with dietary α-tocopherol intake (but no association with supplemental tocopherol intake), while the other[27] showed no association with total vitamin E. In the only other cohort investigation of this association,[7] vitamin E intake (with and without supplements) had an inverse association with risk of breast cancer.

It has been postulated recently[2] that a relatively high dietary-fiber intake might be associated with reduced risk of breast cancer. This hypothesis is based predominantly on the central role of the reproductive hormones (in particular, the estrogens) in the etiology of breast cancer, and on the elucidation of biologically plausible, hormonally mediated mechanisms of action of fiber-containing foods. Fiber-rich foods appear to be able to interfere with the enterohepatic cycling of estrogen, either by binding unconjugated estrogens in the gut,[34] or by reducing deconjugating enzyme activity (deconjugation precedes reabsorption).[2] Also, estrogen-like compounds called lignans (or phyto-estrogens), which are derived by bacterial action on precursors in unrefined grains, can reduce the bioavailability of estrogen, either by stimulating the production of sex hormone-binding globulin, or by occupying estrogen-binding sites and thereby acting as anti-estrogens.[35] Experimentally, supplementation with wheat bran (but not oat or corn brans) for two months has been shown[2] to produce significant reductions in serum estrone and estradiol in premenopausal women (levels of non-protein-bound estradiol, in particular, are higher in women with breast cancer than in controls[36]). Also, supplementation of high fat diets with wheat bran has been shown[37] to reduce the occurrence of N-nitrosomethylurea-induced mammary tumors in rats. Against this background, the fiber hypothesis receives some support from the present study, by virtue of the statistically nonsignificant, inverse association with dietary fiber intake, and the stronger (and significant) inverse association with cereal intake. The results for dietary fiber persisted after adjustment (separately) for vitamins A, C, and E, suggesting (as implied earlier) that dietary fiber was not acting as a marker for these substances. Similar findings for dietary fiber and cereal products were reported from a recent case-control study in Holland,[28] while two other studies[6,22] also have shown inverse associations with dietary fiber intake. Several other studies have investigated the association between fiber-rich foods or food groups and risk of breast cancer: a case-control study in Singapore[29] showed a significant decrease in risk with intake of soya beans, a good source of both dietary fiber and phyto-estrogens; a case-control study in Moscow[30] showed a strong inverse association with cellulose intake in postmenopausal women; while findings with respect to vegetable intake have been mixed.[21,25-27,38]

In conclusion, the results of the present cohort study, in combination with those from several previous studies (both case-control and cohort), provide some evidence for inverse associations between risk of breast cancer and dietary intake of fiber (from cereal sources), and vitamins A (from β-carotene, in particular) and C; previous studies provide some evidence for an inverse association with vitamin E. The associations which have been observed to date generally have been relatively modest, which may reflect the attenuation of risk estimates due to the measurement error which accompanies use of the currently available methods for assessment of dietary intake.[39] As such, the true associations may be stronger, which suggests that if the relationships are shown to be causal, the potential for dietary modification to reduce the risk of breast cancer might be substantial.

Addendum

The results of the present cohort study with respect to dietary fiber are countered by those contained in a recent report[40] (published days before acceptance of the present article), based on eight years of follow-up in the large, prospective, Nurses' Health Study, which showed no association between dietary fiber intake and risk of breast cancer.

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