

INTAKE OF FOOD GROUPS AND ASSOCIATED MICRONUTRIENTS IN RELATION TO RISK OF EARLY-STAGE BREAST CANCER

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Epidemiologic studies have evaluated the risk of breast cancer related to dietary fat intake, but only recently have other dietary factors received attention. Frequent intakes of fruit, vegetables and fiber have been associated with low risk of the disease in some studies but results are inconsistent. In a large case-control study of early-onset breast cancer, we evaluated risk related to a variety of food groups, associated micronutrients and non-nutritive constituents. Cases treated with chemotherapy appeared to have altered reporting of food intake and were excluded. Analyses were restricted to 568 cases with *in situ* and localized disease and 1,451 population-based controls. Reduced risks were observed for high intake of cereals and grains [odds ratio (OR) = 0.84, 95% confidence interval (CI) = 0.6–1.1 for highest compared with lowest quartile], vegetables (OR = 0.86, 95% CI = 0.6–1.1), beans (OR = 0.87, 95% CI = 0.7–1.2) and fiber from beans (OR = 0.88, 95% CI = 0.7–1.2). However, no trends of decreasing risk across quartiles of increasing intake were observed. Risk was not associated with dietary constituents related to these food groups including dietary fiber, carotenoids, vitamins A, C and E and folate. Incorporation of information from vitamin supplements did not alter the results for micronutrients. Our data suggest that intakes of cereals and grains, vegetables and beans are associated with minimal, if any, reduction in risk of early-stage breast cancer among young women. *Int. J. Cancer* 82:315–321, 1999.

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A large number of epidemiologic studies have evaluated the association of breast cancer risk and intake of fat (Hunter and Willett, 1996), but evaluation of other dietary factors has been more limited. Analytic studies have suggested that intake of vegetables is associated with reduced risk of breast cancer (Katsouyanni *et al.*, 1986; La Vecchia *et al.*, 1987; van't Veer *et al.*, 1990; Rohan *et al.*, 1993; Holmberg *et al.*, 1994; Hirose *et al.*, 1995; Freudenheim *et al.*, 1996; Franceschi *et al.*, 1997; Longnecker *et al.*, 1997), with some studies specifically focused on premenopausal women (Katsouyanni *et al.*, 1986; La Vecchia *et al.*, 1987; Hirose *et al.*, 1995; Freudenheim *et al.*, 1996). The components of vegetable intake related to risk are unclear, but reduced risks have been observed for high intake of vegetables rich in vitamins A and C (Rohan *et al.*, 1993), for green vegetables, cucumbers, lettuce or spinach (Katsouyanni *et al.*, 1986; La Vecchia *et al.*, 1987; Hirose *et al.*, 1995; Longnecker *et al.*, 1997) and for carrots (Katsouyanni *et al.*, 1986; Hirose *et al.*, 1995; Longnecker *et al.*, 1997). Fruit intake has also been associated with decreased risk (van't Veer *et al.*, 1990; Rohan *et al.*, 1993; Trichopoulou *et al.*, 1995; Freudenheim *et al.*, 1996; Holmberg *et al.*, 1994; Franceschi *et al.*, 1997). Investigators have observed a decreased risk of breast cancer associated with micronutrients related to vegetable and fruit intake, particularly vitamins A and C, B-carotene and carotenoids (van't Veer *et al.*, 1990; Rohan *et al.*, 1993; Hunter *et al.*, 1993; Holmberg *et al.*, 1994; Freudenheim *et al.*, 1996; Mezzetti *et al.*, 1998), although results are inconsistent across studies.

Another area of interest has been with dietary fiber intake. Lubin *et al.* (1986) showed that high fiber intake, particularly in conjunction with diets low in fat and protein, were associated with a reduced risk of breast cancer. The effect was more pronounced among young women. Reduced risks have been associated with intake of cereal, dietary fiber or fiber components in several investigations (van't Veer *et al.*, 1990; Rohan *et al.*, 1993; Baghurst and Rohan, 1994; Freudenheim *et al.*, 1996; La Vecchia and Chatenoud, 1998). In a combined analysis, 10 of 12 case-control studies had data on dietary fiber for evaluation (Howe *et al.*, 1990). Slightly reduced risks of breast cancer were observed for both pre- and postmenopausal women, although results were stronger for postmenopausal disease. Evaluation of large cohorts (Willett *et al.*, 1992; Kushi *et al.*, 1992), however, has not shown trends or associations between dietary fiber intake and risk of breast cancer.

In a large study focused on early-onset breast cancer, we had the opportunity to further evaluate food group and micronutrient associations with risk of disease. The availability of a new carotenoid database and more extensive fiber delineation, as well as information on dietary supplement usage in our study, provided distinctive data to address dietary hypotheses. Specifically, we evaluated the influence on breast cancer risk of fruit, vegetable and fiber food groups, as well as vitamins A, C and E, folate, calcium and carotenoids.

MATERIAL AND METHODS

Our case-control study was conducted in 3 centers in the United States: Atlanta, GA; Seattle/Puget Sound, WA; and 5 counties in central New Jersey. Methods have been described in detail elsewhere (Brinton *et al.*, 1995; Swanson *et al.*, 1996). In brief, between 1 May 1990 and 31 December 1992, cases 20–44 years old newly diagnosed with *in situ* or invasive breast cancer were identified through rapid-ascertainment systems for potential participation. All geographic regions were covered by population-based cancer registries, and periodic checks of these registries ensured completeness of patient ascertainment. Controls were frequency-matched by region and age to the expected distribution of cases and were identified through Mitofsky-Waksberg random digit dialing (RDD) techniques (Waksberg, 1978).

Subjects were interviewed regarding demographic factors; reproductive and medical histories; contraceptive behavior; adolescent diet; physical activity; smoking; alcohol consumption; and occupation. As part of the interview, subjects were asked whether they had been diagnosed with breast cancer during the past 12 months and

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follow-up questions ascertained what kind of treatment they had received. Anthropometric measurements were taken following the interview (Swanson *et al.*, 1996). Participants were given a food frequency questionnaire to complete about dietary intake in the past year. Respondents completed this questionnaire at their leisure and returned it by mail or they completed the dietary questionnaire while the interviewer was present. Occasionally, the questionnaire was completed by telephone interview when receipt of the mailed questionnaire seemed improbable.

The dietary questionnaire was a scannable, modified version of the standard 100-item NCI-Block food frequency questionnaire (Block *et al.*, 1986). Modifications included expansion of questions to differentiate low and high fat dairy items, low and high caffeine beverages with and without artificial sweeteners, separation of items that differed in fiber or fat content, added food items relevant to the Atlanta population (Coates *et al.*, 1991) and an open-ended section to include foods consumed more than once per week that were missing from the food list. Frequency of consumption was asked as follows: "Over the last 12 months, how often did you eat the following foods (ignoring any recent changes)?" There were 9 frequency categories for foods, 10 frequency categories for beverages and 3 portion size groups. The dietary questionnaires were processed using the NCI-Block analysis program (HHHQ-DIETSYS, 1993), version 3.5. We created food groups (see Appendix) to circumvent errors associated with food composition data and to indirectly address hypotheses related to dietary constituents not available in typical food composition tables. In addition, multiple dietary constituents in whole foods may impart different risk than single nutrients. Food groups included items reported in the open-ended section of the questionnaire.

Of the 1,939 eligible cases, 1,668 (86.0%) women were interviewed. The main reasons for non-participation were subject refusal (6.6% of eligible cases) and physician refusal (5.8% of cases). A response rate of 90.5% was obtained from the telephone identification screener for RDD controls, resulting in 1,912 eligible controls. Of these subjects, 1,505 (78.7%) completed interviews. Among eligible case and control subjects, 1,632 (84.2%) and 1,471 (76.9%), respectively, completed dietary questionnaires. Consideration of the telephone screener rate showed an overall response rate of 69.6% among controls for the dietary questionnaire. Five controls were removed due to a previous history of breast cancer and 21 cases without residential telephones were eliminated because of non-comparability with the controls who were identified by RDD techniques. Twenty-three cases and 15 controls were excluded from the analysis because severe errors in their dietary questionnaires were identified through the NCI-Block edit program. Errors included less than 3 or more than 30 foods consumed per day, more than 15% of food items skipped and 3 or more foods with questionably high frequencies. Preliminary analyses focused on the remaining 1,588 cases and 1,451 controls, but the majority of analyses were conducted on the 568 cases with either *in situ* or invasive localized disease. These cases did not report chemotherapy treatment, which was found to be associated with altered reporting of dietary intake (Potischman *et al.*, 1997), as described below.

Logistic regression was utilized to estimate odds ratios (ORs) and 95% confidence intervals (CIs) as measures of the relationships between dietary variables and risk of breast cancer (Breslow and Day, 1980). Quartiles for each dietary factor were defined based on the distribution in the control group. Age in the models was defined as age at date of diagnosis for cases and date of RDD telephone identification screener for controls. Variables considered to be potential confounders included study site, ethnicity, age at first birth, parity, cigarette smoking, age at menarche, years of oral contraceptive usage, level of education, recent alcohol consumption, history of previous breast biopsy, family history of breast cancer in a first degree relative, frequency of mammograms in the

past 5 years excluding the past year and body mass index (kg/m²). Among the controls, the following variables were related to the key dietary variables of fiber, B-carotene or vitamin C and therefore were included in models for all nutrient and food group analyses in addition to age: site (Atlanta, New Jersey, Seattle), ethnicity (white, African-American, other), years of oral contraceptive usage (<6 months, 6 months to <5 years, 5–9 years, 10+ years), age at first birth (<20, 20–24, 25–29, 30+, nulliparous, missing), smoking (never, past, current), education (high school, vocational, some college, college graduate, postgraduate) and recent alcohol consumption (non-drinker, 1–6.9 drinks/week, 7–13 drinks/week, 14+ drinks/week, missing). Separate analyses of potential confounders were conducted for micronutrients derived from food and supplements. With one exception, the models were similar to those restricted to dietary sources of nutrients. A combination variable of age at first birth and number of births was utilized in place of age at first birth in models for foods plus supplements.

RESULTS

Previous analyses (Potischman *et al.*, 1997) had indicated that cases who reported chemotherapy treatment for their breast cancer during the interview ($n = 953$) had higher intakes of macronutrients and calories than did cases not receiving chemotherapy ($n = 635$). We evaluated the impact of treatment in the present analysis of micronutrients (Table I) and found similar relationships as had been previously observed for macronutrients and calories. Elevated risk was associated with high intake of vitamin C, vitamin E, folate, retinol, calcium, B-carotene, cryptoxanthin and lycopene among cases reporting chemotherapy treatment but not among those not reporting this treatment. Likewise, high intakes of dietary fiber (data not shown) were related to disease risk among cases who reported chemotherapy [OR and 95% CI for highest compared with lowest quartile = 1.27 (1.0–1.6)], whereas cases who did not receive this treatment were not at increased risk (OR = 0.94, 95% CI = 0.7–1.2). In most instances, adjustment for caloric intake attenuated these associations among chemotherapy cases and had no effect on estimates for cases not treated with chemotherapy. For example, risk associated with high vitamin C intake among chemotherapy cases was reduced from 1.37 to 1.17 (95% CI = 0.9–1.5) after adjustment for calories. There was no evidence that treatment with radiation or tamoxifen altered risk estimates. All further analyses were restricted to cases not receiving chemotherapy because of concern about inference from analyses that included cases with an observed bias. The analyses were also limited to women with *in situ* or localized invasive disease (hereafter referred to as early-stage cases) since it was unclear whether the treatment information was accurate for 60 of the 580 cases with regional and distant invasive breast cancer who reported no treatment beyond surgery. Among the 568 cases in the present analyses, there was no association between caloric intake and breast cancer risk (OR = 0.93, 0.85, 1.05 for quartiles 2, 3, 4). Further, adjustment for energy did not alter the risk estimates and had minimal influence on CIs so estimates were unadjusted for energy with exceptions noted in the text.

ORs for nutrients among early-stage cases not treated with chemotherapy are shown in Table II. In general, there were no significant associations between breast cancer and dietary intakes of key nutrients. Although overall dietary fiber showed no clear association with disease risk (Table III), intake of fiber from beans suggested reduced risk of disease. Adjustment for energy indicated similar risk estimates for fiber from beans (OR = 0.89, 0.73, 0.85 for quartiles 2, 3, 4). An additional food group representing the frequency of intake of bean items, without regard to the fiber content, was created to further evaluate risk noted from the fiber from bean group. This bean group also suggested reduced risk of disease across increasing consumption quartiles (OR = 0.74, 0.88, 0.87 for quartiles 2, 3, 4).

TABLE I – RISK OF EARLY-STAGE BREAST CANCER ASSOCIATED WITH DIETARY VARIABLES BY CHEMOTHERAPY STATUS OF CASES AND AMONG ALL CONTROLS

Dietary factor (daily intake)	Controls (n = 1,451)	Chemotherapy cases		Non-chemotherapy cases	
		Cases (n = 935)	OR ¹ (95% CI)	Cases (n = 628)	OR ¹ (95% CI)
Vitamin C (mg)					
<68	363	201	1.00	163	1.00
68–102	363	225	1.10 (0.9–1.4)	139	0.79 (0.6–1.0)
103–152	363	233	1.09 (0.9–1.4)	154	0.88 (0.7–1.2)
≥153	362	276	1.37 (1.1–1.7)	172	1.00 (0.8–1.3)
Vitamin E (α-TE)					
<6.3	363	225	1.00	169	1.00
6.3–8.3	364	194	0.85 (0.7–1.1)	137	0.79 (0.6–1.0)
8.4–11.3	362	230	1.03 (0.8–1.3)	144	0.86 (0.7–1.1)
≥11.4	362	286	1.27 (1.0–1.6)	178	1.11 (0.8–1.4)
Folate (μg)					
<173	363	203	1.00	163	1.00
173–231	363	183	0.87 (0.7–1.1)	133	0.80 (0.6–1.1)
232–326	363	278	1.35 (1.1–1.7)	180	1.08 (0.8–1.4)
≥327	362	271	1.31 (1.0–1.7)	152	0.92 (0.7–1.2)
Retinol (μg)					
<365	363	188	1.00	172	1.00
365–529	363	210	1.09 (0.9–1.4)	148	0.85 (0.7–1.1)
530–750	363	246	1.29 (1.0–1.7)	145	0.86 (0.7–1.1)
≥751	362	291	1.53 (1.2–2.0)	163	0.96 (0.7–1.3)
Calcium (mg)					
<463	363	203	1.00	167	1.00
463–648	363	225	1.08 (0.9–1.4)	136	0.83 (0.6–1.1)
649–934	363	246	1.19 (0.9–1.5)	181	1.11 (0.9–1.5)
≥935	362	261	1.32 (1.0–1.7)	144	0.92 (0.7–1.2)
α-Carotene (μg)					
<135	363	224	1.00	174	1.00
135–255	363	216	0.97 (0.8–1.2)	143	0.77 (0.6–1.0)
256–424	363	242	1.09 (0.9–1.4)	150	0.83 (0.6–1.1)
≥425	362	253	1.14 (0.9–1.4)	161	0.91 (0.7–1.2)
β-Carotene (μg)					
<1,385	363	203	1.00	148	1.00
1,385–2,191	363	240	1.14 (0.9–1.5)	170	1.05 (0.8–1.4)
2,192–3,528	363	226	1.10 (0.9–1.4)	147	0.88 (0.7–1.2)
≥3,529	362	266	1.31 (1.0–1.7)	163	1.00 (0.8–1.3)
Cryptoxanthin (μg)					
<46	363	191	1.00	159	1.00
46–78	363	228	1.19 (0.9–1.5)	151	0.94 (0.7–1.2)
79–125	363	253	1.29 (1.0–1.7)	154	0.92 (0.7–1.2)
≥126	362	263	1.41 (1.1–1.8)	164	1.03 (0.8–1.4)
Lutein (μg)					
<1,141	363	225	1.00	162	1.00
1,141–1,908	363	203	0.85 (0.7–1.1)	133	0.78 (0.6–1.0)
1,909–3,639	363	273	1.17 (0.9–1.5)	167	0.94 (0.7–1.2)
≥3,640	362	234	1.01 (0.8–1.3)	166	0.93 (0.7–1.2)
Lycopene (μg)					
<590	363	196	1.00	156	1.00
590–1,125	363	244	1.22 (1.0–1.6)	166	1.09 (0.8–1.4)
1,126–1,771	363	232	1.13 (0.9–1.5)	172	1.13 (0.9–1.5)
≥1,772	362	263	1.32 (1.0–1.7)	134	0.86 (0.6–1.2)

¹ORs adjusted for age at diagnosis, study site, ethnicity, education, age at first birth, alcohol intake, years of oral contraceptive use and smoking status.

We evaluated risk associated with dietary plus supplemental sources of vitamins (Table IV) and observed no association for total intake of vitamins C and E, folate, calcium or B-carotene. Evaluation of supplemental vitamin D (0, 1–399 and 400+ IU/day) was not associated with risk of early-stage breast cancer. Results were similar to those presented after further adjustment for the potential confounders of previous breast biopsy, frequency of mammograms and body mass index. There was no association between using vitamin supplement preparations on a regular basis (*i.e.*, at least once per week) and risk of disease (OR = 1.04, 95% CI = 0.8–1.3 for non-users *vs.* users).

Risk of early-stage breast cancer and intake of food groups (Table V) revealed a non-significant but slightly reduced risk associated with intake of vegetables and of cereals and grains.

Including both of these food groups in a model did not substantially alter risk estimates (OR = 0.83, 0.96, 0.90 and 0.81, 0.88, 0.86 for quartiles 2–4 of vegetables and cereals and grains, respectively). A combined fruit and vegetable variable showed no further discrimination of risks or linear trends. Additional adjustment for body mass index and height did not change the risk estimates for the food groups. Adjustment for energy yielded comparable risk estimates for vegetables and cereals and grains of 0.81, 0.92, 0.84 and 0.78, 0.82, 0.78, respectively, and similar CIs. Finally, limiting the analysis to the 353 cases with localized disease or to those cases who were interviewed within 3 months of diagnosis showed similar results to the overall group (data not shown).

We assessed risk related to the number of different items in a food group consumed per week because this variability may

TABLE II – RISK OF EARLY-STAGE BREAST CANCER ASSOCIATED WITH MICRONUTRIENTS AMONG CASES NOT TREATED WITH CHEMOTHERAPY AND ALL CONTROLS

Dietary factor (daily intake)	Cases (n = 568)	Controls (n = 1,451)	OR ¹ (95% CI)
Vitamin C (mg)			
<68	144	363	1.00
68–102	134	363	0.88 (0.7–1.2)
103–152	130	363	0.86 (0.6–1.1)
≥153	160	362	1.08 (0.8–1.4)
Vitamin E (α-TE)			
<6.3	154	363	1.00
6.3–8.3	124	364	0.79 (0.6–1.0)
8.4–11.3	127	362	0.83 (0.6–1.1)
≥11.4	163	362	1.13 (0.9–1.5)
Folate (μg)			
<173	153	363	1.00
173–231	117	363	0.75 (0.6–1.0)
232–326	162	363	1.03 (0.8–1.4)
≥327	134	362	0.89 (0.7–1.2)
Calcium (mg)			
<463	157	363	1.00
463–648	120	363	0.76 (0.6–1.0)
649–934	163	363	1.05 (0.8–1.4)
≥935	128	362	0.87 (0.7–1.2)
Retinol (μg)			
<365	161	363	1.00
365–529	137	363	0.84 (0.6–1.1)
530–750	129	363	0.81 (0.6–1.1)
≥751	141	362	0.90 (0.7–1.2)
α-Carotene (μg)			
<135	157	363	1.00
135–255	130	363	0.77 (0.6–1.0)
256–424	133	363	0.81 (0.6–1.1)
≥425	148	362	0.90 (0.7–1.2)
β-Carotene (μg)			
<1,385	138	363	1.00
1,385–2,191	152	363	1.02 (0.8–1.4)
2,192–3,528	136	363	0.90 (0.7–1.2)
≥3,529	142	362	0.96 (0.7–1.3)
Cryptoxanthin (μg)			
<46	147	363	1.00
46–78	131	363	0.89 (0.7–1.2)
79–125	143	363	0.94 (0.7–1.3)
≥126	147	362	1.02 (0.8–1.4)
Lutein (μg)			
<1,141	155	363	1.00
1,141–1,908	120	363	0.74 (0.6–1.0)
1,909–3,639	152	363	0.92 (0.7–1.2)
≥3,640	141	362	0.86 (0.6–1.2)
Lycopene (μg)			
<590	136	363	1.00
590–1,125	153	363	1.14 (0.9–1.5)
1,126–1,771	158	363	1.20 (0.9–1.6)
≥1,772	121	362	0.89 (0.7–1.2)

¹ORs adjusted for age at diagnosis, study site, ethnicity, education, age at first birth, alcohol intake, years of oral contraceptive use and smoking status.

indicate a dietary pattern that could be related to risk of disease. The patterns of risk for early-stage disease were similar to those for the total frequency of intake of the food group with 2 exceptions. A slightly reduced risk was observed for cruciferous vegetables (OR = 0.78, 95% CI = 0.5–1.2 for >2 per week vs. none) and carotenoid-rich foods (OR = 0.76, 95% CI = 0.5–1.1 for >3 vs. <1 per week). No other patterns associated with risk were demonstrated.

DISCUSSION

We have observed evidence of altered reporting for some micronutrients among cases who had received chemotherapy. When analyses were restricted to cases with early-stage cancers (*in*

TABLE III – RISK OF EARLY-STAGE BREAST CANCER ASSOCIATED WITH FIBER AND COMPONENTS OF FIBER

Dietary factor (daily intake)	Cases (n = 568)	Controls (n = 1,451)	OR ¹ (95% CI)
Dietary fiber (g)			
<7.6	142	363	1.00
7.6–10.2	157	363	1.06 (0.8–1.4)
10.3–13.8	133	363	0.90 (0.7–1.2)
≥13.9	136	362	0.94 (0.7–1.3)
Fiber from beans (g)			
<0.72	163	367	1.00
0.72–1.18	145	359	0.90 (0.7–1.2)
1.19–1.88	122	363	0.74 (0.6–1.0)
≥1.89	138	362	0.88 (0.7–1.2)
Fiber from grains (g)			
<2.43	136	364	1.00
2.43–3.59	163	363	1.22 (0.9–1.6)
3.60–5.09	136	362	1.00 (0.7–1.3)
≥5.10	133	362	0.98 (0.7–1.3)
Fiber from vegetables (g)			
<3.30	161	364	1.00
3.30–4.87	132	365	0.81 (0.6–1.1)
4.88–6.94	110	360	0.63 (0.5–0.8)
≥6.95	165	362	1.00 (0.8–1.3)

¹ORs adjusted for age at diagnosis, study site, ethnicity, education, age at first birth, alcohol intake, years of oral contraceptive use and smoking status.

TABLE IV – RISK OF EARLY-STAGE BREAST CANCER ASSOCIATED WITH NUTRIENTS FROM DIETARY AND SUPPLEMENTAL SOURCES

Nutrient (daily intake)	Cases (n = 568)	Controls (n = 1,451)	OR ¹ (95% CI)
Vitamin C (mg)			
<95	141	363	1.00
95–165	130	363	0.91 (0.7–1.2)
166–389	127	363	0.89 (0.7–1.2)
≥390	170	362	1.13 (0.9–1.5)
Vitamin E (α-TE)			
<8.2	138	363	1.00
8.2–16.4	142	363	1.06 (0.8–1.4)
16.5–31.1	107	363	0.77 (0.6–1.0)
≥31.2	181	362	1.28 (1.0–1.7)
Folate (μg)			
<213	137	363	1.00
213–374	141	363	0.98 (0.7–1.3)
375–612	130	363	0.93 (0.7–1.2)
≥613	160	362	1.11 (0.8–1.5)
Calcium (mg)			
<516	148	363	1.00
516–736	129	363	0.87 (0.7–1.2)
737–1,096	154	363	1.05 (0.8–1.4)
≥1,097	137	362	0.94 (0.7–1.3)
β-Carotene (μg)			
<1,755	142	363	1.00
1,755–2,758	127	363	0.86 (0.6–1.2)
2,759–4,347	149	363	0.97 (0.7–1.3)
≥4,348	150	362	0.98 (0.7–1.3)
Vitamin D (IU) ²			
0	332	848	1.00
1–399	65	186	0.89 (0.6–1.2)
≥400	171	417	0.98 (0.8–1.2)

¹ORs adjusted for age at diagnosis, study site, ethnicity, combination age at first birth and parity, years of oral contraceptive use, smoking, education and alcohol consumption. ²Vitamin D from supplemental sources only.

situ or localized) and not receiving this treatment, there was suggestive evidence of reduced risk of breast cancer associated with higher intakes of cereals and grains, and possibly of vegetables, beans or fiber from beans. However, risk estimates were modest, not statistically significant and no trends were observed.

TABLE V – RISK OF EARLY-STAGE BREAST CANCER ASSOCIATED WITH FOOD GROUPS

Food group (times per week)	Cases (n = 568)	Controls (n = 1,451)	OR ¹ (95% CI)
Fruit and fruit juices			
<3.5	152	382	1.00
3.5–6.9	140	346	1.04 (0.8–1.4)
7.0–11.1	116	361	0.76 (0.6–1.0)
≥11.2	160	362	1.08 (0.8–1.4)
Fruit			
<2.1	158	384	1.00
2.1–4.8	154	422	0.93 (0.7–1.2)
4.9–8.3	116	316	0.86 (0.6–1.2)
≥8.3	140	329	1.02 (0.8–1.4)
Vegetables			
<8.4	165	384	1.00
8.4–12.5	138	390	0.82 (0.6–1.1)
12.6–18.1	137	340	0.93 (0.7–1.2)
≥18.2	128	337	0.86 (0.6–1.1)
Fruit and vegetables			
<14	166	388	1.00
14.1–20.2	120	366	0.73 (0.6–1.0)
20.3–29.3	139	356	0.86 (0.7–1.1)
≥29.4	143	341	0.94 (0.7–1.2)
Cruciferous vegetables			
<1.4	261	671	1.00
1.4–2.0	74	215	0.87 (0.6–1.2)
2.1–3.4	132	296	1.11 (0.9–1.4)
≥3.5	101	269	0.95 (0.7–1.3)
Vitamin C-rich			
<3.5	178	458	1.00
3.5–5.5	112	282	0.98 (0.7–1.3)
5.6–9.7	138	390	0.85 (0.7–1.1)
≥9.8	140	321	1.10 (0.8–1.5)
Carotenoid rich			
<2.8	190	494	1.00
2.8–4.1	116	285	1.00 (0.8–1.3)
4.2–6.9	126	341	0.90 (0.7–1.2)
≥7	136	331	1.02 (0.8–1.3)
Cereals and grains			
<7.7	175	399	1.00
7.7–11.1	129	354	0.80 (0.6–1.1)
11.2–15.3	129	336	0.86 (0.7–1.1)
≥15.4	135	362	0.84 (0.6–1.1)
Caffeine			
<6.3	157	394	1.00
6.3–13.9	160	342	1.20 (0.9–1.6)
14.0–21.6	130	363	0.91 (0.7–1.2)
≥21.7	121	352	0.87 (0.7–1.2)

¹ORs adjusted for age at diagnosis, study site, ethnicity, education, age at first birth, alcohol intake, years of oral contraceptive use and smoking status.

None of the micronutrients assessed from food alone or from food plus supplements appeared to be associated with breast cancer risk.

Our results suggest that total dietary fiber and fiber from grains were not related to breast cancer risk. Given these findings, the reduced risk associated with the cereals and grains food group was unexpected. Such discordant results could arise from measurement error associated with food composition tables for fiber or from distinct risks unrelated to fiber itself but associated with cereal intake. Thus, dietary patterns associated with cereal intake or other components of cereal intake may be related to risk of disease. Other studies are consistent with reduced risk associated with cereals and fibers, though some inconsistencies arise across studies due to heterogeneity in cereal and fiber intakes. A study focused on premenopausal disease showed a strong reduction in risk (OR = 0.52) associated with dietary fiber but not fiber from grain (Freudenheim *et al.*, 1996). In studies that evaluated fiber constituents, investigators reported reduced risk of premenopausal breast cancer associated with non-starch polysaccharides (Baghurst and Rohan, 1994), cellulose and soluble fiber (Baghurst and Rohan,

1994; La Vecchia and Chatenoud, 1998) and little association with insoluble fiber (Baghurst and Rohan, 1994) and lignin (La Vecchia and Chatenoud, 1998). In 2 other studies that evaluated a cereal food group, reduced risks were observed (van't Veer *et al.*, 1990; Rohan *et al.*, 1993). A recent consensus statement indicated suggestive evidence that cereal fiber is protective for breast cancer (ECP Consensus Panel, 1998), though no differentiation was made for early- or late-onset disease. In the present study, high intake of fiber from bean sources was protective. The observed associations with beans, bean fiber and cereal groups may indicate a role for insulin metabolism (Kaaks, 1996) or phytoestrogens (Salvin *et al.*, 1997) in early-onset breast cancer.

Our analyses are consistent with previous findings for vegetables but not for some other dietary constituents. Similar to one study of premenopausal disease (Hunter *et al.*, 1993), we observed no association between breast cancer and dietary intake of vitamin C, dietary plus supplemental vitamin C or a vitamin C-rich food group. In contrast, an analysis of combined case-control studies showed reduced risk of breast cancer with vitamin C (Howe *et al.*, 1990) with results being stronger among postmenopausal (OR = 0.63) than premenopausal women (OR = 0.84). The interaction by menopausal status was not significant, however. Four previous studies investigating vegetable and carotenoid intake had large numbers of premenopausal cases and delineated results for this group of cases (Hunter *et al.*, 1993; Hirose *et al.*, 1995; Freudenheim *et al.*, 1996; Mezzetti *et al.*, 1998). In contrast with our findings, Hunter *et al.* (1993) observed reduced risks associated with vitamin A from both retinol and carotenoid sources, with results for vitamin A being stronger among premenopausal than postmenopausal women. A large case-control study of both premenopausal and postmenopausal women showed that intake of carrots and spinach but not preformed vitamin A (from food and supplements) was associated with reduced risk (Longnecker *et al.*, 1997). Consistent with these findings, high intakes of green vegetables, carrots, potatoes and sweet potatoes (Hirose *et al.*, 1995) and high B-carotene intake (Mezzetti *et al.*, 1998) were associated with reduced risk of breast cancer, particularly among premenopausal women. Results of a case-control study on premenopausal breast cancer patients indicated reduced risk associated with individual carotenoids and vitamin C (Freudenheim *et al.*, 1996). More importantly, vegetable intake was associated with a marked reduction in risk (OR = 0.46, 95% CI = 0.28–0.74), which persisted after adjustment for micronutrients also associated with risk. Those analyses suggested that the foods rather than discrete dietary constituents were associated with the reduced risk. Smaller analytic studies of premenopausal disease are also supportive of reduced risks associated with vegetable intake (Katsouyanni *et al.*, 1986; La Vecchia *et al.*, 1987; van't Veer *et al.*, 1990; Rohan *et al.*, 1993).

Lack of strong findings in our study may be due to a variety of factors including error associated with food composition data, a population with a homogenous diet or restriction of our cases to early-stage disease. A recent analysis showed that the carotenoid database used in our analysis ranked individuals comparably to the carotenoid database recently developed at the U.S. Department of Agriculture (USDA) (Vandenlangenberg *et al.*, 1996). Thus, use of the new carotenoid database may have resulted in misclassification error but this error should be comparable with that experienced in other studies. Lack of heterogeneity in dietary intakes, as assessed with our dietary instrument, also may have limited our analyses. Although the quartile cut-points do not reflect true absolute intakes, they suggest limited range of intake. In particular, there was only a 2-fold difference in the relative amounts in the highest and lowest quartiles of vegetable intake. Alternatively, in contrast with other case groups, our analysis was restricted to early-stage disease and, in particular, to those breast cancers not treated with chemotherapy. Thus, our results may be relevant only to early-stage disease or to particular tumor characteristics.

Although this was a large, population-based case-control study, several limitations warrant consideration. The young age of women and limited analytic sample among cases in our study may have resulted in cases with increased health awareness and potentially altered dietary habits. We could not evaluate this potential bias. Response rates were reasonably high (84.2% and 69.6% for the dietary component for cases and controls, respectively) but could have resulted in selection bias, particularly among controls. To evaluate potential bias in this study, we investigated frequency of intake of 7 key food items for hypotheses related to fat and vegetable intake among non-respondents. Among potential control subjects who were non-respondents, 122 agreed to a short telephone interview and all but 1 gave responses to the dietary questions. Control subjects who did not participate in the study were more likely than interviewed controls to eat carrots frequently. For example, 22.1% and 16.4% of non-respondents and

respondents, respectively, reported frequent carrot consumption (3–7 times per week), whereas 29.5% and 42.3%, respectively, reported infrequent consumption (1–3 times per month). These data suggest a possible underestimation of risk related to vegetable or carotenoid-rich food intakes. There were no food items on the non-respondent questionnaire regarding markers of cereal or grain intake.

We observed a slight reduction in risk associated with the intake of cereal and grains, vegetables and beans in this study of breast cancer in women less than 45 years old. Risks from food groups may have been underestimated due to misclassification error associated with dietary assessment (Willett, 1990), limited range of intakes and a select group of cases. Nonetheless, our data suggest minimal relationships between intakes of food groups and associated micronutrients and risk of early-onset breast cancer.

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- We observed a slight reduction in risk associated with the intake of cereal and grains, vegetables and beans in this study of breast cancer in women less than 45 years old. Risks from food groups may have been underestimated due to misclassification error associated with dietary assessment (Willett, 1990), limited range of intakes and a select group of cases. Nonetheless, our data suggest minimal relationships between intakes of food groups and associated micronutrients and risk of early-onset breast cancer.
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APPENDIX – COMPOSITION OF FOOD GROUPS

-
1. Fruit and fruit juices
 - Apples and applesauce, pears
 - Bananas
 - Peaches, apricots (canned, frozen)
 - Peaches, apricots (fresh, in season)
 - Cantaloupe (in season)
 - Watermelon (in season)
 - Strawberries (fresh, in season)
 - Oranges, tangerines
 - Orange juice, grapefruit juice
 - Grapefruit
 - Coconut, dried (sweetened)
 - Kiwi
 - Apricot nectar, papaya nectar
 - Plantain
 - Apple juice, unsweetened
 - Pineapple
 - Cranberry juice cocktail
 - Grapes
 - Mangoes
 - Papayas
 - Lemons, lemon juice
 - Berries
 - Raisins
 - Figs, prunes
 - Sweet cherries
 2. Fruit
 - Group 1 minus:
 - Orange juice, grapefruit juice
 - Apricot nectar, papaya nectar
 - Apple juice, unsweetened
 - Cranberry juice cocktail
 - Lemons, lemon juice
 3. Vegetables
 - Green beans
 - Peas
 - Corn
 - Winter squash
 - Tomatoes and tomato juice
 - Broccoli
 - Cauliflower, brussels sprouts
 - Spinach (raw)
 - Spinach (cooked)
 - Collards, kale, greens
 - Coleslaw, cabbage
 - Carrots, mixed vegetables with carrots
 - Green salad
 - Sweet potatoes
 - Other potatoes
 - Eggplant
 - Green chilis
 - Salsa picante
 - Carrot juice
 - Olives, green, commercial
 - Onions
 - Asparagus
 - Green pepper
 - Beets
 - Bean sprouts
 - Avocado
 - Seaweed
 - Summer squash
 - Garlic, raw
 - Cucumber
 3. Vegetables (*continued*)
 - Chayote squash
 - Mushrooms, canned
 - Artichokes, jarred
 - Celery
 4. Fruit and vegetables
 - Groups 1 and 3
 5. Cruciferous vegetables
 - Broccoli
 - Cauliflower, brussels sprouts
 - Collards, kale, greens
 - Coleslaw, cabbage
 6. Vitamin C-rich foods
 - Cantaloupe (in season)
 - Oranges, tangerines
 - Orange juice, grapefruit juice
 - Grapefruit
 - Plantain
 - Mangoes
 - Papayas
 - Broccoli
 - Cauliflower, brussels sprouts
 - Collards, kale, greens
 - Kiwi
 - Green pepper
 7. Carotenoid-rich foods
 - Peaches, apricots (canned, frozen)
 - Peaches, apricots (fresh, in season)
 - Cantaloupe (in season)
 - Watermelon (in season)
 - Apricot nectar, papaya nectar
 - Mangoes
 - Winter squash
 - Broccoli
 - Spinach (raw)
 - Spinach (cooked)
 - Collards, kale, greens
 - Carrots, mixed vegetables with carrots
 - Sweet potatoes
 - Carrot juice
 8. Cereals and grains
 - Rice
 - Cooked cereal
 - Bran and granola cereal
 - Highly fortified cereals
 - Dry cereal, excluding fiber fortified
 - Biscuits and muffins
 - Diet bread
 - White bread, rolls
 - Dark bread
 - Crackers
 - Cornbread
 - Brown rice
 - Bran
 - Wheat germ
 9. Caffeine
 - Regular colas with caffeine
 - Diet colas with caffeine
 - Caffeinated coffee
 - Caffeinated tea
 - Hot chocolate
 - Chocolate cake, brownies, cookies
 - Chocolate candy