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Dietary Fat, Fiber, Vegetable, and Micronutrients Are Associated With Overall Survival in Postmenopausal Women Diagnosed With Breast Cancer

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Abstract: *Relatively few studies have assessed the relationship between dietary intakes and survival after breast cancer diagnosis. We investigated the influence of diet, including dietary fat (percentage energy), fiber, vegetable, and fruit intakes, and micronutrients (folate, carotenoids, and vitamin C) on overall survival in women diagnosed with breast cancer. Subjects were postmenopausal women diagnosed with breast cancer (*N *= 516) between 1994 and 1995 with a mean survival time of 80 mo (SD: 18). Subjects completed a food frequency questionnaire for the year prior to diagnosis. Cox proportional hazards models were used to measure the relationship between dietary intakes and death due to any cause after breast cancer diagnosis. In the multivariate analysis, we found that the hazard ratio [HR and 95% confidence interval (CI)] of dying in the highest tertile compared to the lowest tertile of total fat, fiber, vegetable, and fruit was 3.12 (95% CI = 1.79–5.44), 0.48 (95% CI = 0.27–0.86), 0.57 (95% CI = 0.35–0.94), and 0.63 (95% CI = 0.38–1.05), respectively (*P *≤ 0.05 for trend, except for fruit intake). Other nutrients including folate, vitamin C, and carotenoid intakes were also significantly associated with reduced mortality (*P *≤ 0.05 for trend). These results suggest that in postmenopausal women diagnosed with breast cancer, reduced dietary fat and increased fiber, vegetable, fruit, and other nutrient intakes associated with a plant-based, high-fiber diet improves overall survival after breast cancer diagnosis.*

Introduction

Many studies have examined the relationship between dietary constituents and breast cancer risk (1–4). Several dietary factors including dietary fat, fiber, and vegetable and fruit consumption, as well as micronutrients such as carotenoids and vitamin C, have been implicated in the etiology of breast cancer incidence (1–5). However, over the last two decades only 16 studies have investigated the influence of dietary variables on breast cancer progression, recurrence, and/or overall survival after breast cancer diagnosis (6–9).

Several large cohort studies have examined the relationship between diet, particularly dietary fat, on either overall or breast cancer-specific mortality after breast cancer diagnosis (10–12). Jain and colleagues assessed premorbid diets, via a food frequency questionnaire (FFQ), in 89,835 women of which 678 were diagnosed with invasive breast carcinoma (10). Results from this cohort indicated that after energy adjustment, total fat intake was not associated with breast cancer-specific mortality, however a 5% increase in saturated fat corresponded with a 50% increased risk of dying from breast cancer [hazard ratio (HR) = 1.50, 95% CI = 1.08–2.08) (10). Additional cohort studies investigating the relationship between diet and survival after breast cancer diagnosis have produced mixed results (11–15). Holmes et al. indicated a lack of association between total dietary fat consumption (energy-adjusted) and overall survival, while Zhang et al. reported a significant association between nonenergy adjusted mono-saturated fat intake and overall survival after breast cancer diagnosis (11,12). Three additional prospective studies did not find a relationship between dietary fat and risk of death (13–15), and two of these studies adjusted for confounding factors, including stage and age at diagnosis (13,14).

Studies investigating vegetable and fruit consumption or micronutrients found in these sources (such as vitamin C or carotenoids) suggest a modest to moderate protective effect (HR range = .20–.81) with increased intakes of fruits and vegetables on survival after breast cancer; but, studies on fiber, a major component of vegetable and fruits, have reported little to no significant association between consuming a high-fiber diet and reduced recurrence and/or improvement in survival (10–12,16–18). In addition, the large Nurses Health cohort reported a borderline significant inverse association ($P = 0.07$ for trend) for vegetable consumption and a nonsignificant association for fruit intake with all-cause mortality. However, a subanalysis of women without metastatic

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lymph nodes in this cohort revealed that vegetable, fiber, and other nutrients from vegetables such as lutein/zeaxanthin were significantly related to reduced [relative risk (RR) range of highest strata = 0.59–0.65] overall mortality after breast cancer diagnosis (11).

Currently two ongoing randomized clinical trials (RCTs) are investigating the influence of a dietary intervention on breast cancer recurrence and mortality (19,20). The Women's Intervention in Nutrition Study assessed the effects of a low fat diet (≤15% energy from fat) on recurrence-free survival after breast cancer diagnosis, and in an earlier report showed a decrease in fat intake and a reduction in serum cholesterol in the intervention group (19). The second RCT, the Women's Healthy and Eating Living (WHEL) Study, is investigating the influence of a daily dietary goal of 5 servings of vegetable, 3 servings of fruit, 30 g of fiber, 16 fl oz of vegetable juice, and 15–20% energy from fat on breast cancer recurrence (20). The WHEL Study has reported significant dietary changes (in vegetable, fruit, fiber, and reduced fat from baseline to follow up) in women enrolled in the intervention group and has reported on circulating carotenoids concentrations (20–22).

For this study, we examined the effects of dietary factors on overall survival after breast cancer diagnosis in postmenopausal women. In particular, we investigated whether dietary fat and fat-subtypes (percentage energy), vegetable, fruit, fiber, and micronutrients are related to overall survival after breast cancer diagnosis.

Material and Methods

Study Population and Recruitment

The population under study was a cohort of breast cancer cases diagnosed in Orange County, California, during the 1-yr period beginning March 1, 1994. Eligible breast cancer cases were identified within 6 mo of diagnosis through the existing population-based cancer registry of the Cancer Surveillance Program of Orange County (CSPOC) (23–27). Thereafter, subjects were consented and enrolled into a population-based study examining environmental and hereditary factors associated with breast and ovarian cancer (26,27).

Methodology, recruitment, and participation rates of the larger population based study have been described previously (26,27). For this study, women who had complete dietary data, as well as descriptive and other variable data, including body mass index (BMI), ethnicity, parity, and hormone replacement therapy (HRT) use were included in this study. Of the 980 who completed the FFQ, 691 were postmenopausal and/or were diagnosed at ≥50 yrs. Of the 691, 629 had valid FFQ data, while 516 had complete reproductive, descriptive, and dietary data. The study protocol, including questionnaires, was approved by the Internal Review Board (IRB) of the University of California, Irvine (UCI, IRB #: HS91–137).

Dietary Assessment

The 100-item NCI-Block FFQ (28) was used to assess the usual dietary intakes of subjects enrolled in this study. The FFQ was self-administered and completed via mail after enrollment in the study. Subjects were provided specific instructions to answer all questions accurately and carefully and to complete the FFQ based on their "usual" dietary pattern. Women diagnosed with breast cancer were instructed to complete the questionnaire based on dietary habits during the year prior to diagnosis. Details regarding development and dietary assessment capabilities of the FFQ have been previously published (28). Nutrient analysis was calculated by the DietSys 4.0 program.

Other Measures

Stage and age at cancer diagnosis were obtained through the cancer registry database. Stage of disease at diagnosis was the summary stage defined by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute as follows: In situ stage was defined as malignant, noninvasive carcinoma; localized disease was defined as invasive carcinoma confined to the breast; regional stage was defined as invasive carcinoma spread beyond the breast, by direct extension and/or to regional lymph nodes; and distant disease was defined as direct extension beyond adjacent organs specified as regional, metastasis to distant lymph nodes, or development of discontinuous secondary or metastatic tumors. In terms of TNM classification, localized disease includes tumors T1–T3, N0, M0. Regional disease includes tumors T4, N0, M0, or any T, N1–N3, M0; and distant disease corresponds to any T, and N, M1. To increase sample size and power, we included women diagnosed with in situ breast cancer (n = 77) and with metastatic disease (n = 8). Results were similar when including women either with or without in situ breast cancer and/or metastatic disease (data not shown).

Height and weight, used to calculate BMI (kg/m^2), and alcohol use data were obtained via self-report from the FFQ. Menopausal status, parity, and HRT use were self-reported via a questionnaire. If a woman reported being postmenopausal or if this data item was missing (approximately 6% missing) but the woman was ≥50 years at time of diagnosis, then she was considered to be postmenopausal.

For the present analysis, follow-up data was obtained by the cancer registry and was available through January 1, 2003 (range = 1.0–101 mo). Follow up was ascertained from periodic reports from hospital-based registries and from annual linkage with the mortality records from the California Department of Vital Statistics, the Department of Motor Vehicles, the National Death Index, the National Change of Address, and several other linkages with national and local databases. The mean follow-up/survival time was 80 mo (SD = 18). For the present analysis, we had complete follow-up data on 98% of the sample.

Statistical Methods

We calculated descriptive statistics for stage, age at diagnosis, BMI, and ethnicity for our population. Women who consumed <600 Kcal or >5,000 Kcal ($n = 62$) were excluded from the analysis. All subjects alive at last follow up were treated as censored observations, and their survival time was computed from the date of diagnosis to date of last contact. Death from any cause was the main outcome.

Cox proportional hazards multivariate regression models were used to test for significance and estimate risk of death related to dietary factors, while adjusting for covariates previously shown to be associated with breast cancer risk and/or survival after cancer diagnosis: stage of disease, age at diagnosis, energy intake, BMI, parity, HRT, alcohol and vitamin use. Dietary intakes of total fat (percentage energy), fat-subtypes (percentage energy), vegetable, fruit, fiber, and other nutrients, including folate, vitamin C, and carotenoids from food alone and food plus supplements were included as tertiles in the model. Food groups, macro-, and micronutrients were modeled separately. In the multivariate model, stage of disease was included as the SEER summary stage, and age at diagnosis, energy intake, BMI, and parity were included as continuous variables. HRT use was categorized as no use (reference), estrogen only, progesterone only, and both estrogen and progesterone. Alcohol and vitamin use were dichotomized as use or no use. Vitamin use included use of multivitamins and individual vitamin supplementation, including vitamin A, vitamin E, calcium, and vitamin C. Other vitamin use (e.g., folate and iron) were derived from the multivitamin category/question. In addition, we included a variable representing time since diagnosis to completion of the FFQ [Mean (yrs) and SD = 1.34 (±0.67)], as well as education; however, both variables were not significantly associated with overall survival in a majority of the models and had little to no effect on the results and therefore were not included in the multivariate model. We also conducted a subanalysis of the dietary variables as described previously using Cox proportion multivariate hazards models to assess the influence of diet on breast cancer specific mortality.

Hazard ratios (HR) and 95% confidence intervals (CI) are shown for the 2nd and 3rd tertile with the lowest category of intake as the reference group. The minimum value of each tertile is shown in the tables. We tested for trend as shown in a previous study on diet and survival after breast cancer diagnosis (11). The linear trend test across the tertiles was calculated by assigning an ordinal value to each category. The ordinal values were then modeled as a continuous variable, which limited the influence of outlying values that would have been more apparent if continuous values of food intakes were used.

Results

Overall, 96 deaths were reported and of the 96 deaths in the study, 41 (43%) were due to breast cancer, 9 (9%) were due to other cancers, 13 (14%) were due to cardiovascular disease, 22 (23%) were due to other causes, and 11 (11%) were unknown. The mean duration of follow up for the study sample was 80 (±18) mo. A majority of the population was non-Hispanic White (92.25%), followed by Asians (2.91%), Hispanics (2.33%), and Unknown/other (2.52%; Table 1). Covariates used in the multivariate model are also shown in Table 1. The mean age at diagnosis was 64.78 yr (±9.25). The proportion of women diagnosed with in situ stage was 14.92%, with localized stage was 59.30%, with regional stage was 24.22%, and with metastatic disease was 1.55%. BMI distribution in the study sample was 48.64% normal weight, 31.59% overweight, and 19.77% obese. Approximately a quarter (26.74%) did not use HRT, while 36.24% used estrogen only, 1.94% used progesterone only, and 35.08% used both estrogen and progesterone. The mean number of children for the cohort was 2.38 (SD = 1.71). Also, over half (52.91%) the women used alcohol, and a majority (75.97%) reported taking vitamins. In the multivariate model for the covariates, regional (HR = 4.54, 95% CI = 2.02, 10.22, $P < 0.0003$) and distant stage (HR = 21.35, 95% CI = 6.85, 66.55, $P < 0.0001$), age at diagnosis (HR = 1.05, 95% CI = 1.03, 1.08, $P < 0.0001$), parity (HR = 1.18, 95% CI = 1.06, 1.08), and estrogen use (HR =0.58, 95% CI = 0.36, 0.94, $P < 0.03$) were significantly associated with overall survival after breast cancer diagnosis, while BMI, alcohol, and vitamin use were not associated with overall survival.

In the multivariate analysis for dietary intakes (Table 2), women in the highest tertile of percentage energy from fat in-

Table 1. Covariates and Descriptive Statistics

Characteristics	Study Population ($N = 516$)
Time to follow-up, mo (SD)	80 (18)
Age at Diagnosis, mean (SD)	64.78 (9.25)
Race/ethnicity, *n* (%)	
Non-Hispanic White	476 (92.25)
Asian	15 (2.91)
Hispanic	12 (2.33)
Unknown	13 (2.52)
Stage, *n* (%)	
In situ	77 (14.92)
Localized	306 (59.30)
Regional	125 (24.22)
Metastatic	8 (1.55)
Body mass index, *n* (%)	
Normal (<25 kg/m^2)	251 (48.64)
Overweight (25–29.9 kg/m^2)	163 (31.59)
Obese (>30 kg/m^2)	102 (19.77)
Hormone replacement, *n* (%)	
No use	138 (26.74)
Estrogen only	187 (36.24
Progesterone only	10 (1.94)
Estrogen and progesterone	181 (35.08)
Parity, mean (SD)	2.38 (1.71)
Alcohol use, *n* (%)	
No	243 (47.09)
Yes	273 (52.91)
Vitamin use, *n* (%)	
No	124 (24.03)
Yes	392 (75.97)
Energy intake, mean (SD)	1315.99 (519.38)

Table 2. Multivariate Hazard Ratios (HR)[a] of Death (all cause mortality) by Tertiles[b] of Selected Food Groups and Macronutrient Intakes (per day) Among Postmenopausal Women Diagnosed With Breast Cancer ($N = 516$)

	Dietary Intakes			
Dietary Nutrient	Tertile 1	Tertile 2	Tertile 3	*P*-Value (trend)
Total fat (% energy)		30.27	38.37	
HR	1.0	1.69	3.12	<0.0001
95% CI	ref	0.94–3.06	1.79–5.44	
Saturated fat (% energy)		11.56	19.21	
HR	1.0	1.78	4.45	
95% CI	ref	0.99–3.25	2.26–8.78	<0.0001
Oleic fatty acid (% energy)		12.48	21.01	
HR	1.0	2.57	3.56	
95% CI	ref	1.41–4.65	1.67–7.59	0.0007
Linoleic fatty acid (% energy)		6.28	10.69	
HR	1.0	1.62	2.39	
95% CI	ref	0.94–2.80	1.21–4.69	0.01
Fiber (g)		8.74	13.28	
HR	1.0	0.78	0.48	0.01
95% CI	ref	0.48–1.28	0.27–0.86	
Vegetable (servings)		2	3.1	
HR	1.0	0.43	0.57	0.02
95% CI	ref	0.25–0.74	0.35–0.94	
Fruit (servings)		1.1	2	
HR	1.0	0.93	0.63	0.08
95% CI	ref	0.55–1.56	0.38–1.05	

a: Dietary variables are controlled for stage of disease, age at diagnosis, body mass index, parity, harmone replacement therapy use, alcohol use, multivitamin use, and energy intake. Food groups and macronutrients are modeled separately.
b: The minimum values/points of the tertiles are shown.

take were nearly three times at increased risk (HR = 3.12, 95% CI = 1.79–5.44) of dying compared with the lowest tertile of intake ($P < 0.0001$ for trend). Similarly, increased consumption of saturated fat (percentage energy), oleic acid (percentage energy), and linoleic acid (percentage energy) were significantly associated with reduced survival ($P < 0.01$). The HR comparing the highest tertile to the lowest tertile for fiber was 0.48 (95% CI = 0.27–0.86), 0.57 (95% CI = 0.35–0.94) for vegetable, and 0.63 (95% CI = 0.38–1.05) for fruit. There was a significant linear trend for fat (percentage energy) and fat subtypes (percentage energy), fiber, and vegetable intakes ($P < 0.05$), and a borderline significant ($P = 0.08$) linear trend across tertiles for fruit intake in relation to risk of death from any cause after breast cancer diagnosis.

Table 3 shows the association between folate, vitamin C, and carotenoids intakes with all-cause mortality. Women in the highest tertile of dietary folate intake had a HR of 0.34 (0.18–0.67) compared with the lowest tertile. Similarly, women consuming the highest tertile of vitamin C, and the carotenoids β-carotene, lutein, and β-cryptoxanthin, from food alone were significantly more likely to survive compared to the group in the lowest tertile of intakes ($P \leq 0.05$). Overall, nutrients from the diet of food rather than from diet plus supplements were associated with survival. Also, additional nutrients available from the database are shown in the Appendix.

The subanalysis of patients dying specifically from breast cancer ($n = 41$) revealed that although the direction of the HR for a majority of the dietary variables, including food groups, macro-, and micronutrients, were similar to the overall models described previously, only total dietary fat (percentage energy) was significantly ($P < 0.05$, for trend) related to increased mortality due to breast cancer (data not shown).

Discussion

We found that self-reported premorbid dietary intakes of percentage energy from fat, fat subtypes (percentage energy), fiber, vegetable, and fruit and other nutrients related to a plant-based diet were significantly associated with overall survival in postmenopausal women with a history of breast cancer. The risk of dying was nearly three times higher for the group who consumed fat in the highest tertile compared with the lowest tertile. Also, higher vegetable and fiber intakes were associated with >40–50% reduced risk of dying after breast cancer diagnosis. Dietary nutrients, including folate, carotenoids, and vitamin C, rich in vegetable and fruits were also significantly associated with reduced overall mortality (range 33–50%) after breast cancer diagnosis.

Large cohort studies (10–12) and other relatively smaller studies (29,30) assessing the influence of dietary fat and dietary fat subtypes on either breast cancer specific and/or overall survival and recurrence after breast cancer diagnosis have produced mixed results. The Nurses Health Study assessed premorbid diet in 1,504 women via a FFQ and reported no significant trend in dietary total fat intake and all-cause mortality after breast cancer diagnosis (11). An-

Table 3. Multivariate Hazard Ratios (HR)[a] of Death (all cause mortality) by Tertiles[b] of Selected Micronutrient Intakes, Primarily Found in Fruits and Vegetables, Among Postmenopausal Women Diagnosed With Breast Cancer ($N = 516$)

	Dietary Intakes (per day)			
Dietary Nutrient[c]	Tertile 1	Tertile 2	Tertile 3	*P*-Value (trend)
Folate (μg)		200.62	279.10	
HR	1.0	0.37	0.34	0.0006
95% CI	ref	0.22–0.65	0.18–0.67	
Vitamin C (mg)		80.08	135.43	
HR	1.0	0.50	0.45	0.0037
95% CI	ref	0.30–0.84	0.25–0.78	
Carotenoids				
α-Carotene (μg)		150.87	329.86	
HR	1.0	1.03	0.77	0.32
95% CI	ref	0.62–1.70	0.45–1.30	
β-Carotene (μg)		1393.88	2378.42	
HR	1.0	0.86	0.50	0.01
95% CI	ref	0.52–1.42	0.29–0.85	
β-Cryptoxanthin (μg)		53.7	102.65	
HR	1.0	1.12	0.54	0.05
95% CI	ref	0.69–1.83	0.30–0.96	
Lutein (μg)		760.28	1573.96	
HR	1.0	0.62	0.50	0.0072
95% CI	ref	0.38–1.01	0.30–0.84	
Lycopene (μg)		835.43	1612.00	
HR	1.0	0.58	0.76	0.22
95% CI	ref	0.35–0.96	0.45–1.30	
Provitamin A, “carotene” (μg)		1636.8	2862.32	
HR	1.0	0.96	0.58	0.04
95% CI	ref	0.58–1.60	0.34–0.99	
Total folate, with supplements (μg)		304.66	619.48	
HR	1.0	1.58	1.05	0.96
95% CI	ref	0.92–2.73	0.54–2.03	
Total vitamin C, with supplements (mg)		148.67	569.35	
HR	1.0	1.10	0.58	0.09
95% CI	ref	0.66–1.83	0.31–1.09	
Total β-carotene, with supplements (μg)		2127.60	3293.72	
HR	1.0	0.71	0.69	0.18
95% CI	ref	0.43–1.17	0.40–1.20	

a: Dietary variables are controlled for stage of disease, age at diagnosis, body mass index, parity, harmone replacement therapy use, alcohol use, multivitamin use, and energy intake. Micronutrients are modeled separately.
b: The minimum values/points of the tertiles are shown.
c: Dietary nutrients shown are from food except for total values, which are from food plus supplements/vitamin use.

other large Danish cohort study ($n = 2{,}445$) showed no relationship between dietary fat intake and survival after breast cancer diagnosis (13). However, in contrast with our study, the Ewertz study did not adjust for total energy intake when analyzing dietary fat, which could contribute to differences in study results. Jain and colleagues also assessed self-reported dietary intakes prior to diagnosis in 678 breast cancer cases and reported no significant association between total fat intake and survival after breast cancer diagnosis; however, for every 5% increase in saturated fat intake, the risk of dying from breast cancer increased by 50% (10). Similar to our study, two other cohort studies showed a relationship between dietary fat and overall prognosis after breast cancer diagnosis (12,29). Nomura showed a three times (95% CI = 1.2–8.6) increased risk of dying in Caucasian women with breast cancer in the highest category of fat intake compared with the lowest category; however, the data were unadjusted for total energy intake (29). Zhang and colleagues reported a two time increased risk of dying (all-cause) after breast cancer in women who consumed high dietary total, saturated, and monounsaturated fat (12) after adjusting for total energy intake. Similarly, our study suggested that saturated fat and oleic acid (the first five sources of oleic acid in our sample included cooking oil; margarine; doughnuts, cookies, cake; biscuits, muffins; cheese and cheese spread) were associated with a three to four times increased risk of dying. A more recent study showed that the relationship between dietary fat intake (energy adjusted), as well as the ratio of polyunsaturated fat:saturated fat, with breast cancer survival may be U shaped (HR ranged from 2.1–6.5) rather than linear (7).

We found a significant protective effect of dietary fiber intake on overall survival after breast cancer diagnosis. Previous studies have shown little to no association between dietary fiber intake and breast cancer recurrence and/or survival (10–12,16–18). The larger cohort studies assessing premorbid diet found no significant association between fiber and survival after breast cancer risk; however, the relative risk (RR = 0.77, 95% CI = 0.47–1.25) and point estimates suggested a protective effect (10,11). Other cohort studies reported no relationship between fiber and overall survival and/or recurrence (17,18,30). The observed differences between these studies and/or with our results can be possibly explained by differences in sample size, different methods of dietary data assessment, and variations in dietary intakes of macro- and micronutrients across study populations.

We found a significant inverse linear trend between vegetable intake, and a borderline positive linear trend of fruit intake with overall survival after breast cancer diagnosis. Other studies have shown a modest protective effect of vegetable and fruit intake and/or nutrients related to these foods on survival after breast cancer diagnosis (11,18). A study of 103 pre- and postmenopausal women with breast cancer showed that women in the highest tertile of vegetable intake had a RR of 0.60 ($P = 0.04$) of dying compared with the lowest tertile (18). Results from a subsample ($n = 1,982$) of the Nurses Health Cohort Study suggested a significant protective effect (RR = 0.62 for highest quartile; $P = 0.02$ for trend) of vegetable intake on all-cause mortality in women without metastases to the lymph nodes (11). Previous studies confirm our results, both in magnitude and direction of the relationship between vegetable and fruit intakes with overall survival; however, further studies with a wider variability of intakes, as well as pre- and postmorbid dietary data assessments, may produce more conclusive evidence regarding the relationship between vegetable and fruit intakes with survival after breast cancer diagnosis.

In our study, increased consumption of nutrients, including folate, vitamin C, and the carotenoids, lutein, β-carotene and β-cryptoxanthin are all markers of a vegetable-rich/high-fiber diet, and therefore were also (most likely) associated with reduced risk of dying after breast cancer diagnosis. Jain and colleagues reported a protective hazards ratio of 0.43 (95% CI = 0.21–0.86) for vitamin C and 0.48 (95% CI = 0.23–0.99) for β-carotene on the risk of dying from breast cancer (10). Also, Holmes and colleagues showed a reduced risk of all-cause mortality with increasing intake of fiber and lutein (11). A recent study from the WHEL RCT examined plasma carotenoid concentrations only in the control group (that was recommended the USDA dietary guidelines) and found that women in the highest quartile of total circulating carotenoid concentrations had significantly (HR = 0.57; 95% CI = 0.37–0.89) better recurrence free survival compared with the group in the lowest strata (9); however data on the association between dietary and plasma carotenoids concentrations with recurrence and/or disease-free outcomes in the intervention group has yet to be reported.

The significant associations between dietary nutrients and overall survival observed when assessing dietary food and supplements were primarily from nutrients in food rather than from nutrients plus supplements, suggesting that nutrients obtained from food confers protection related to overall survival after breast cancer diagnosis in the present study. This may be due to varying absorption/metabolism of nutrients from food compared with supplements and/or limitations with ascertainment of complete supplement data with FFQs, but further detailed analysis of nutrients from food verses supplements is beyond the scope of this study. Also, we found no association between alcohol use and overall survival after breast cancer diagnosis. Most studies on breast cancer risk suggest alcohol use modestly increases breast cancer risk, however a majority of the studies assessing the relationship between alcohol use and overall survival after breast cancer reported that alcohol use had no influence on survival (11,12,16–18).

In our subanalysis of breast cancer specific mortality, we found that only total dietary fat was positively associated with dying from breast cancer; however, although in the right direction and similar magnitude, the other food groups and nutrients were not significantly associated with deaths due to breast cancer. Because the direction and magnitude for many of the dietary variables were similar to that of the primary analysis on overall survival, it is likely that the small sample size of deaths due to breast cancer only was a limitation in this subanalysis. More important, it is also possible that the observed effect of diet on overall survival is due to the effect on causes of death known to be associated with diet, such as heart disease and/or causes of death unrelated to breast cancer. However, these data on breast cancer specific deaths need to be replicated in a larger sample size. In addition, limitations of the consistency and accuracy of cause specific mortality data should be recognized and therefore cause specific death analysis should be interpreted with caution.

This study contributes to the literature on the relationship between dietary factors and overall survival after breast cancer. As indicated previously, few studies (relative to those examining diet and breast cancer incidence) have assessed the influence of food groups (vegetable and fruits), fiber, and fat, as well as micronutrients on overall survival after breast cancer diagnosis. In addition, this study obtained cancer statistic data, including stage and age of diagnosis, and dietary data from patients enrolled in a population-based cancer registry, making the results generalizable to postmenopausal women diagnosed with breast cancer. Also, even after adjusting for factors potentially associated with breast cancer (reproductive factors), with overall survival (BMI, energy intake, age, and stage of disease), and with other lifestyle factors (alcohol and multivitamin use), we observed a significant trend between the dietary variables of interest and overall survival after breast cancer diagnosis.

We assessed the relationship between premorbid diet and overall survival after breast cancer diagnosis. We do not have information on whether the women changed their dietary intakes of fat, fiber, vegetable and/or other nutrients subsequent to breast cancer diagnosis and/or treatment. Studies indicate that after breast cancer diagnosis, women are motivated to change their diet, but this is observed primarily in younger women, and the mean age for the current population was 64.7 (31,32). Also, even if a portion of the women improve their health behaviors after diagnosis, a substantial percentage (50%) of women continue to engage in health-risk behaviors, including consuming less than the recommended 5 servings of vegetable and fruit/day and consuming >30% energy from fat (23% of the sample) (33). Therefore, subjects in this study may have continued to follow their premorbid diets after breast cancer diagnosis, which could provide a rationale for the current findings of an association between premorbid dietary intakes and overall survival. If the women in this study continued to consume their premorbid diet after diagnosis, then implications of these results are that women in the general population should be encouraged (either pre- or post-diagnosis) to consume and/or modify their diet to reflect a high vegetable, fruit, fiber, and low fat dietary pattern.

Other limitations of the study should be acknowledged. First, subjects were asked to report dietary data 1 yr prior to their breast cancer diagnosis; therefore, some of the subjects may have either recalled and reported a less healthful diet or may have reported a more healthful diet. Possibly when assessing breast cancer risk in a case/control design, this may influence the risk estimates, however, the current sample includes only cases diagnosed with breast cancer and strata of dietary intakes were compared within this group, therefore the effects of recall bias on the estimation of overall survival after breast cancer diagnosis (with a mean follow-up time of 80 mo) should be minimal in this study. Nonetheless, misclassification of exposure due to reporting/recall bias is a limitation, but we do not know to what extent and/or whether the data has been misreported. Also, other well-recognized limitations in nutritional epidemiology studies include imprecision in dietary assessments using FFQs and the quality of food content databases, which could effect observed associations between dietary intakes and breast cancer outcomes. In addition, we have no information on whether treatment was unsuccessful among certain women, which may influence reporting of dietary data, and if these women were likely to die then, potentially, the present results may be affected. Finally, due to the relatively small sample size, the types of contrasts that can be assessed, and the capability to examine multicollinearity between the dietary variables are limited. In addition, the hazard ratios and confidence intervals, particularly when assessing dietary fat and fat subtypes, observed in our study are more extreme than other studies (10–13) and may be due to chance because of the small size in the current study.

Overall, different methods of dietary assessment, varying sample sizes, differences in statistical adjustment factors (i.e., energy, prognostic, and reproductive variables), and variation in dietary intakes in the study sample, in addition to the relatively few studies assessing the relationship between diet and mortality after breast cancer diagnosis, contributes to the mixed results when assessing the effects of diet on overall survival. But, consistent with previous research, we found a protective effect on overall survival with increased folate, vitamin C, and carotenoid consumption, which are highly concentrated in green leafy vegetables and are excellent markers of fruit and vegetables. Although previous studies have found a modest association between dietary fat and fiber intake and survival, these findings indicate that modifying dietary intakes, such as increasing fiber intake (at least >13 g/day) and reducing fat (<31% energy from fat) may improve and promote overall survival. Therefore, based on the present results women should be encouraged to consume vegetables and fruit rich in folate, vitamin C, carotenoids, and fiber, while consuming a diet low in fat. Additional studies, not only on premorbid diet but also on dietary changes made after diagnosis, are needed to fully understand the clinical consequences of diet and dietary modification on overall survival after breast cancer diagnosis. These results need to be confirmed by additional studies, as well as by the on-going randomized clinical trials assessing the effects of diet on breast cancer recurrence and survival (19,20).

Acknowledgments and Notes

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Appendix. Multivariate Hazard Ratios (HR)[a] of Death (all cause mortality) by Tertiles[b] of Additional Nutrient Intakes Among Postmenopausal Women Diagnosed With Breast Cancer (N = 516)

	Dietary Intakes			
Dietary nutrient[c]	Tertile 1	Tertile 2	Tertile 3	*P*-Value (trend)
Iron (mg)		7.92	11.26	
HR	1.0	0.77	0.47	0.04
95% CI	ref	0.47–1.28	0.24-0.94	
Vitamin E (α-TE)		5.51	8.30	
HR	1.0	0.82	1.51	0.31
95% CI	ref	0.46–1.46	0.76–2.98	
Dietary B1 (mg)		0.82	1.17	
HR	1.0	0.74	0.36	0.01
95% CI	ref	0.44–1.24	0.16-0.79	
Riboflavin (mg)		1.13	1.74	
HR	1.0	0.55	0.51	0.04
95% CI	ref	0.31-0.96	0.26–1.00	
Niacin (mg)		11.38	15.75	
HR	1.0	0.86	0.91	0.76
95% CI	ref	0.51–1.47	0.45–1.87	
Vitamin B6 (mg)		1.08	1.56	
HR	1.0	0.73	0.69	0.23
95% CI	ref	0.42–1.26	0.36–1.30	
Magnesium (mg)		181.43	249.36	
HR	1.0	0.59	0.33	0.0022
95% CI	ref	0.35–1.01	0.16-0.68	

(continued)

Appendix. (*Continued*)

Dietary nutrient[c]	Dietary Intakes Tertile 1	Tertile 2	Tertile 3	*P*-Value (trend)
Dietary calcium (mg)		440.32	756.27	
HR	1.0	0.79	0.57	0.10
95% CI	ref	0.46–1.35	0.29–1.12	
Phosphorous (mg)		702	1068.42	
HR	1.0	0.77	0.68	0.29
95% CI	ref	0.44–1.33	0.32–1.45	
Sodium (mg)		1675.60	2442.58	
HR	1.0	1.03	1.31	0.50
95% CI	ref	0.59–1.80	0.63–2.73	
Potassium (mg)		1829.30	2550.22	
HR	1.0	0.66	0.38	0.01
95% CI	ref	0.39–1.13	0.18-0.82	
Dietary vitamin A (IU)		4311.50	6935.43	
HR	1.0	0.81	0.48	0.02
95% CI	ref	0.48–1.36	0.26-0.89	
Retinol (μg)		358.55	599.95	
HR	1.0	0.99	0.72	0.32
95% CI	ref	0.58–1.69	0.38–1.37	
Cholesterol (mg)		123.34	210.66	
HR	1.0	2.38	1.85	0.09
95% CI	ref	1.35–4.22	0.96–3.53	
Protein (% energy)		15.03	17.61	
HR	1.0	0.58	0.68	0.99
95% CI	ref	0.34 - 0.97	0.41 - 1.12	
Carbohydrate (% energy)		42.66	51.76	
HR	1.0	0.65	0.32	<0.0001
95% CI	ref	0.40–1.05	0.18-0.56	
Total B1, with supplements (mg)		1.28	2.63	
HR	1.0	1.14	1.19	0.63
95% CI	ref	0.63–2.06	0.61–2.33	
Total B6, with supplements (mg)		1.68	3.46	
HR	1.0	1.03	1.25	0.47
95% CI	ref	0.58–1.83	0.66–2.39	
Total calcium, with supplements (mg)		640.06	1030.33	
HR	1.0	0.59	0.54	0.06
95% CI	ref	0.34–1.02	0.28 – 1.05	
Total iron, with supplements (mg)		11.3	26.4	
HR	1.0	1.29	1.17	0.66
95% CI	ref	0.74–2.23	0.61–2.22	
Total vitamin A,with supplements (IU)		7005.50	11312.00	
HR	1.0	0.77	0.57	0.06
95%CI	ref	0.46 – 1.30	0.32 – 1.02	
Total vitamin E, with supplements (α-TE)		20.78	101.08	
HR	1.0	1.59	0.87	0.37
95% CI	ref	0.78–3.25	0.41–1.87	
Total zinc, with supplements (mg)		9.05	21.42	
HR	1.0	1.08	1.48	0.22
95% CI	ref	0.61–1.92	0.77–2.86	

a: Dietary variables are controlled for stage of disease, age at diagnosis, body mass index, parity, hormone replacement therapy use, alcohol use, multivitamin use, and energy intake.
b: The minimum values/points of the tertiles are shown.
c: Dietary nutrients shown are from food except for total values, which are from food plus supplements/vitamin use.