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Epidemiology

Fruits, vegetables, and micronutrient intake in relation to breast cancer survival

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Summary

Objective. To determine whether fruit, vegetable, and micronutrient intake 1 year prior to breast cancer diagnosis is associated with a reduction in the subsequent risk of all-cause or breast cancer-specific mortality.

Methods. Follow-up data from 1,235 invasive breast cancer cases age 25–98 years from the Long Island Breast Cancer Study Project were analyzed. At the 1996–1997 case-control interview, respondents completed a food frequency questionnaire, which assessed dietary intake of fruits, vegetables, and vitamin supplement use in the previous 12 months. All-cause mortality ($n = 186$ deaths) and breast cancer-specific mortality status ($n = 125$ deaths, 67.2%) were determined through December 31, 2002.

Results. Hazard ratios (HRs) for all-cause mortality were insignificantly reduced for intake of any fruits, fruit juices, and vegetables (HR = 0.68, 95% CI: 0.42–1.09) and leafy vegetables (HR = 0.72, 95% CI: 0.41–1.24) among post-menopausal women only. Both of these associations were more pronounced among those with ER + PR + tumors (HR = 0.54, 95% CI: 0.27–1.10, and HR = 0.66, 95% CI: 0.33–1.31, respectively). Similar associations were observed for breast cancer-specific mortality.

Conclusions. In a cohort of women diagnosed with breast cancer, higher intake of fruits, vegetables, and micronutrients was associated with a non-significant survival advantage in post-menopausal women only.

Introduction

Fruit, vegetable, and antioxidant intake around the time of breast cancer diagnosis may be associated with an improved prognosis. Previous research, however, has provided inconclusive results. Several studies [1–5], but not all [3,6,7], have suggested that intake of these food items may prolong survival, with estimates ranging from a 20 to 90% reduction in risk of death. However, because of variability in the results and in the dietary factors examined [1–5], the data do not provide conclusive evidence.

Components of fruits and vegetables have demonstrated the ability to inhibit breast tumor cell proliferation in cell culture and animal studies [8,9], which may result in potential beneficial influences on survival among breast cancer patients. Retinoic acid and some of its isomers and derivatives have been shown to promote cell differentiation in many epithelial cells and to inhibit mammary cell growth [10]. Carotenoids, which are rich in many fruits and vegetables, have demonstrated similar effects through induction of apoptosis and inhibition of mammary cell proliferation [11–13].

Isothiocyanates found in broccoli have demonstrated favorable effects on estrogen metabolism via the induction of cytochrome P450 enzymes [2,14]. In mammalian biologic systems, soluble and insoluble fiber, which is found in high quantities in fruits and vegetables, binds with estrogen and interferes with reabsorption, thus reducing circulating estrogen concentrations [2].

Fruit and vegetable intake may be differentially associated with survival by estrogen and progesterone receptor (ERPR) status [15]. ERPR status is an important prognostic indicator for breast cancer survival [16,17] with ER+ or PR+ tumors associated with better prognosis compared to ER− or PR− tumors [7,18–24]. In a previous report [25], we noted that the inverse association between fruit and vegetable intake and breast cancer development was more

pronounced among women with ER + PR + tumors, which are the most frequently diagnosed hormone receptor subtype among post-menopausal women in the U.S. [26]. Determination of whether these foods also differentially affect breast cancer survival by hormone receptor subtype is therefore of public health importance.

We examined whether intake of fruits, vegetables, or micronutrients around the time of diagnosis is associated with subsequent mortality among a population-based sample of women with breast cancer who participated in the Long Island Breast Cancer Study Project (LIBCSP) [27]. The large number of cases and detailed information on diet and other important exposures permitted consideration of whether the association between consumption of fruits, vegetables, and antioxidants and breast cancer survival varied with menopausal status, as well as a joint measure of ER and PR status. Further, LIBCSP study participants have been found to have a high and varied intake of fruits and vegetables [25], comparable to the range of intake found in Mediterranean countries, which should increase our ability to detect any potential beneficial effects on prognosis.

Methods

Overview

This study draws upon data collected as part of the LIBCSP, which began as a case-control study [27] and now includes assessment of survival among the breast cancer cases. For the analysis reported here, we estimated the risk of mortality among the LIBCSP case participants, who were initially diagnosed with invasive breast cancer in 1996–1997, in relation to fruit and vegetable intake in the year prior to the baseline, case-control interview ($n = 1{,}235$). Vital status through the end of 2002 was determined through the National Death Index (NDI). Information on dietary intake, confounders, and effect modifiers used in this analysis are based on data collected at the baseline, case-control study in 1996–1997. Treatment information is derived from the baseline (1996–1997) and follow-up (2002–2004) interviews, and the medical records abstracted as part of the baseline and follow-up studies. Details of the relevant study methods are as follows.

Study subjects

Eligible cases for the original LIBCSP case-control study included English-speaking women who were newly diagnosed with a first primary *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997 and who were residents of Nassau and Suffolk counties, Long Island, New York. Cases were identified through a rapid reporting system that was developed specifically for this study. The attending physician was contacted to confirm study eligibility and to seek permission to contact the patient. A total of 1,273 women with invasive breast cancer provided written consent to participate in the case-control study interview [27].

Exposure assessment

Baseline data

The dietary and covariate data used in this analysis are based on information that was collected as part of the baseline case-control interview [27]. The baseline questionnaire was administered by a trained interviewer approximately 3 months after diagnosis (average time was 96 days), and elicited information on reproductive and menstrual histories, active and passive smoking, alcohol intake, body size, physical activity, and medical history (http://www.epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html).

As part of the baseline interview, information on diet history in the previous 12 months was obtained using a respondent-completed, modified Block food frequency questionnaire (FFQ) [28], which covered approximately 100 foods and beverages and included assessment of the frequency and portion size of fruit and vegetable intake, fruit juice consumption, and vitamin supplement use. Additional details on the food items included in the fruit and vegetable groups (see Appendix 1) and the derived nutrient database have been described previously [25]. To facilitate the comparison of our results with other studies, 38 invasive cases with daily energy intakes above or below three standard deviations of the log-transformed mean were excluded from the analysis [25], resulting in a final case total of 1,235 women.

Treatment data

Treatment information is based on data from respondent reports at the interviews and the medical records collected as part of the baseline/case-control and follow-up studies. At baseline, medical records were abstracted to obtain information on disease stage, initial course of breast cancer treatment, and ERPR status. Nearly two-thirds of the baseline case interviews occurred prior to the initiation of chemotherapy [27]. Thus, additional treatment information was obtained by re-interviewing case participants or their proxy in 2002–2004 and re-abstracting medical records as part of the follow-up study.

During follow-up in 2002–2004, case women or their proxy were interviewed via telephone by a trained interviewer to assess more detailed information for the initial breast cancer diagnosis. Of the 1,273 case participants with invasive breast cancer in the case-control study, 868 gave us permission to re-contact them and the remaining 405 refused to participate in the follow-up interview, were untraceable, or were deceased and had no identifiable proxy. Respondents were asked about the treatment modalities undergone for the initial breast cancer diagnosis, and outcomes and treatments for those

outcomes since the initial breast cancer diagnosis. Respondents or their proxy were asked to sign a Health Insurance Portability and Accountability Act (HIPAA)-approved medical record release form. Medical records regarding all treatment types and outcomes were retrieved from the appropriate hospitals.

Trained abstractors reviewed and abstracted all medical records to determine each case's treatment regimen for their initial breast cancer (i.e., surgery, radiation therapy, chemotherapy, hormone therapy). For the LIBCSP follow-up, medical records were abstracted for 474 cases with invasive breast cancer. A high correspondence was found between treatment (radiation (98.5%), chemotherapy (98.3%), and hormone therapy (96.4%)) reported by the respondent during the follow-up interview with the information abstracted from the medical record. Thus, for our analysis, treatment is based on the information reported by the respondent at the baseline and follow-up interviews.

Study outcome

The NDI was used to ascertain all-cause and breast cancer-specific mortality. Among the 1,235 women diagnosed with invasive breast cancer in 1996–1997 with adequate dietary intake data available for these analyses, 186 (15.1%) deaths occurred by December 31, 2002. Of these, 125 (67.2%) deaths were due to breast cancer determined based on ICD codes 174.9 and C-50.9 listed as a primary or secondary code on the death certificate. Other causes of death among this cohort include 5 deaths from lung cancer, 17 from other cancers, 24 from cardiovascular disease, and 21 from other causes. Of the 1,210 case women with known menopausal status, 175 died during the follow-up period.

Statistical analysis

Kaplan–Meier survival curves [29] were used to compare the survival function by intake of fruits, vegetables, and micronutrients assessed at the baseline case-control study with vital status. Each dietary factor of interest was evaluated to determine whether the proportional hazards assumption was met. Cox proportional hazards regression [29] was used to estimate hazard ratios and 95% confidence intervals (CI) for the association of selected fruit and vegetable groups, as well as antioxidants, and risk of all-cause and breast cancer-specific mortality. Variables for age at diagnosis (continuous) and dietary energy intake (continuous) were included in all models. Tests of trend were conducted using the continuous values for the food groups and micronutrients.

Effect measure modification on the multiplicative scale was evaluated using the log likelihood ratio test to compare proportional hazards regression models with and without the interaction term [29]. Factors considered as potential effect measure modifiers were based on data collected as part of the baseline case-control interview and included: menopausal status (pre- and post-menopausal), family history of breast cancer in a first-degree relative, physical activity levels from menarche to reference date (hours/day), active/passive cigarette smoking, body mass index (BMI) [weight (kg)/height $(m)^2$] at reference date, average lifetime alcohol intake (g/day), education, income, and radiation treatment and chemotherapy undergone for the original breast cancer diagnosis. None of the potential effect measure modifiers were statistically significant at the $p < 0.05$ level.

Because results were found to vary modestly by menopausal status, all models were constructed for pre- and post-menopausal women separately. Menopausal status was defined according to criteria previously published [27]. A total of 25 cases had missing data on menopausal status and were not included in the menopause-specific analyses. Menopause-specific quintiles of intake (based on the distributions in controls) were evaluated, but were nearly identical to those based on all invasive cases, regardless of menopausal status. To facilitate comparisons between the two groups, only the latter are shown.

To test for potential heterogeneity by ERPR status, stratified analyses were conducted, with ER+PR+ cases considered as one group because of their high frequency, and all other hormonal receptor types (ER+PR−, ER−PR+, ER−PR−) were grouped together because of their relative infrequency. In addition, when the latter receptor types were analyzed individually, their respective hazard ratios and confidence intervals were similar.

Confounding was evaluated starting with a full model and using backward elimination. Factors considered as potential confounders were the same as those considered as effect modifiers, except that menopausal status was excluded and parity was included. Potential confounding by radiation therapy and chemotherapy treatment was evaluated utilizing data collected at the case-control and follow-up studies. None of the potential confounders altered the effect estimates of the fruit, vegetable, and micronutrient intake exposures by more than 10% (data not shown).

Results

As shown in Table 1, among post-menopausal women, risk of mortality was decreased in relation to intake of fruits, fruit juices, and vegetables, though none of the results were statistically significant at the $p < 0.05$ level. The HRs were reduced by approximately 30% among post-menopausal women, comparing the highest quintile of intake to the lowest quintile, of leafy vegetables (HR = 0.72, 95% CI: 0.41–1.24) and any fruits, fruit juices, and vegetables (HR = 0.68, 95% CI: 0.42–1.09). However, there was no evidence of a trend with increasing consumption. Intake of several other

Table 1. Age and energy-adjusted HRs and 95% CIs stratified by menopausal status for the association between fruit and vegetable intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996–1997

Variable	Pre-menopausal			Post-menopausal		
	Cases ($n=376$)	Deaths ($n=43$)	HR (95%CI)	Cases ($n=834$)	Deaths ($n=132$)	HR (95% CI)
Any fruits, fruit juices, and vegetables[a]						
0–18	95	8	1.00	160	28	1.00
19–25	70	7	0.91 (0.40–2.07)	161	27	1.24 (0.80–1.90)
26–33	79	10	1.13 (0.56–2.30)	174	21	0.69 (0.43–1.10)
34–45	68	7	0.78 (0.35–1.76)	172	33	1.30 (0.88–1.94)
46+	64	11	1.38 (0.65–2.91)	167	23	0.68 (0.42–1.09)
p for trend*			0.31			0.33
Any fruits and fruit juices[a]						
0–6	106	12	1.00	130	23	1.00
7–12	88	8	0.79 (0.36–1.71)	201	31	1.02 (0.68–1.54)
13–16	63	7	0.94 (0.42–2.11)	140	21	0.96 (0.60–1.53)
17–23	66	8	0.97 (0.45–2.10)	179	28	0.94 (0.62–1.42)
24+	53	8	1.10 (0.48–2.52)	184	29	0.87 (0.57–1.35)
p for trend*			0.28			0.34
Citrus fruits[a]						
0–1	115	15	1.00	163	23	1.00
2–4	85	7	0.65 (0.29–1.45)	180	33	1.36 (0.91–2.02)
5–7	62	7	1.03 (0.46–2.33)	176	26	0.93 (0.60–1.42)
8–11	75	6	0.56 (0.24–1.33)	168	27	0.93 (0.61–1.42)
12+	39	8	1.70 (0.75–3.89)	137	22	0.90 (0.56–1.44)
p for trend*			0.51			0.46
Any vegetables[a]						
0–8	74	5	1.00	165	29	1.00
9–13	92	13	1.41 (0.73–2.72)	200	31	1.02 (0.68–1.53)
14–17	59	5	0.67 (0.27–1.71)	152	27	1.09 (0.71–1.66)
18–23	70	7	0.80 (0.35–1.80)	167	22	0.79 (0.50–1.25)
24+	80	13	1.40 (0.71–2.76)	138	22	0.92 (0.57–1.48)
p for trend*			0.53			0.52
Leafy vegetables[a]						
0–2	133	19	1.00	289	57	1.00
3	16	5	3.57 (1.39–9.13)	44	6	0.80 (0.35–1.81)
4–5	68	6	0.74 (0.31–1.76)	197	27	0.86 (0.56–1.31)
6–8	84	5	0.40 (0.16–1.02)	172	25	0.87 (0.56–1.35)
9+	74	8	0.85 (0.39–1.85)	117	15	0.72 (0.41–1.24)
p for trend*			0.21			0.31
Yellow vegetables[a]						
0–4	93	5	1.00	170	31	1.00
5–7	70	9	1.21 (0.58–2.54)	198	32	1.04 (0.70–1.55)
8–10	70	10	1.31 (0.64–2.65)	151	18	0.72 (0.44–1.18)
11–15	73	9	1.08 (0.52–2.25)	152	25	1.06 (0.69–1.64)
16+	70	10	1.09 (0.52–2.28)	163	26	0.90 (0.58–1.40)
p for trend*			0.27			0.36
Cruciferous vegetables[a]						
0–1	108	9	1.00	255	40	1.00
2	97	11	1.01 (0.51–2.00)	198	31	0.99 (0.66–1.48)
3	31	3	0.82 (0.25–2.67)	95	13	0.87 (0.49–1.54)
4–5	53	11	2.23 (1.12–4.44)	145	24	1.02 (0.66–1.60)
6+	86	9	0.72 (0.34–1.54)	126	21	1.07 (0.67–1.72)
p for trend*			0.78			0.82

**p*-Value for linear trend for continuous variable.
[a]In 0.5 cup servings per week.

categories fruits and vegetables showed smaller reductions. Only cruciferous vegetable intake was not associated with a decreased risk of mortality. In pre-menopausal women, those consuming the most cruciferous vegetables (HR = 0.72, 95% CI: 0.34–1.54) and leafy vegetables (HR = 0.85, 95% CI: 0.39–1.85) had a slight reduction in mortality compared to those consuming the least of these products, respectively. Among pre-menopausal women, mortality was non-significantly increased in the remaining food groups, although there was no dose–response relationship.

As shown in Table 2, weak inverse associations were found with all antioxidants (cryptoxanthin HR = 0.82, 95% CI: 0.53–1.28; lutein HR = 0.68, 95% CI: 0.42–1.12; lycopene HR = 0.79, 95% CI: 0.48–1.30; vitamin E HR = 0.77, 95% CI: 0.47–1.27), except alpha and beta-carotene, and vitamin C in post-menopausal women. In pre-menopausal women, inverse associations were found with all antioxidants (alpha-carotene HR = 0.76, 95% CI: 0.35–1.67; beta-carotene HR = 0.82, 95% CI: 0.37–1.82; lycopene HR = 0.61, 95% CI: 0.29–1.29; vitamin C HR = 0.90, 95% CI: 0.42–1.94; vitamin E HR = 0.96, 95% CI: 0.44–2.09) except cryptoxanthin and lutein. However, none of the associations were statistically significant and there was no evidence of a dose–response.

Among post-menopausal women with ER + PR + tumors (Table 3), there appears to be a consistent, reduced mortality for vegetable intake, comparing the highest two-fifths of intake to the lowest three-fifths of intake (HR = 0.54, 95% CI: 0.27–1.10 for all vegetables, HR = 0.66, 95% CI: 0.33–1.31 for leafy vegetables, HR = 0.53, 95% CI: 0.26–1.09 for cruciferous vegetables, HR = 0.83, 95% CI: 0.44–1.59 for yellow vegetables), although none of the results are statistically significant. For micronutrient intake among post-menopausal women, there was little or no heterogeneity by hormone receptor status (data not shown). Pre- and post-menopausal consumers of any vitamin supplement did not experience a reduction in risk of mortality (data not shown). For post-menopausal cases with ER + PR + tumors, the HRs in relation to micronutrient intake ranged from 0.52 to 0.92 and for all other hormonal receptor types, the HRs ranged from 0.60 to 0.89 (data not shown).

All models were re-run using breast cancer-specific mortality as the outcome (data not shown). These results were approximately equal to those for all-cause mortality, and the subsequent conclusions were identical.

Discussion

In this cohort of women with invasive breast cancer, we observed some suggestion of a slight, non-significant decrease in the risk of all-cause and breast cancer-specific mortality associated with higher consumption of leafy vegetables and any fruits, fruit juices, and vegetables among post-menopausal women only. In pre-menopausal women, inverse associations were not observed for most foods. However, higher intakes of leafy and cruciferous vegetables, as well as lycopene and vitamin E, indicated some beneficial effect at the highest quintiles of intake for both pre- and post-menopausal women. There was little effect modification with hormone receptor status, although the reduction in mortality associated with cruciferous vegetable intake was more pronounced among post-menopausal women with ER + PR + tumors.

A recent review of eight prior studies [2,30] provides some supportive but inconsistent evidence of a slight beneficial effect of fruits, vegetables, and antioxidants. Of the eight studies that examined these dietary constituents [1,3–7,31,32], three found a significant inverse association with mortality [1,4,5] while the remaining studies found no significant associations [31] or no relationship [3,6,7]. All of these studies, similar to ours, assessed dietary intake, usually in the 12 months prior to the interview with a FFQ. However, reasons for the inconsistent results across studies may be associated with differences in: sample sizes; the participants' age or menopausal status distributions; or lengths of follow-up.

Only one [4] of the previous reports on fruit, vegetable, and/or micronutrient intake and breast cancer survival [1,3–5,32,33] showed results stratified by ERPR status. The authors [4] found that with increasing levels of vitamin C and beta-carotene intake, mortality risk was more strongly reduced among women with ER + PR + tumors than in women with ER−PR− tumors. Consistent with this, in the LIBCSP, mortality among post-menopausal women was reduced by 47% in relation to cruciferous vegetable intake if the tumor was ER + PR +, but was increased by 45% for all other hormonal receptor types.

As with all epidemiologic studies that rely on the FFQ to assess dietary intake, our results should be interpreted cautiously. FFQs are imprecise methods of dietary assessment, particularly for micronutrients and macronutrients [34]. When micronutrient data, such as carotenoids, are assessed, this imprecision is especially problematic [34]. However, FFQs ability to rank individuals according to their position in the distribution of intake provides information on *relative*, not absolute, intake [35]. This feature facilitates the estimation of disease association risks [35].

While our results suggest that dietary intake of fruits and vegetables around the time of diagnosis may beneficially affect prognosis, they do not provide information on whether changes in dietary intake after diagnosis affect risk, unless intakes in the two periods are correlated. Although selected interventions [36] have helped some breast cancer survivors increase their fruit and vegetable intake, for most women, it is not clear whether intake around diagnosis is correlated with intake long after diagnosis [37–39].

Some researchers have recommended against taking any antioxidant supplements during treatment, because antioxidants could repair cellular oxidative damage to cancer cells caused by treatments such as radiation therapy and chemotherapy [40,41]. Thus, fruit and

Table 2. Age and energy-adjusted HRs and 95% CIs stratified by menopausal status for the association between dietary and supplemental sources of micronutrients in relation to all-cause mortality among breast cancer cases diagnosed in 1996–1997

Variable	Pre-menopausal HR (95% CI)	Post-menopausal HR (95% CI)
Dietary α-carotene, μg/d		
0–74.5	1.00	1.00
74.5–150.8	1.58 (0.79–3.16)	1.57 (1.07–2.29)
150.8–254.3	1.07 (0.53–2.18)	0.72 (0.45–1.16)
254.3–401.9	0.92 (0.43–2.00)	0.74 (0.46–1.18)
401.9+	0.76 (0.35–1.67)	1.20 (0.79–1.81)
p for trend*	0.85	0.79
Dietary β-carotene, μg/d		
0–1067.9	1.00	1.00
1067.9–1724.9	0.88 (0.39–2.01)	1.74 (1.19–2.53)
1724.9–2487.6	1.48 (0.75–2.90)	0.69 (0.42–1.13)
2487.6–3753.8	1.15 (0.57–2.30)	0.67 (0.42–1.08)
3753.8+	0.82 (0.37–1.82)	1.07 (0.70–1.64)
p for trend*	0.69	0.29
Dietary cryptoxanthin, μg/d		
0–31.2	1.00	1.00
31.2–59.4	0.58 (0.24–1.37)	1.19 (0.78–1.82)
59.4–90.0	1.84 (0.92–3.68)	0.98 (0.65–1.49)
90.0–133.6	1.10 (0.54–2.23)	1.01 (0.66–1.54)
133.6+	1.13 (0.53–2.41)	0.82 (0.53–1.28)
p for trend*	0.10	0.34
Dietary lutein, μg/d		
0–675.6	1.00	1.00
675.6–1169.8	0.77 (0.32–1.82)	0.93 (0.60–1.45)
1169.8–1774.4	1.20 (0.59–2.45)	1.40 (0.94–2.07)
1774.4–3073.5	0.82 (0.38–1.77)	0.71 (0.44–1.15)
3073.5+	1.71 (0.89–3.29)	0.68 (0.42–1.12)
p for trend*	0.32	0.80
Dietary lycopene, μg/d		
0–548.6	1.00	1.00
548.6–1030.6	1.47 (0.67–3.22)	1.03 (0.68–1.56)
1030.6–1517.0	1.35 (0.68–2.69)	1.57 (1.06–2.33)
1517.0–2263.9	0.96 (0.48–1.90)	0.55 (0.32–0.94)
2263.9+	0.61 (0.29–1.29)	0.79 (0.48–1.30)
p for trend*	0.20	0.11
Dietary vitamin C, mg/d		
0–60.7	1.00	1.00
60.7–93.4	1.36 (0.68–2.70)	1.03 (0.66–1.60)
93.4–127.2	0.96 (0.43–2.16)	1.02 (0.67–1.54)
127.2–173.0	1.15 (0.57–2.34)	0.68 (0.42–1.09)
173.0+	0.90 (0.42–1.94)	1.08 (0.70–1.66)
p for trend*	0.33	0.52
Dietary vitamin E, a-te/d		
0–4.4	1.00	1.00
4.3–5.9	0.69 (0.26–1.84)	0.86 (0.55–1.34)
5.9–7.6	1.44 (0.71–2.89)	1.05 (0.68–1.60)
7.6–10.4	0.70 (0.32–1.52)	0.97 (0.63–1.50)
10.4+	0.96 (0.44–2.09)	0.77 (0.47–1.27)
p for trend*	0.18	0.27

**p*-Value for linear trend for continuous variable.

Table 3. Age and energy-adjusted HRs and 95% CIs stratified by ERPR status for the association between fruit and vegetable intake and all-cause mortality among post-menopausal breast cancer cases ($n = 834$) diagnosed in 1996–1997

Variable	ER + PR + HR (95% CI)	ER + PR−, ER−PR +, ER−PR− HR (95% CI)
Any fruits, fruit juices, and vegetables[a]		
0–33	1.00	1.00
34 +	0.93 (0.48–1.77)	1.00 (0.57–1.74)
p for trend*	0.46	0.70
Any fruits and fruit juices[a]		
0–16	1.00	1.00
17 +	0.74 (0.39–1.40)	1.08 (0.63–1.84)
p for trend*	0.93	0.39
Citrus fruits[a]		
0–7	1.00	1.00
8 +	1.01 (0.54–1.89)	0.82 (0.47–1.43)
p for trend*	0.92	0.29
Any vegetables[a]		
0–17	1.00	1.00
18 +	0.54 (0.27–1.10)	1.02 (0.59–1.75)
p for trend*	0.38	0.96
Leafy vegetables[a]		
0–5	1.00	1.00
6 +	0.66 (0.33–1.31)	0.90 (0.52–1.57)
p for trend*	0.33	0.85
Yellow vegetables[a]		
0–10	1.00	1.00
11 +	0.83 (0.44–1.59)	1.00 (0.58–1.71)
p for trend*	0.54	0.65
Cruciferous vegetables[a]		
0–3	1.00	1.00
4 +	0.53 (0.26–1.09)	1.45 (0.86–2.45)
p for trend*	0.23	0.60

*p-Value for linear trend for continuous variable.
[a]In 0.5 cup servings per week.

vegetable intake following diagnosis may not be beneficial to breast cancer patients. Although, others have noted there may be a net benefit to help protect normal cells from the damage associated with these therapies [42].

Dietary recall has been found to vary with whether or not a woman has initiated chemotherapy, as higher intakes of macronutrients and calories have been reported among those receiving chemotherapy compared to those who were not [28]. These recall differences were not observed in our study sample [27].

Potential confounding is another consideration that may affect interpretation of our study results. For example, many lifestyle factors are highly correlated with fruit and vegetable intake and may confound the relationship between fruits and vegetables and breast cancer mortality [4,32,43,44]. However, when we controlled for physical activity, cigarette smoking, alcohol, and vitamin supplements, our results were not substantially altered.

This follow-up study of a population-based sample of breast cancer survivors provides only weak evidence for an inverse association between all-cause or breast cancer-specific mortality and leafy vegetable intake and any fruit, fruit juice, and vegetable intake in post-menopausal women. Results were less consistent among pre-menopausal women, with slight reductions observed for intake of leafy or cruciferous vegetables only. Lycopene and vitamin E intake were associated with decreased risks in both pre- and post-menopausal women. To clarify these important issues, future studies will need to follow large numbers of women previously diagnosed with breast cancer and include assessments of dietary intake at diagnosis as well as any changes after diagnosis. Further research that examines the association between survival and specific phytochemicals in fruits and vegetables may also be useful.

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Appendix 1: Composition of food groups

Fruits	Fruit juices	Any fruits and fruit juices	Citrus fruits	Any vegetables	Any fruits and vegetables, including juices	Leafy vegetables	Yellow vegetables (and fruits)	Cruciferous vegetables
Apples, applesauce, pears	Orange juice or grapefruit juice	All items in fruit and fruit juices	Oranges	String beans, green beans	All items in fruits and fruit juices and vegetables	Spinach (raw)	Peaches, apricots, nectarines (fresh in season)	Coleslaw, cabbage, sauerkraut
Bananas	Fruit drinks with added vitamin C, such as Hi-C		Grapefruit	Green peas		Spinach (cooked)	Peaches, apricots (canned, frozen, or dried)	Broccoli
Peaches, apricots (in season)	Tomatoes, tomato juice, V8 juice[a]		Orange juice or grapefruit juice	Corn, including corn on the cob		Mustard greens, turnip greens, collards, kale	Cantaloupe (in season)	Cauliflower or Brussel sprouts
Peaches, apricots (canned, frozen, or dried)				Winter squash, baked squash		Green salad	Watermelon (in season)	Mustard greens, turnip greens, collards, kale
Cantaloupe (in season)				Broccoli			Winter squash, baked squash	
Watermelon (in season)				Cauliflower or Brussel sprouts			Broccoli	
Strawberries (in season)				Spinach (raw)			Spinach (raw)	
Cherries (in season)				Spinach (cooked)			Spinach (cooked)	
Oranges				Mustard greens, turnip greens, collards, kale			Mustard greens, turnip greens, collards, kale	
Grapefruit				Cole slaw, cabbage, sauerkraut			Carrots, or mixed vegetables containing carrots	

Appendix 1: Continued

Fruits	Fruit juices	Any fruits and fruit juices	Citrus fruits	Any vegetables	Any fruits and vegetables, including juices	Leafy vegetables	Yellow vegetables (and fruits)	Cruciferous vegetables
Tomatoes, tomato juice, V8 juice[a]				Carrots, or mixed vegetables containing carrots			Sweet potatoes, yams	
				Red or green peppers			Tomatoes, tomato juice, V8 juice[a]	
				Green salad			Red or green peppers	
				Alfalfa sprouts				
				Sweet potatoes, yams				
				Other potatoes, including boiled, baked, mashed, and potato salad				

[a]A woman's intake of was split between the categories of any fruit and fruit juice.

References

1. Rohan TE, Hiller JE, McMichael AJ: Dietary factors and survival from breast cancer. Nutr Cancer 20: 167–177, 1993
2. Rock CL, Demark-Wahnefried W: Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol 20: 3302–3316, 2002
3. Saxe GA, Rock CL, Wicha MS, Schottenfeld D: Diet and risk for breast cancer recurrence and survival. Breast Cancer Res Treat 53: 241–253, 1999
4. Jain M, Miller AB, To T: Premorbid diet and the prognosis of women with breast cancer. J Natl Cancer Inst 86(18): 1390–1397, 1994
5. Ingram D: Diet and subsequent survival in women with breast cancer. Br J Cancer 69(3): 592–595, 1994
6. Holm LE, Nordevang E, Hjalmar ML, Lidbrink E, Callmer E, Nilsson B: Treatment failure and dietary habits in women with breast cancer. J Natl Cancer Inst 85(1): 32–36, 1993
7. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD: Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. Cancer 76: 275–283, 1995
8. Zhang Y, Vareed SK, Nair MG: Human tumor cell growth inhibition by nontoxic anthocyanidins, the pigments in fruits and vegetables. Life Sci 76(13): 1465–1472, 2005
9. Kanno S, Tomizawa A, Hiura T, Osanai Y, Shouji A, Ujibe M, Ohtake T, Kimura K, Ishikawa M: Inhibitory effects of naringenin on tumor growth in human cancer cell lines and sarcoma S-180-implanted mice. Biol Pharm Bull 28(3): 527–530, 2005
10. Bollag W, Matter A: From vitamin A to retinoids in experimental and clinical oncology: achievements, failures, and outlook. Ann N Y Acad Sci 359: 9–23, 1981
11. Sumantran VN, Zhang R, Lee DS, Wicha MS: Differential regulation of apoptosis in normal versus transformed mammary epithelium by lutein and retinoic acid. Cancer Epidemiol Biomarkers Prev 9(3): 257–263, 2000
12. Prakash P, Krinsky NI, Russell RM: Retinoids, carotenoids, and human breast cancer cell cultures: a review of differential effects. Nutr Rev 58(6): 170–176, 2000
13. Dawson MI, Chao WR, Pine P, Jong L, Hobbs PD, Rudd CK, Quick TC, Niles RM, Zhang XK, Lombardo A: Correlation of retinoid binding affinity to retinoic acid receptor alpha with retinoid inhibition of growth of estrogen receptor-positive MCF-7 mammary carcinoma cells. Cancer Res 55(19): 4446–4451, 1995
14. Fowke JH, Longcope C, Hebert JR: Brassica vegetable consumption shifts estrogen metabolism in healthy postmenopausal women. Cancer Epidemiol Biomarkers Prev 9(8): 773–779, 2000
15. Olsen A, Tjonneland A, Thomsen BL, Loft S, Stripp C, Overvad K, Moller S, Olsen JH: Fruits and vegetables intake differentially affects estrogen receptor negative and positive breast cancer incidence rates. J Nutr 133(7): 2342–2347, 2003
16. Ruder AM, Lubin F, Wax Y, Geier A, Alfundary E, Chetrit A: Estrogen and progesterone receptors in breast cancer patients. Cancer 64: 196–202, 1989
17. Jakovljevic J, Touillaud MS, Bondy ML, Singletary SE, Pillow PC, Chang S: Dietary intake of selected fatty acids, cholesterol and carotenoids and estrogen receptor status in premenopausal breast cancer patients. Breast Cancer Res Treat 75(1): 5–14, 2002
18. MacGregor JI, Jordan VC: Basic guide to the mechanisms of antiestrogen action. Pharmacol Rev 50(2): 151–196, 1998
19. Schairer C, Mink PJ, Carroll L, Devesa SS: Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 96(17): 1311–1321, 2004
20. Tutera AM, Sellers TA, Potter JD, Drinkard CR, Wiesner GL, Folsom AR: Association between family history of cancer and breast cancer defined by estrogen and progesterone receptor status. Genet Epidemiol 13(2): 207–221, 1996
21. Allemani C, Sant M, Berrino F, Aareleid T, Chaplain G, Coebergh JW, Colonna M, Contiero P, Danzon A, Federico M, Gafa L, Grosclaude P, Hedelin G, Mace-Lesech J, Garcia CM, Paci E, Raverdy N, Tretarre B, Williams EM: Prognostic value of morphology and hormone receptor status in breast cancer – a population-based study. Br J Cancer 91(7): 1263–1268, 2004
22. Maynard PV, Blamey RW, Elston CW, Haybittle JL, Griffiths K: Estrogen receptor assay in primary breast cancer and early recurrence of the disease. Cancer Res 38(11 Pt 2): 4292–4295, 1978
23. Parl FF, Schmidt BP, Dupont WD, Wagner RK: Prognostic significance of estrogen receptor status in breast cancer in relation to tumor stage, axillary node metastasis, and histopathologic grading. Cancer 54(10): 2237–2242, 1984

24. Putti TC, El-Rehim DM, Rakha EA, Paish CE, Lee AH, Pinder SE, Ellis IO: Estrogen receptor-negative breast carcinomas: a review of morphology and immunophenotypical analysis. Mod Pathol 18(1): 26–35, 2005
25. Gaudet MM, Britton JA, Kabat GC, Steck-Scott S, Eng SM, Teitelbaum SL, Terry MB, Neugut AI, Gammon MD: Fruits, vegetables, and micronutrients in relation to breast cancer modified by menopause and hormone receptor status. Cancer Epidemiol Biomarkers Prev 13(9): 1485–1494, 2004
26. Yasui Y, Potter JD: The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control 10(5): 431–437, 1999
27. Gammon MD, Neugut AI, Santella RM, Teitelbaum SL, Britton JA, Terry MB, Eng SM, Wolff MS, Stellman SD, Kabat GC, Levin B, Bradlow HL, Hatch M, Beyea J, Camann D, Trent M, Senie RT, Garbowski GC, Maffeo C, Montlavan P, Berkowitz GS, Kemeny M, Citron M, Schnabel F, Schuss A, Hajdu S, Vinceguerra V, Collman GW, Obrams GI: The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. Breast Cancer Res Treat 74: 233–254, 2002
28. Potischman N, Swanson CA, Coates RJ, Gammon MD, Brogan DR, Curtin J, Brinton LA: Intake of food groups and associated micronutrients in relation to risk of early-stage breast cancer. Int J Cancer 82(3): 315–321, 1999
29. Allison P: Survival Analysis Using SAS: A Practical Guide. SAS Publishing, Cary, 1995
30. Rock CL, Demark-Wahnefried W: Can lifestyle modification increase survival in women diagnosed with breast cancer? J Nutr 132: 3504S–3509S, 2002
31. Ewertz M, Gillanders S, Meyer L, Zedeler K: Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 49: 526–530, 1991
32. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC: Dietary factors and the survival of women with breast carcinoma. Cancer 86: 826–835, 1999
33. Hebert JR, Hurley TG, Ma Y: The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Res Treat 51: 17–28, 1998
34. Briefel RR, Flegal KM, Winn DM, Loria CM, Johnson CL, Sempos CT: Assessing the nation's diet: limitations of the food frequency questionnaire. J Am Diet Assoc 92(8): 959–962, 1992
35. Nelson M, Bingham SA: Assessment of food composition and nutrient intake. In: Margetts B, Nelson M (eds) Design Concepts in Nutritional Epidemiology (2nd ed). Oxford University Press, Oxford, p 451, 1998
36. Maunsell E, Drolet M, Brisson J, Robert J, Deschenes L: Dietary change after breast cancer: extent, predictors, and relation with psychological disorders. J Clin Oncol 20: 1017–1025, 2002
37. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML: Life After Cancer Epidemiology (LACE) Study: a cohort of early stage breast cancer survivors (United States). Cancer Causes Control 16(5): 545–556, 2005
38. Rock CL, Flatt SW, Newman V, Caan BJ, Haan MN, Stefanick ML, Faerber S, Pierce JP: Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. J Am Diet Assoc 99(10): 1212–1221, 1999
39. Winters BL, Mitchell DC, Smiciklas-Wright H, Grosvenor MB, Liu W, Blackburn GL: Dietary patterns in women treated for breast cancer who successfully reduce fat intake: the Women's Intervention Nutrition Study (WINS). J Am Diet Assoc 104(4): 551–559, 2004
40. Lamson DW, Brignall MS: Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev 4(5): 304–329, 1999
41. Labriola D, Livingston R: Possible interactions between dietary antioxidants and chemotherapy. Oncology (Williston Park) 13(7): 1003–1008, 1999; discussion 1008, 1011–2
42. Prasad KN, Kumar A, Kochupillai V, Cole WC: High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy. J Am Coll Nutr 18(1): 13–25, 1999
43. Thompson B, Demark-Wahnefried W, Taylor G, McClelland JW, Stables G, Havas S, Feng Z, Topor M, Heimendinger J, Reynolds KD, Cohen N: Baseline fruit and vegetable intake among adults in seven 5 a day study centers located in diverse geographic areas. J Am Diet Assoc 99(10): 1241–1248, 1999
44. Trudeau E, Kristal AR, Li S, Patterson RE: Demographic and psychosocial predictors of fruit and vegetable intakes differ: implications for dietary interventions. J Am Diet Assoc 98(12): 1412–1417, 1998

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