Dietary Flavonoid Intake and Breast Cancer Survival among Women on Long Island

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Abstract

Background: **Laboratory research and a growing number of epidemiologic studies have provided evidence for a reduced risk of breast cancer associated with dietary intake of certain classes of flavonoids. However, the effects of flavonoids on survival are not known. In a population-based cohort of breast cancer patients, we investigated whether dietary flavonoid intake before diagnosis is associated with subsequent survival.**

Methods: **Women ages 25 to 98 years who were newly diagnosed with a first primary invasive breast cancer between August 1, 1996, and July 31, 1997, and participated in a population-based, case-control study (n = 1,210) were followed for vital status through December 31, 2002. At the case-control interview conducted shortly after diagnosis, respondents completed a FFQ that assessed dietary intake in the previous 12 months. All-cause mortality (n = 173 deaths) and breast cancer–specific mortality (n = 113 deaths) were determined through the National Death Index.**

Results: **Reduced hazard ratios [age- and energy-adjusted hazard ratio (95% confidence interval)] for all-cause mortality were observed among premenopausal and postmenopausal women for the highest quintile of intake, compared with the lowest, for flavones [0.63 (0.41-0.96)], isoflavones [0.52 (0.33-0.82)], and anthocyanidins [0.64 (0.42-0.98)]. No significant trends in risk were observed. Results were similar for breast cancer–specific mortality only.**

Conclusion: **Mortality may be reduced in association with high levels of dietary flavones and isoflavones among postmenopausal U.S. breast cancer patients. Larger studies are needed to confirm our findings.** (Cancer Epidemiol Biomarkers Prev 2007; 16(11):2285–92)

Introduction

Prior laboratory research suggests that flavonoids may inhibit breast cancer development by decreasing estrogen production (1, 2), inhibiting breast cancer cell proliferation (3), and decreasing reactive oxygen species production (4, 5). Several population-based studies (6-8), including analyses from the Long Island Breast Cancer Study (LIBCSP; ref. 6), reported inverse associations between dietary flavonoid intake and breast cancer risk, but to the best of our knowledge, there are no reports on the association between flavonoids and survival among women with breast cancer in the United States.

Some (9-13), but not all (14, 15), observational studies have observed a reduced risk of all-cause mortality among breast cancer patients in relation to intake of fruit and vegetables, which have high flavonoid content (16). A previous analysis of fruits, vegetables, and micronutrients in relation to survival of breast cancer cases who participated in the LIBCSP (13) found that the risk of mortality was not substantially reduced in relation to increasing intake of fruits, fruit juices, and vegetables at diagnosis. Intake of micronutrients, including vitamin C, vitamin E, and α- and β-carotene, were also not strongly associated with mortality in this population.

Examining associations with flavonoids may help to identify food sources that enhance breast cancer survival, and clarify inconsistent results from previous studies assessing fruits and vegetables and breast cancer survival. This study evaluated whether flavonoid intake reported near the time of diagnosis is associated with reduced all-cause and breast cancer–specific mortality in a population-based sample of women with incident breast cancer (17).

Materials and Methods

Overview. This research draws upon data collected as part of the LIBCSP, which began as a case-control study (17) and now includes assessment of survival among the

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breast cancer cases. For this analysis, flavonoid intake in the year before the baseline case-control study interview was used to examine survival among LIBCSP participants diagnosed with invasive breast cancer in 1996 to 1997 (n = 1,273). Vital status, and cause of death if deceased, through 2002 was determined using the National Death Index. Information on dietary intake and potential confounders and effect modifiers also was collected at the baseline interview, which took place shortly after diagnosis (mean 96 days; ref. 17). Treatment information was derived from baseline (1996-1997) and follow-up (2002-2004) interviews and medical records.

Study Subjects. Eligible cases for the parent LIBCSP case-control study (17) included English-speaking women newly diagnosed with a first invasive primary breast cancer between August 1, 1996, and July 31, 1997, 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 the LIBCSP. The attending physician was contacted to confirm study eligibility and to seek permission to contact each patient. Of the 1,837 eligible cases with physician consent, 1,508 (82%) agreed to participate and completed the main questionnaire (n = 1,273 invasive cases, 235 *in situ* cases). This follow-up study focuses on case participants who were diagnosed with invasive breast cancer.

Exposure Assessment

Baseline, Case-Control Interview. For the parent case-control study, participants were administered a standardized questionnaire by trained interviewers that asked about a variety of known and suspected breast cancer risk factors. Participants were also asked to self-complete a modified version of the Block food frequency questionnaire (FFQ; ref. 18), which assessed intake of frequency and portion size of 100 food items in the year before the interview. The instrument was modified to include questions regarding flavonoid-rich foods such as tofu, cherries, soups, fruit drinks, and alfalfa sprouts (19). A total of 1,273 invasive cases completed the case-control questionnaire and FFQ. To facilitate comparisons with other studies, 38 invasive cases with daily energy intakes above or below 3 SDs of the log-transformed mean were excluded from the analysis (20). Of the remaining cases, 25 had unknown menopausal status (which was defined using information provided by the subject on her date of last menstrual period, prior surgical information on hysterectomy or oophorectomies, her cigarette smoking status, and use of hormone replacement; ref. 17) and were also excluded, resulting in a final sample size of 1,210 women with breast cancer.

Dietary Flavonoid Intake Assessment at Baseline. Details on the food items included in each flavonoid class have been described previously (19). Briefly, food and beverage contents of total flavonoids and seven classes of flavonoids (flavonols, flavones, flavan-3-ols, flavanones, anthocyanidins, isoflavones, and lignans) were estimated using a database created for the LIBCSP (19) that included values from both the Department of Agriculture Database for the Flavonoid Content of Selected Foods (16) and the Department of Agriculture Iowa State University Database on the Isoflavone Content of Selected Foods (21). Additional sources (22-30) were used to estimate the isoflavone content of products not included on the Department of Agriculture database, including selected fruits, vegetables, nuts, and grains that are important dietary contributors of flavonoids among American women (31). These sources also provided information for lignans, a class of flavonoids for which laboratory and epidemiologic evidence has shown potential anticarcinogenic properties (32-37), that is not included in the Department of Agriculture databases.

Fifty items listed on the modified Block FFQ were found to contain at least one flavonoid class. The richest sources of total flavonoids were ''tea, including herb tea,'' which consists primarily of flavan-3-ols (111.41 mg per 100 g); ''cherries,'' which consist primarily of anthocyanidins (116.31 mg per 100 g); and ''grapefruit,'' which consists primarily of flavanones (54.50 mg per 100 g; ref. 16).

Treatment Data. Treatment information was based on data from respondent reports at the baseline case-control and follow-up interviews and the medical records collected as part of each study.

Case-Control Interview. At baseline, medical records were abstracted to obtain information on disease stage (*in situ* versus invasive), initial course of breast cancer treatment, and estrogen receptor (ER) and progesterone receptor (PR) status. Three-fourths of the baseline case interviews occurred before the initiation of chemotherapy (17).

Follow-up Interview. Additional treatment information was obtained from follow-up telephone interviews of case participants or proxies in 2002 to 2004, and from medical records. Of the original 1,508 case participants, 1,414 gave permission to recontact them. Of these, a total of 1,098 cases (n = 868 invasive cases) were successfully reinterviewed by phone. The remaining cases refused to participate in the follow-up interview, were untraceable, or were deceased and had no identifiable proxy. During the follow-up telephone interview, respondents were asked their complete course of treatment for the initial breast cancer diagnosis. Respondents or proxies were asked to sign a Health Insurance Portability and Accountability Act–approved medical record release form.

Follow-up medical records were retrieved and abstracted for 474 invasive cases to determine treatments for their first diagnosis of breast cancer. A high concordance was found between treatment reported by the respondent during the follow-up interview and information abstracted from the medical records for radiation (κ = 0.97), chemotherapy (κ = 0.96), and hormone therapy (κ = 0.92).

Study Outcome. The National Death Index was used to ascertain vital status of all case women and the cause and date of death if deceased. For these analyses, we focused on the 173 (14.3%) deaths that occurred by December 31, 2002, among the 1,210 women diagnosed with invasive breast cancer in 1996 to 1997 with adequate dietary intake data available for analysis. Of these, 113 (65.3% of all deaths) were due to breast cancer based on International Classification of Diseases codes 174.9 and C-50.9 listed as a primary or secondary code on the death certificate. Other causes of death included cardiovascular disease (n = 24), lung cancer (n = 5), other cancers (n = 17), and other (n = 21).

Statistical Analysis. Total flavonoids and each of the seven flavonoid classes of interest were evaluated with log-hazard plots to determine whether the proportional hazards assumption was met. Cox proportional hazards regression (38) was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between total flavonoids, as well as each of the seven flavonoid classes, with all-cause mortality and breast cancer–specific mortality. All models were adjusted for age at diagnosis (continuous) and dietary energy intake (continuous). Models were rerun with follow-up time limited to 5 years, and the results were nearly identical to those where actual follow-up time was included (data not shown). Flavonoid intake was categorized based on the distribution of flavonoid intake for premenopausal and postmenopausal invasive cases combined to facilitate comparisons between the two groups. Analyses were undertaken with flavonoids categorized in quintiles, deciles, quartiles, tertiles, and dichotomously at the median intake, and results were similar; thus, quintiles of flavonoid intake are presented here. When menopause-specific cut points were examined, results were not substantially different than those shown. Tests of trend were conducted using the continuous values in milligrams per day.

Effect modification was examined through use of stratified analysis and by comparing the log-likelihood statistic for models that included multiplicative interaction terms to those without (38). Potential modifiers included covariates assessed at the baseline interview: menopausal status at the time of diagnosis (premenopausal or postmenopausal); family history of breast cancer in a first-degree relative; physical activity level from menarche to date of diagnosis (h/d); active/passive cigarette smoking; body mass index (BMI) [weight (kg)/height $(m)^2$] at diagnosis; average lifetime alcohol intake (g/d); education; income; hormone replacement therapy; and comorbidities, including history of hypertension, diabetes, high cholesterol, myocardial infarction, and stroke. None of these covariates were found to modify the association between flavonoids and survival based on a P value of 0.05. However, because breast cancer survival has been shown to vary with menopausal status in some studies (39, 40), results were stratified by menopausal status.

We also investigated potential effect modification by the primary treatment for breast cancer at diagnosis in a subset of the women for whom we had obtained additional information, including radiation treatment and chemotherapy, as part of the follow-up study, and no effects were observed (data not shown). We examined associations between flavonoids and survival according to tumor characteristics, including tumor size and hormone receptor status (ER/PR) obtained from the medical record as part of the case-control and follow-up studies. No effect measure modification was observed, even when cases were stratified by each individual hormone receptor type.

Potential confounders included those considered as effect modifiers (which included both tumor and host characteristics, as listed above). None of the potential confounders altered effect estimates for flavonoid classes by >10% (data not shown). We also checked for potential residual confounding by age and energy intake, and thus considered models with age as a continuous variable and with energy adjustments using the residual method (41); however, effect estimates remained unchanged (data not shown). Thus, only the age- and energy-adjusted results are shown.

Results

Invasive cases were predominantly White (94.1%), ever married (96.4%), and postmenopausal at diagnosis (Table 1). The proportion of cases with at least some college education was approximately equal to the proportion with a high school diploma or less. Approximately 30% had a household income of at least $50,000 before taxes.

As shown in Table 2, flavones (HR, 0.63 for the highest compared with the lowest quintile of intake; 95% CI, 0.41-0.96), isoflavones (HR, 0.52; 95% CI, 0.33-0.82), and anthocyanidins (HR, 0.64; 95% CI, 0.42-0.98) were inversely associated with all-cause mortality when

Table 1. Demographic characteristics of invasive cases in the LIBCSP

Demographic factor	Cohort (n = 1,210)	Deaths (n = 173)
	n (%)	n (%)
Age at reference (y)		
<44	176 (14.5)	21 (12.1)
45-54	293 (24.2)	33 (19.1)
55-64	301 (24.9)	34 (19.7)
65-74	302 (25.0)	47 (27.1)
75+	138 (11.4)	38 (22.0)
Missing	0	0
Race		
White	1,138 (94.1)	158 (91.3)
Black	50 (4.2)	14 (8.1)
Other	21 (1.7)	1 (0.6)
Missing	1	0
Education		
<High school	161 (13.3)	36 (20.5)
High school graduate	439 (36.4)	75 (43.9)
Some college	283 (23.5)	34 (19.9)
College graduate	149 (12.3)	16 (9.3)
Postcollege	175 (14.5)	11 (6.4)
Missing	3	2
BMI at reference (kg/m^2)		
0-22.4	301 (25.1)	33 (19.3)
22.5-25.6	301 (25.1)	40 (23.4)
25.7-29.4	300 (25.0)	37 (21.6)
≥29.5	296 (24.8)	61 (35.7)
Missing	12	2
ER/PR status		
ER+PR+	534 (44.1)	57 (32.9)
ER+PR−	130 (10.7)	26 (15.0)
ER−PR+	47 (3.9)	7 (4.0)
ER−PR−	194 (16.0)	47 (27.2)
Missing	305	36
Ever had mammogram		
Yes	1,143 (94.5)	150 (86.7)
No	67 (5.5)	23 (13.3)
Missing	0	0
Tumor size (cm)		
0-1.9	370 (78.2)	21 (70.0)
2.0-5.0	84 (19.9)	8 (26.7)
>5.0	9 (1.9)	1 (3.3)
Missing	737	737

NOTE: The table include values for missing income, which were imputed using age, race, and education.

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

Variable (mg/d)	Deaths/cohort, 43/376	Premenopausal HR (95% CI)	Deaths/cohort, 130/834	Postmenopausal HR (95% CI)	Deaths/cohort, 173/1,210	Premenopausal and postmenopausal HR (95% CI)
Total flavonoids						
0-42.4	3/82	1.00	25/161	1.00	28/243	1.00
42.5-95.0	15/72	2.49 (1.32-4.69)	23/171	0.81 (0.52-1.28)	38/243	1.10 (0.77-1.57)
95.1-216.2	6/79	0.58 (0.24-1.36)	28/162	1.09 (0.71-1.65)	34/241	0.95 (0.66-1.39)
216.3-340.4	6/75	0.61 (0.26-1.46)	32/168	1.24 (0.83-1.86)	38/243	1.11 (0.77-1.59)
340.5+	13/68	1.77 (0.91-3.46)	22/172	0.78 (0.49-1.25)	35/240	0.96 (0.66-1.40)
P_{trend}*		0.15		0.49		0.96
Total flavonols						
0-3.4	4/58	1.00	31/185	1.00	35/243	1.00
3.5-5.9	12/81	1.65 (0.84-3.26)	23/162	0.89 (0.57-1.40)	35/243	1.03 (0.71-1.49)
6.0-10.1	8/83	0.78 (0.36-1.68)	25/159	0.99 (0.64-1.54)	33/242	0.94 (0.64-1.37)
10.2-14.4	5/76	0.47 (0.19-1.19)	26/164	1.02 (0.66-1.57)	31/240	0.86 (0.58-1.27)
14.5+	14/78	1.64 (0.84-3.17)	25/164	0.98 (0.62-1.53)	39/242	1.12 (0.78-1.62)
P_{trend}*		0.16		0.41		0.90
Total flavones						
0-0.03	7/61	1.00	32/180	1.00	39/241	1.00
0.04-0.07	9/80	1.07 (0.51-2.25)	29/163	1.24 (0.82-1.88)	38/243	1.20 (0.83-1.72)
0.08-0.12	11/75	1.36 (0.69-2.70)	27/167	1.13 (0.74-1.73)	38/242	1.17 (0.82-1.68)
0.13-0.19	7/70	0.87 (0.39-1.95)	25/172	0.92 (0.59-1.44)	32/242	0.88 (0.60-1.29)
0.20+	9/90	0.69 (0.32-1.47)	17/152	0.59 (0.35-0.99)	26/242	0.63 (0.41-0.96)
P_{trend}*		0.65		0.60		0.45
Total flavanones						
0-4.0	12/97	1.00	21/143	1.00	33/240	1.00
4.1-16.3	8/84	0.80 (0.37-1.73)	28/156	1.49 (0.97-2.29)	36/240	1.25 (0.86-1.81)
16.4-29.9	6/67	0.75 (0.32-1.78)	19/176	0.60 (0.37-0.98)	25/243	0.64 (0.42-0.97)
30.0-48.5	9/74	1.04 (0.50-2.17)	30/172	1.13 (0.75-1.71)	39/246	1.10 (0.77-1.57)
48.6+	8/54	1.08 (0.48-2.43)	32/187	0.99 (0.66-1.49)	40/241	1.03 (0.72-1.48)
P_{trend}*		0.39		0.92		0.68
Total flavan-3-ols						
0-5.0	3/66	1.00	29/178	1.00	32/244	1.00
5.1-34.4	8/84	0.80 (0.37-1.74)	22/158	0.88 (0.56-1.39)	30/242	0.83 (0.56-1.23)
34.5-140.0	12/78	1.42 (0.73-2.77)	26/164	1.01 (0.66-1.56)	38/242	1.12 (0.78-1.61)
140.1-263.7	7/79	0.72 (0.32-1.63)	29/162	1.21 (0.80-1.83)	36/241	1.10 (0.76-1.59)
263.8+	13/69	1.76 (0.91-3.42)	24/172	0.84 (0.53-1.32)	37/241	1.01 (0.70-1.46)
P_{trend}*		0.10		0.53		0.83
Total anthocyanidins						
0-0.03	6/60	1.00	39/181	1.00	45/241	1.00
0.04-0.40	16/86	2.12 (1.14-3.93)	28/158	1.18 (0.77-1.79)	44/244	1.42 (1.01-2.00)
0.41-1.60	10/70	1.33 (0.66-2.71)	25/178	0.92 (0.59-1.42)	35/248	1.00 (0.69-1.45)
1.61-4.23	4/81	0.36 (0.13-1.01)	20/157	0.74 (0.46-1.19)	24/238	0.62 (0.40-0.95)
4.24+	7/79	0.62 (0.27-1.40)	18/160	0.66 (0.40-1.08)	25/239	0.64 (0.42-0.98)
P_{trend}*		0.18		0.82		0.38
Total isoflavones						
0-0.29	8/70	1.00	19/172	1.00	27/242	1.00
0.30-0.78	7/58	1.10 (0.49-2.48)	43/185	1.58 (1.09-2.30)	50/243	1.49 (1.07-2.08)
0.79-2.34	9/69	1.23 (0.59-2.56)	25/175	0.89 (0.58-1.38)	34/244	0.96 (0.66-1.39)
2.35-7.47	10/88	0.93 (0.46-1.90)	31/152	1.59 (1.06-2.38)	41/240	1.36 (0.96-1.94)
7.48+	9/91	0.71 (0.34-1.48)	12/150	0.44 (0.24-0.81)	21/241	0.52 (0.33-0.82)
P_{trend}*		0.92		0.34		0.37
Total lignans						
0-2.2	7/72	1.00	26/171	1.00	33/243	1.00
2.3-3.9	5/72	0.60 (0.24-1.53)	28/170	1.09 (0.72-1.65)	33/242	0.96 (0.65-1.40)
4.0-5.9	14/82	1.69 (0.89-3.21)	25/162	0.98 (0.63-1.51)	39/244	1.14 (0.80-1.63)
6.0-8.9	6/77	0.61 (0.26-1.45)	26/163	0.96 (0.62-1.48)	32/240	0.88 (0.60-1.30)
9.0+	11/73	1.27 (0.63-2.54)	25/168	0.98 (0.63-1.54)	36/241	1.03 (0.71-1.49)
P_{trend}*		0.15		0.38		0.86

*P_{trend} for continuous variable.

analyses included both premenopausal and postmenopausal women, although dose-response trends were not observed. When analyses were restricted to postmenopausal women only, risk of all-cause mortality was decreased in relation to flavones (HR, 0.59; 95% CI, 0.35-0.99) and isoflavones (HR, 0.44; 95% CI, 0.24-0.81), comparing the highest quintile of intake to the lowest quintile (Table 2). Total flavonoids and anthocyanidins were also associated with a modest reduction in mortality. Among premenopausal women, similar reductions in all-cause mortality were observed for flavones, isoflavones, and anthocyanidins, although CIs were wide. Total flavonoids, flavonols, flavan-3-ols, and lignans were positively associated with mortality; however, estimates were imprecise and no clear dose-response trends were evident.

With results stratified by hormone receptor status, effects were slightly more pronounced among those with ER+PR+ tumors, but the CIs were wide (data not shown). Among postmenopausal women with ER+PR+ tumors, nonsignificant inverse associations with all-cause mortality were observed comparing the highest quintile of intake to the lowest quintile, for anthocyanidins (HR, 0.57; 95% CI, 0.28-1.17) and flavones (HR, 0.59; 95% CI, 0.29-1.21). More modest reductions in all-cause mortality were found for flavonols, flavan-3-ols, lignans, and total flavonoids. For women with all other hormone receptor types (ER+PR−, ER−PR+, and ER+PR+; n = 458), no consistent associations were observed.

Results for breast cancer–specific mortality were similar to those for all-cause mortality, including an inverse association with mortality for flavones among postmenopausal women (HR, 0.49; 95% CI, 0.24-0.99) and all women (HR, 0.48; 95% CI, 0.27-0.84), comparing the highest quintile of intake to the lowest quintile (Table 3). Total flavonoids (HR, 0.62; 95% CI, 0.33-1.16), anthocyanidins (HR, 0.62; 95% CI, 0.33-1.18), and isoflavones (HR, 0.79; 95% CI, 0.43-1.44) were also associated with a modest reduction in breast cancer mortality among postmenopausal women, although the CIs were wide. Modest reductions in breast cancer mortality were observed among women who were premenopausal at the time of diagnosis for flavones (HR, 0.45; 95% CI, 0.17-1.19) and anthocyanidins (HR, 0.81; 95% CI, 0.35-1.89), but again the CIs were wide. Total flavonoids (HR, 1.75; 95% CI, 0.82-3.72), flavanols, flavan-3-ols, and lignans were positively associated with breast cancer mortality among premenopausal women, although no dose-response relationship was evident.

Discussion

To the best of our knowledge, this is the first study to examine the influence of dietary flavonoid intake before diagnosis on subsequent breast cancer survival in an American population. We found inverse associations for intake of flavones and isoflavones with all-cause mortality that were more pronounced among postmenopausal women, although dose-response trends were not observed for either association. Total flavonoids and anthocyanidins also showed modest inverse associations with mortality in this group (19). In our population, consumption of green salad, tomatoes, and tomato juice contributed the highest proportions of flavones in our population. To consume at least 0.20 mg of flavones per day, postmenopausal women would need to eat approximately one-half cup of green salad or drink approximately one and one-fourth cup of tomato juice each day.

The observation in our study of a reduced risk of mortality associated with total isoflavones in postmenopausal women is inconsistent with one recent study conducted in Shanghai, China (42). This Chinese study focused solely on the prognostic effects of soy, which is rich in isoflavones and traditionally consumed more frequently by Asian populations than in the United States. The investigators found that soy intake before cancer diagnosis was unrelated to disease-free breast cancer survival among premenopausal and postmenopausal women (42). Reasons for the inconsistent results between the two studies are not clear, although it is possible that consumption of soy is uniformly high in this Asian population, which would make it more difficult to detect differences in mortality associated with little variability in intake. The mechanisms by which flavonoids may affect breast cancer survival are unclear, but the prior research on flavonoid-rich fruits and vegetables (9-13) suggests that antioxidant, antiestrogenic, and apoptotic effects may inhibit the growth and spread of breast cancer tumors.

Interpretation of the lack of any statistically significant trends observed in our data is challenging. Our findings of effects that are restricted to those consuming the largest intake of flavonoids suggest a possible threshold effect. Alternatively, a population with a more substantial variation in flavonoid intake may be required to observe any dose-response. Or, perhaps a study with a larger sample size, or a longer follow-up period, may be required to detect more subtle associations between levels of flavonoid intake and breast cancer survival.

Similarly, the differences we observed by menopausal status could be due to the unstable estimates among the younger women. Power would have been modestly improved if we were able to consider breast cancer recurrence as an outcome. Although women were asked to report these data at the follow-up interview, we were unable to consistently confirm these events in the medical records for many women. [Because the κ coefficients for the comparisons between the medical record and the self-report were poor (data not shown), we were unable to conduct any analyses using this outcome.] Thus, we focused our analyses on mortality, which is reliably and consistently reported in the National Death Index.

The Block FFQ has been shown to be a valid and reliable dietary assessment tool for estimating usual food intake and ranking individuals into categories of intake of micronutrients (43, 44). However, a potential limitation of this instrument is its lack of complete assessment of commonly consumed flavonoid-rich products. Although the Block FFQ was modified for the LIBCSP to include more flavonoid-rich foods, it did not include blueberries and raspberries, which are rich sources of anthocyanidins (16). In the future, FFQs and other dietary history assessment tools should incorporate newly developed and commonly consumed soy products to enhance coverage of isoflavones. These products include meatless hamburger, chicken, and sausage made from soy protein, as well as soy protein found in some fast food hamburgers. Inclusion of these foods on FFQs used in future studies would improve both the estimation of flavonoid intake and thus the ability to detect an association with breast cancer survival.

Flavonoid consumption may reflect part of an overall healthy diet and lifestyle (45). Furthermore, many lifestyle factors that may potentially confound the relationship between flavonoids and breast cancer are highly correlated with high flavonoid intake, making it difficult to firmly establish their independent effects (46). However, in our analyses, age- and energy-adjusted estimates were very similar to multivariate-adjusted results, indicating that confounding by the variables examined was not evident. However, residual confounding by unmeasured or poorly measured confounders could have biased the estimates.

Table 3. Age- and energy-adjusted HRs and 95% CIs stratified by menopausal status for the association between flavonoid intake in relation to breast cancer–specific mortality

Variable (mg/d)	Deaths/cohort, 34/367	Premenopausal HR (95% CI)	Deaths/cohort, 79/781	Postmenopausal HR (95% CI)	Deaths/cohort 113/1,148	Premenopausal and postmenopausal HR (95% CI)
Total flavonoids						
0-42.4	2/81	1.00	16/152	1.00	18/233	1.00
42.5-95.0	13/70	2.88 (1.44-5.78)	16/164	0.97 (0.56-1.68)	29/234	1.37 (0.90-2.10)
95.1-216.2	5/78	0.61 (0.24-1.58)	14/148	0.90 (0.51-1.61)	19/226	0.81 (0.49-1.32)
216.3-340.4	4/73	0.50 (0.18-1.42)	21/156	1.40 (0.84-2.33)	25/229	1.10 (0.70-1.73)
340.5+	10/65	1.75 (0.82-3.72)	12/161	0.62 (0.33-1.16)	22/226	0.88 (0.55-1.42)
P_{trend}*		0.36		0.44		0.96
Total flavonols						
0-3.4	4/58	1.00	17/171	1.00	21/229	1.00
3.5-5.9	10/79	1.80 (0.85-3.80)	16/155	1.04 (0.60-1.81)	26/234	1.22 (0.78-1.89)
6.0-10.1	6/81	0.73 (0.30-1.77)	14/148	0.92 (0.52-1.65)	20/229	0.86 (0.53-1.39)
10.2-14.4	3/74	0.34 (0.10-1.12)	15/152	0.87 (0.49-1.55)	18/226	0.69 (0.41-1.16)
14.5+	11/75	1.64 (0.78-3.46)	17/155	1.02 (0.59-1.79)	28/230	1.20 (0.77-1.87)
P_{trend}*		0.72		0.31		0.61
Total flavones						
0-0.03	4/58	1.00	16/163	1.00	20/221	1.00
0.04-0.07	9/80	1.46 (0.67-3.15)	17/151	1.24 (0.72-2.13)	26/231	1.30 (0.83-2.01)
0.08-0.12	10/74	1.62 (0.77-3.39)	19/158	1.20 (0.71-2.03)	29/232	1.32 (0.86-2.02)
0.13-0.19	6/69	0.94 (0.39-2.27)	18/165	1.06 (0.62-1.80)	24/234	1.01 (0.64-1.59)
0.20+	5/86	0.45 (0.17-1.19)	9/144	0.49 (0.24-0.99)	14/230	0.48 (0.27-0.84)
P_{trend}*		0.15		0.14		0.15
Total flavanones						
0-4.0	10/95	1.00	12/133	1.00	22/228	1.00
4.1-16.3	7/83	0.89 (0.39-2.05)	19/146	1.52 (0.89-2.61)	26/229	1.27 (0.81-1.99)
16.4-29.9	6/67	0.97 (0.40-2.35)	9/166	0.47 (0.23-0.94)	15/233	0.60 (0.35-1.03)
30.0-48.5	7/72	1.03 (0.45-2.38)	19/161	1.21 (0.72-2.03)	26/233	1.15 (0.74-1.78)
48.6+	4/50	0.61 (0.21-1.81)	20/175	1.09 (0.65-1.82)	24/225	0.98 (0.62-1.56)
P_{trend}*		0.55		0.45		0.89
Total flavan-3-ols						
0-5.0	2/65	1.00	19/168	1.00	21/233	1.00
5.1-34.4	6/82	0.76 (0.31-1.85)	13/149	0.83 (0.46-1.50)	19/231	0.78 (0.48-1.28)
34.5-140.0	11/77	1.75 (0.85-3.60)	14/152	0.90 (0.50-1.60)	25/229	1.14 (0.73-1.78)
140.1-263.7	5/77	0.63 (0.24-1.63)	21/153	1.46 (0.88-2.43)	26/230	1.19 (0.76-1.86)
263.8+	10/66	1.75 (0.83-3.69)	12/159	0.63 (0.34-1.18)	22/225	0.89 (0.55-1.43)
P_{trend}*		0.25		0.45		0.89
Total anthocyanidins						
0-0.03	4/58	1.00	21/163	1.00	25/221	1.00
0.04-0.40	11/81	1.80 (0.88-3.69)	15/145	1.05 (0.60-1.85)	26/226	1.28 (0.82-1.98)
0.41-1.60	8/68	1.33 (0.60-2.95)	21/173	1.27 (0.76-2.12)	29/241	1.30 (0.85-1.99)
1.61-4.23	4/81	0.46 (0.16-1.31)	11/148	0.65 (0.35-1.24)	15/229	0.58 (0.34-1.00)
4.24+	7/79	0.81 (0.35-1.89)	11/152	0.62 (0.33-1.18)	18/231	0.68 (0.41-1.13)
P_{trend}*		0.24		0.84		0.39
Total isoflavones						
0-0.15	7/76	1.00	11/150	1.00	18/226	1.00
0.16-0.26	5/71	0.96 (0.40-2.35)	21/165	1.02 (0.59-1.78)	26/236	0.99 (0.62-1.59)
0.27-0.37	8/67	1.69 (0.79-3.62)	15/159	0.99 (0.57-1.72)	23/226	1.17 (0.75-1.83)
0.38-0.59	8/71	0.48 (0.17-1.36)	24/158	1.08 (0.63-1.84)	32/229	0.86 (0.54-1.39)
0.60+	6/82	1.03 (0.46-2.28)	8/149	0.79 (0.43-1.44)	14/231	0.87 (0.54-1.41)
P_{trend}*		0.43		0.32		0.21
Total lignans						
0-2.2	6/71	1.00	15/160	1.00	21/231	1.00
2.3-3.9	4/71	0.60 (0.21-1.71)	18/160	1.17 (0.69-1.98)	22/231	0.99 (0.62-1.57)
4.0-5.9	12/80	1.92 (0.95-3.89)	16/153	1.04 (0.60-1.80)	28/233	1.28 (0.84-1.97)
6.0-8.9	4/75	0.50 (0.18-1.42)	15/151	0.88 (0.49-1.57)	19/226	0.76 (0.46-1.26)
9.0+	8/70	1.16 (0.52-2.58)	15/157	0.87 (0.49-1.55)	23/227	0.95 (0.60-1.51)
P_{trend}*		0.31		0.36		0.86

*P_{trend} for continuous variable.

Dietary modification following disease diagnosis is an increasingly commonplace behavior among survivors (47-50). Breast cancer survivors concerned about recurrence have been reported to consume more fruits and vegetables compared with those who are not as concerned (51, 52). Thus, it is possible that a diagnosis of breast cancer motivated dietary behavior change in some of the cases, although it remains unclear whether postdiagnostic changes affect subsequent mortality (10, 12, 42, 53, 54). Any effects due to postdiagnostic dietary changes would not be captured by our analyses, because our assessment includes dietary intake just before and shortly after diagnosis. Changes in lifestyle might also have affected other outcomes (e.g., lung cancer deaths in 2.3% of cases and cardiovascular disease deaths in 12.7% of cases). However, when we restricted

our analyses to breast cancer–specific deaths only, results were similar to those observed for all-cause mortality (although the CIs were wider).

Case reports of food intake may have been affected by whether or not a woman had initiated chemotherapy by the time of the study interview (43). However, in the LIBCSP, most of the case women (> 75%) were interviewed about their dietary history before any chemotherapy. In addition, among those that had started treatment, average intake levels of flavonoid-rich fruits and vegetables did not differ from those who had not started (20).

This study had the advantage of a large sample size and population-based design, reducing the likelihood of selection bias and allowing for greater generalizability compared with smaller, hospital-based studies. However, future studies may need larger sample sizes to have sufficient power to detect potential dose-response associations between levels of flavonoid intake and breast cancer survival. The LIBCSP population consumed relatively large quantities of a wide variety of flavonoid-containing products, such as fruits, vegetables, and tea (6, 19), and intakes of several flavonoid classes were comparable with those from the populations in Italy (7) and Greece (8). However, our study population consumed, on average, higher levels of flavan-3-ols and isoflavones (6, 19).

In summary, this follow-up study among a population-based sample of breast cancer patients suggests that there may be a beneficial effect of high intake of flavones and isoflavones on all-cause mortality. The effects were more pronounced among postmenopausal women than premenopausal women. Given that few modifiable lifestyle factors for breast cancer survival have been identified, future studies with larger sample sizes are needed to elucidate whether there is a possible threshold effect or a dose-response association. Subsequent research should also include thorough assessments of flavonoid-rich food intake at diagnosis and following diagnosis to determine the role of flavonoid intake on breast cancer prognosis.

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