Original Article

Dietary Isoflavone Intake and All-Cause Mortality in Breast Cancer Survivors: The Breast Cancer Family Registry

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BACKGROUND: Soy foods possess both antiestrogenic and estrogen-like properties. It remains controversial whether women diagnosed with breast cancer should be advised to eat more or less soy foods, especially for those who receive hormone therapies as part of cancer treatment. **METHODS:** The association of dietary intake of isoflavone, the major phytoestrogen in soy, with all-cause mortality was examined in 6235 women with breast cancer enrolled in the Breast Cancer Family Registry. Dietary intake was assessed using a Food Frequency Questionnaire developed for the Hawaii-Los Angeles Multiethnic Cohort among 5178 women who reported prediagnosis diet and 1664 women who reported postdiagnosis diet. Cox proportional-hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). **RESULTS:** During a median follow-up of 113 months (approximately 9.4 years), 1224 deaths were documented. A 21% decrease was observed in all-cause mortality for women who had the highest versus lowest quartile of dietary isoflavone intake ($\geq$1.5 vs $<$ 0.3 mg daily: HR, 0.79; 95% confidence interval CI, 0.64-0.97; $P_{trend} = .01$). Lower mortality associated with higher intake was limited to women who had tumors that were negative for hormone receptors (HR, 0.49; 95% CI, 0.29-0.83; $P_{trend} = .005$) and those who did not receive hormone therapy for their breast cancer (HR, 0.68; 95% CI, 0.51-0.91; $P_{trend} = .02$). Interactions, however, did not reach statistical significance. **CONCLUSIONS:** In this large, ethnically diverse cohort of women with breast cancer living in North America, a higher dietary intake of isoflavone was associated with reduced all-cause mortality. [See editorial on pages 0000-000, this issue.] ***Cancer* 2017;000:000–000.** © *2017 American Cancer Society.*

KEYWORDS: breast cancer, breast cancer survivors, isoflavone, mortality, soy, survival.

INTRODUCTION

It has been suggested that isoflavone inhibits the development of breast cancer by decreasing estrogen production, inhibiting cell proliferation, and reducing reactive oxygen species production.[1] However, isoflavone is also known for its estrogenic activity by binding and activating estrogen receptors (ERs) in breast tumors,[1] which may interfere with tamoxifen therapy by reducing its treatment effect. It remains controversial whether women should be advised to avoid or to increase their intake of food products or supplements that contain isoflavone to reduce breast cancer risk or progression.[2,3]

Only a few epidemiologic studies have evaluated the association between intake of soy foods or dietary isoflavone, either before or after cancer diagnosis, and survival in women with breast cancer.[4] Although several lines of evidence indicate a reduced risk of mortality or recurrence associated with increasing soy consumption in Chinese women,[5-7] the evidence is still very limited for women living in Western countries, where soy product consumption is much lower than in Asian countries. In Western countries, the intake of soy products varies by race/ethnicity.[8] It remains unclear whether dietary isoflavone intake is associated with different mortality rates among Caucasian, Hispanic, African American, and Asian American women living in the United States. Studies are needed to further quantify whether associations between dietary isoflavone intake and survival vary by tumor hormone receptor status and by receipt of hormone therapy for the treatment of breast cancer. These analyses will contribute to the evidence base for developing targeted dietary recommendations for

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breast cancer survivors. The current study examined the association between dietary intake of isoflavone and all-cause mortality in a multiethnic cohort of women diagnosed with breast cancer living in the United States and Canada and assessed whether the associations differ by race/ethnicity, tumor hormone receptor status, and receipt of hormone therapy.

MATERIALS AND METHODS

Study Population

The Breast Cancer Family Registry (BCFR) is an international research infrastructure that was established in 1995, with 6 participating sites from the United States, Canada, and Australia that recruited breast cancer families either through population-based cancer registries (population-based families) or cancer clinics and community outreach (clinic-based families).[9] Population-based families were recruited through incident breast cancer cases identified by the regional cancer registries in the greater San Francisco Bay area, the province of Ontario, Canada, and the metropolitan areas of Melbourne and Sydney, Australia. Clinic-based families were recruited from the local populations in New York City, Philadelphia, Utah, Ontario, and Melbourne/Sydney. The first family member recruited into the BCFR is referred to as the proband, regardless of breast cancer status. Population-based probands were sampled according to site-specific criteria based on sex, race/ethnicity, family history, and age at diagnosis. Permission was sought from the probands to contact eligible family members. Between 1996 and 2011, more than 13,000 families were recruited and followed prospectively. Because a different food frequency questionnaire (FFQ) was used to assess dietary intake in Australia, the current analysis only includes women from the 5 North American BCFR sites who completed the same FFQ at baseline and is limited to women who were diagnosed with a first primary, invasive breast cancer (n = 7471). We further excluded 588 women who died within the first year after the baseline questionnaire to minimize the impact of reverse causation. The remaining 6883 women included 5279 (77%) population-based probands (5105 women enrolled in the BCFR as affected probands and 174 enrolled as unaffected relatives who were diagnosed with breast cancer during follow-up) and 1604 women (23%) from the clinic-based BCFR sites (1471 women enrolled with breast cancer and 133 enrolled as unaffected relatives who developed breast cancer during follow-up).

At enrollment into the BCFR, probands completed a detailed questionnaire on family history of cancer in first-degree and higher degree relatives. All participants completed a structured questionnaire on menstrual and reproductive histories, hormone use, physical activity, alcohol drinking, cigarette smoking, height and weight, as well as a fan FFQ (see below). For women diagnosed with breast cancer, self-reported information on treatment was collected by questionnaire, and information on tumor characteristics (ie, tumor size, number of affected lymph nodes, grade, histology, and ER and progesterone receptor [PR] status) was abstracted from pathology reports or obtained from cancer registry records. The population-based probands reported on their exposures and dietary intake up to or during the year before diagnosis. All other women reported on their exposures and dietary intake up to or during the year before enrollment.

Self-reported weight and height were used to calculate body mass index (BMI) (in kg/m^2) and were classified as normal weight ($BMI < 25\ kg/m^2$), overweight ($BMI = 25\text{-}29.9\ kg/m^2$), and obese ($BMI \geq 30\ kg/m^2$). Minutes per week of recent recreational physical activity (ie, during the 3 years before diagnosis for population-based probands or before enrollment for all others) were calculated by summarizing moderate and vigorous physical activities (MVPAs), which are reported as hours per week and months per year, and by weighting vigorous physical activity at 1.67 minutes for each minute of activity. A binary variable (active vs inactive) was created to reflect whether a women's MVPAs met the Centers for Disease Control and Prevention's physical activity guidelines for Americans ($\geq$150 minutes per week).[10] Usual alcohol consumption was self-reported in drinks per week consumed before diagnosis (population-based probands) or enrollment (all others) and categorized as nondrinkers, <7 drinks per week, or ≥ 7 drinks per week. Smokers were defined as women who reported smoking at least 1 cigarette a day for 3 months or longer. Cigarette smoking status was defined as never, former, or current. Pack-years of smoking were calculated using smoking intensity (packs per day) multiplied by duration (years smoked).

Dietary Assessment

Dietary intake data were collected at enrollment using a self-administered FFQ, which was developed for the Hawaii-Los Angeles Multiethnic Cohort to assess dietary intake in a racially/ethnically diverse population. It was previously validated with repeated 24-hour diet recalls and demonstrated high correlations for most food groups and nutrients.[11] The FFQ asked study participants about

their usual dietary intake of 108 food items and assessed frequency of consumption (never or hardly ever, once a month, 2-3 times a month, once a week, 2-3 times a week, 4-6 times a week, once a day, and $\geq$2 times a day) and portion size (3 categories).

There were 6883 women who completed the FFQ at baseline and were alive within the first year of completing the FFQ. From these, we excluded 55 women with potentially unreliable reporting of dietary intake, defined as total caloric intake exceeding 3 standard deviations above or below the mean value of the natural log-transformed caloric intake in the study population. We also excluded 459 population-based probands who completed the FFQ more than 5 years after diagnosis to reduce error associated with recalling more distant dietary intake. For all other women, we excluded 134 who reported their dietary intake more than 5 years before diagnosis; and, of the remaining 6235 women, 4769 reported on their dietary intake within 5 years before breast cancer diagnosis (ie, prediagnosis diet), and 1466 reported on their dietary intake within 5 years after diagnosis (ie, postdiagnosis diet).

Survival Outcomes

Vital status of women was ascertained through several follow-up activities to ensure completeness, including annual telephone contacts or mailed questionnaires with probands or family members, linkage to cancer registry and death registry records, and review of medical records or contact with physicians' offices. Causes of death were not available for these analyses.

Statistical Analyses

We used multivariable Cox proportional-hazard models to evaluate the association between dietary isoflavone intake and all-cause mortality. Days since diagnosis was used as the time scale, with follow-up time left-truncated at the date of interview to minimize potential survival bias. Individuals were censored at the date of either death or last contact. The rate ratio of all-cause mortality was estimated as the hazard ratio (HR) with 95% confidence interval (CI). All models were adjusted for age, study site, and total caloric intake. Next, we examined a predefined list of additional confounders and adjusted for variables that altered the parameter estimates by greater than 10%, including race/ethnicity, education, total fiber intake, Healthy Eating Index (HEI)-2010, treatment type, recent recreational physical activity, BMI, usual alcohol consumption, and cigarette smoking status. A binary variable (yes vs no) was created for each treatment type (surgery, radiation therapy, chemotherapy, and hormone therapy) based on self-reported treatment. The HEI-2010 was calculated using the methods provided by the US Department of Agriculture and measures the overall diet quality by assessing adherence to the 2010 dietary guidelines for Americans.[12,13] The total HEI-2010 score ranges from 0 (nonadherence) to 100 (perfect adherence), with higher scores indicating better adherence to the dietary guidelines. Wald tests for trend were used to evaluate associations with increasing dietary intake of isoflavone categorized as quartiles based on the intake of all women.

We first performed the analysis in all 6235 women for total isoflavone intake and specific types of isoflavone (genistein, daidzein, and glycitein). Separate analyses were conducted for 4769 women who reported prediagnosis diet and for 1466 who reported postdiagnosis diet (3 women who did not report age at diagnosis were excluded from this analysis). For all women, we evaluated potential effect modification by race/ethnicity (non-Hispanic white, black, Hispanic, and Asian/Pacific Islander/other), menopausal status (premenopausal vs postmenopausal), receipt of hormone therapy (yes vs no), BMI ($<$25, 25-29.9, $\geq$ 30 kg/m^2), and levels of recreational physical activity (inactive vs active) by comparing the log-likelihood statistics of models that included interaction terms and models without interaction terms. P values $<$ .05 were considered a statistically significant effect modification at the multiplicative scale. We further evaluated whether associations differed for tumor hormone receptors defined by ER and PR status (any hormone receptor positive vs hormone receptor negative) by using multinominal Cox proportional-hazard regression. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Table 1 describes the characteristics of the 6235 women diagnosed with a first primary, invasive breast cancer enrolled in the BCFR who reported reliable dietary intake. The mean $\pm$ standard deviation dietary intake of isoflavone was 1.8 $\pm$ 3.9 mg daily, and the median intake was 0.7 mg daily (interquartile range, 1.2 mg daily). Genistein was the major source of isoflavone, followed by daidzein and glycitein. Women who consumed high levels of dietary isoflavone were more likely to be Asian Americans, young, premenopausal, physically active, more educated, not overweight or obese, never smokers, and drank either no alcohol or $<$7 drinks per week (Table 2). Women with the lowest or highest quartiles of isoflavone intake had a higher diet quality index compared with those in the middle quartiles.

TABLE 1. Characteristics of Women with Breast Cancer: the Breast Cancer Family Registry

Characteristic	No. of Women (%), n = 6235
Age at enrollment: Mean ± SD, y	51.8 ± 10.6
Race/ethnicity	
Non-Hispanic whites	3647 (58.5)
Hispanics	1033 (16.6)
Blacks	751 (12)
Asians	690 (11.1)
Other	114 (1.8)
Education	
≤High school	2299 (37.1)
Some college or bachelor's degree	2957 (47.7)
Graduate degree	945 (15.2)
Menopausal status at enrollment	
Premenopausal	3056 (49)
Postmenopausal	3176 (51)
BMI at enrollment: Mean ± SD, kg/m^2	26.4 ± 5.9
<18.5	143 (2.3)
18.5-24.9	2848 (45.7)
25-29.9	1723 (28.5)
≥30	1336 (22.1)
Recreational physical activity[a]	
Active	2725 (45.5)
Inactive	3262 (54.5)
Cigarette smoking	
Never	3626 (58.3)
Ever	2589 (41.7)
Pack-years among smokers: Mean ± SD,	17.2 ± 18
Usual alcohol consumption	
Nondrinkers	3702 (60.7)
<7 drinks/wk	1614 (26.5)
≥7 drinks/wk	787 (12.9)
Cancer treatment received	
Surgery	5378 (86.3)
Radiation therapy	3634 (58.3)
Chemotherapy	3271 (52.5)
Hormone therapy	2862 (45.9)
Tumor ER status	
Positive	3260 (52.3)
Negative	1394 (22.4)
Undetermined	120 (1.9)
Missing/unknown	1461 (23.4)
Tumor PR status	
Positive	2937 (47.1)
Negative	1679 (26.9)
Undetermined	110 (1.8)
Missing/unknown	1509 (24.2)

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation.
[a] Physical activity was defined as active if the current level (during the 3 years before diagnosis or questionnaire completion) of moderate-to-vigorous recreational physical activities was ≥150 minutes per week, and otherwise was defined as inactive.

After a median follow-up of 113 months (approximately 9.4 years), 1224 deaths were documented. Women in the highest quartile of dietary isoflavone intake (≥1.5 mg/d) had a 21% decrease in all-cause mortality compared with women in the lowest quartile (<0.3 mg daily; fourth quartile [Q4] vs first quartile [Q1]: HR, 0.79; 95% CI, 0.64-0.97; P_{trend} = .01) (Table 3). The inverse association was statistically significant for women who reported postdiagnosis intake of total isoflavone (Q4 vs Q1: HR, 0.65; 95% CI, 0.41-1.00; P_{trend} = .02). The association with prediagnosis intake was weaker and was not statistically significant (Q4 vs Q1: HR, 0.84; 95% CI, 0.66-1.06; P_{trend} = .13). The 3 common types of isoflavone (genistein, daidzein, and glycitein) were associated with similar reductions in all-cause mortality (Fig. 1).

In stratified analyses (Table 4), a reduced risk of all-cause mortality associated with high (highest vs lowest quartile) dietary isoflavone intake was statistically significant for women with ER-negative/PR-negative tumors (HR, 0.49; 95% CI, 0.29-0.83; P_{trend} = .006) and women who did not receive hormone therapy as a component of their treatment for breast cancer (Q4 vs Q1: HR, 0.68; 95% CI, 0.51-0.91; P_{trend} = .02). No associations were observed for women who had hormone receptor-positive tumors and those who received hormone therapy. However, the interactions were not statistically significant. Analyses stratified by race/ethnicity, menopausal status, BMI, and physical activity indicated borderline significant trends across quartiles of isoflavone intake for Hispanics (P_{trend} = .05) and normal-weight women (BMI < 25 kg/m^2; P_{trend} = .05) and a significant trend for physically active women (P_{trend} = .04), but none of the HR estimates or interactions were statistically significant.

DISCUSSION

In the current study, we examined the association between dietary intake of isoflavone and all-cause mortality in 6235 women diagnosed with a first primary breast cancer who had been followed for a median of >9 years. Overall, we observed 21% lower all-cause mortality associated with high isoflavone intake. The reduced mortality was largely confined to women who had ER-negative/PR-negative tumors and those who did not receive hormone therapy.

Although several epidemiologic studies reported that higher soy consumption was associated with a lower risk of breast cancer recurrence and/or mortality in Chinese women,[7,14,15] studies in the United States have reported inconsistent findings.[16,17] For prediagnosis intake of dietary isoflavone, 1 study of 3842 women enrolled in the Multiethnic Cohort did not indicate an association with all-cause mortality,[18] but an earlier report in 1210 women detected a 48% reduction in all-cause mortality for those who consumed the highest quintile of isoflavone (>7.5 mg daily).[19] For postdiagnosis intake, a pooled analysis of 2 US cohorts did not indicate a significant reduction in all-cause mortality associated with high isoflavone intake (>10 mg daily).[16,17,20] However, the 2

TABLE 2. Demographic and Lifestyle Characteristics of Women With Breast Cancer by Levels of Dietary Isoflavone Intake: The Breast Cancer Family Registry

Characteristic	No. of Women (%) or Mean ± SD Dietary Isoflavone Intake, mg/d				*P*
	Q1, < 0.342	Q2, 0.343-0.674	Q3, 0.675-1.493	Q4, ≥ 1.494	
Age, y	52.6 ± 11.5	50.9 ± 11.0	49.6 ± 10.2	48.8 ± 9.5	< .0001
Race/ethnicity					
Non-Hispanic white	958 (62.3)	1073 (70.3)	995 (65)	621 (40.8)	< .0001
Black	337 (21.9)	145 (9.5)	158 (10.3)	111 (7.3)	
Hispanic	215 (14)	264 (17.3)	297 (19.4)	257 (16.9)	
Asian	29 (1.9)	45 (3)	81 (5.3)	535 (35.1)	
Education					
≤High school	664 (43)	668 (43.2)	589 (37.9)	378 (24.3)	< .0001
Some college or bachelor's degree	704 (45.6)	713 (46.1)	732 (47)	808 (52)	
Graduate degree	177 (11.5)	166 (10.7)	235 (15.1)	367 (23.6)	
Menopausal status at enrollment					
Premenopausal	642 (41.3)	732 (47)	836 (53.5)	846 (54.2)	< .0001
Postmenopausal	911 (58.7)	825 (53)	726 (46.5)	714 (45.8)	
BMI at enrollment, kg/m^2	27.0 ± 6.2	26.7 ± 5.8	26.7 ± 5.8	25.2 ± 5.3	< .0001
<25	682 (45.2)	714 (47.6)	705 (46.4)	890 (58.5)	< .0001
25-29.9	445 (29.5)	403 (26.9)	478 (31.4)	397 (26.1)	
≥30	382 (25.3)	382 (25.5)	338 (22.2)	234 (15.4)	
Recent recreational physical activity[a]					
Inactive	735 (49.5)	694 (46.6)	651 (43.4)	645 (42.6)	< .001
Active	750 (50.5)	794 (53.4)	850 (56.6)	868 (57.4)	
Cigarette smoking status					
Never	826 (53.4)	853 (54.9)	870 (55.8)	1077 (69.2)	< .0001
Former	470 (30.4)	455 (29.3)	463 (29.7)	370 (23.8)	
Current	251 (16.2)	245 (15.8)	225 (14.4)	110 (7.1)	
Usual alcohol consumption					
Nondrinkers	913 (59.8.)	854 (56)	899 (58.8)	1036 (68.1)	< .0001
<7 drinks/wk	409 (26.8)	446 (29.3)	431 (28.2)	328 (21.6)	
≥7 drinks/wk	206 (13.5)	225 (14.8)	198 (13)	158 (10.4)	
Healthy Eating Index-2010	67.0 ± 11.1	65.3 ± 10.3	65.6 ± 10.1	67.1 ± 9.7	< .0001
Q1, < 59.2	354 (24)	417 (27.9)	409 (26.7)	331 (21.2)	< .0001
Q2, 59.2-66.6	317 (21.4)	401 (26.8)	393 (25.7)	401 (26)	
Q3, 66.7-73.6	363 (24.6)	355 (23.7)	391 (25.5)	402 (26.1)	
Q4, ≥ 73.7	444 (30)	323 (21.6)	338 (22.1)	407 (26.4)	

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; Q, quartile; SD, standard deviation.
[a] Physical activity was defined as active if their current level (during the 3 years before diagnosis or questionnaire completion) of moderate-to-vigorous recreational physical activities was ≥150 minutes per week, and otherwise was defined as inactive.

US cohorts were predominantly non-Hispanic whites (range, 82%-85%) with a small proportion of racial/ethnic minorities (approximately 5% Hispanics, 4% blacks, and 3% Asian Americans). In our more diverse cohort of women living in North America (approximately 17% Hispanics, 12% blacks, and 11% Asian Americans), we observed a significant trend of lower all-cause mortality associated with higher dietary intake of isoflavone. This association was similarly observed across all racial/ethnic groups, although the trend was slightly stronger in Hispanic women. Although Asian American women enrolled in the BCFR had a higher mean intake of dietary isoflavone than women from other racial/ethnic groups (6.1 vs 1.3 mg daily; $P < .0001$), these intake levels were substantially lower than those of women living in Asian countries (eg, the mean intake is 45.9 mg daily among women living in China). Our findings suggest that women living in North American, despite an overall low consumption of isoflavone from diet, may still benefit from increasing their isoflavone intake to a higher level.

Consistent with the pooled analysis in the 2 US cohorts,[16,17,20] we observed that high isoflavone intake was significantly associated with a reduction in all-cause mortality only among women with ER-negative/PR-negative tumors. Cell line studies suggest that soy isoflavone may interact with tamoxifen therapy and potentially reduce the effect of cancer treatment.[1] However, our study did not indicate a negative impact of isoflavone on all-cause mortality in women who received hormone therapy. Among those who did not receive hormone therapy as part of their cancer treatment, high isoflavone intake was associated with reduced all-cause mortality. These results, taken together, may indicate that dietary isoflavone is unlikely to have a negative impact on the survival of women

TABLE 3. Dietary Intake of Isoflavone and All-Cause Mortality in Women With Breast Cancer: The Breast Cancer Family Registry

Variable	No. of Deaths	Person-Years	HR (95% CI)[a]	HR (95% CI)[b]
All women, n = 6235				
Total isoflavone, mg/d				
Q1, < 0.342	359	13,938	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	343	14,072	0.96 (0.83-1.12)	1.01 (0.85-1.19)
Q3, 0.675-1.493	291	14,227	0.81 (0.68-0.95)	0.89 (0.74-1.07)
Q4, ≥ 1.494	231	13,560	0.67 (0.56-0.80)	0.79 (0.64-0.97)
P_{trend}			< .0001	.01
Women who reported prediagnosis diet, n = 4769[c]				
Total isoflavone, mg/d				
Q1, < 0.342	270	10,178	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	265	11,440	0.90 (0.76-1.07)	0.96 (0.80-1.15)
Q3, 0.675-1.493	235	11,124	0.80 (0.67-0.97)	0.90 (0.74-1.10)
Q4, ≥ 1.494	193	10,531	0.68 (0.55-0.83)	0.84 (0.66-1.06)
P_{trend}			< .0001	.13
Women who reported postdiagnosis diet, n = 1466[c]				
Total isoflavone, mg/d				
Q1, < 0.342	89	3761	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	78	2632	1.28 (0.92-1.77)	1.26 (0.90-1.77)
Q3, 0.675-1.493	56	3102	0.84 (0.59-1.20)	0.80 (0.55-1.16)
Q4, ≥ 1.494	38	3029	0.62 (0.41-0.93)	0.65 (0.41-1.00)
P_{trend}			.008	.02

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; Q, quartile; Ref, reference category.
[a] The analysis was adjusted for age (continuous), study site, and total caloric intake (quartiles).
[b] The analysis was also adjusted for race/ethnicity (non-Hispanic white, black, Hispanic, and Asian/Pacific Islander/other), education (high school or less, some college or bachelor's degree, or graduate degree), total fiber intake (quartiles), Health Eating Index-2010 (quartiles), treatment type (surgery, radiation, chemotherapy, and hormone therapy), recreational physical activity (active, inactive), BMI (<25, 25-29.9, ≥ 30 kg/m^2), alcohol use (never, < 7 drinks per week, ≥ 7 drinks per week), smoking status (never, ever), and pack-years (continuous).
[c] Three women did not report age at diagnosis and were excluded in the stratified analyses by prediagnosis versus postdiagnosis diet.

who receive hormone therapy; however, the potential benefit may be limited to women who have negative tumor hormone receptors (ER-negative/PR-negative) or those who do not receive hormone therapy.

For women with breast cancer in the BCFR, information is available on both prediagnosis and postdiagnosis dietary intake. This provides a unique opportunity to assess the potential timing effect of women's diet on survival. A statistically significant, inverse trend was observed for postdiagnosis isoflavone intake only, with an approximately 35% reduction in all-cause mortality associated with high intake. For prediagnosis intake, the inverse association was weaker and was not statistically significant. It is possible that dietary assessment for prediagnostic intake is associated with more measurement errors that postdiagnostic intake, which can bias the findings toward the null. Alternatively, this finding may suggest that a woman's recent diet plays a more important role in survival than a more remote diet, thus highlighting the opportunity for women to improve their survival by increasing dietary intake of isoflavone after a cancer diagnosis.

Some limitations of this study should be considered when interpreting our results. First, the use of an FFQ to assess habitual dietary intake is subject to measurement error in estimating absolute intake. We noticed that the mean intake levels of isoflavone in our study population were lower than those reported in other US women, which may be because of differences in the FFQs used to capture dietary isoflavone intake. Nevertheless, comparing higher versus lower intake, such as comparing the highest quartile with the lowest quartile, is still valid for evaluating diet assessed from FFQs with health outcomes.[21] The FFQ used in the BCFR has also demonstrated reasonable validity compared with repeated 24-hour diet recalls (validity coefficient, $r = 0.5$ for dietary isoflavone intake).[11] To further improve validity, we excluded women who had unreliable dietary reporting and those who completed the FFQ more than 5 years after diagnosis to reduce errors associated with recalling more distant diet. We also adjusted for total energy intake in all analyses to reduce confounding and improve validity by removing correlated errors. Although we cannot rule out misclassification of isoflavone intake, the misclassification error is likely to be nondifferential, thus attenuating the results toward the null.

Second, higher dietary intake of isoflavone was associated with socioeconomic and lifestyle factors, such as education, BMI, recreational physical activity, cigarette

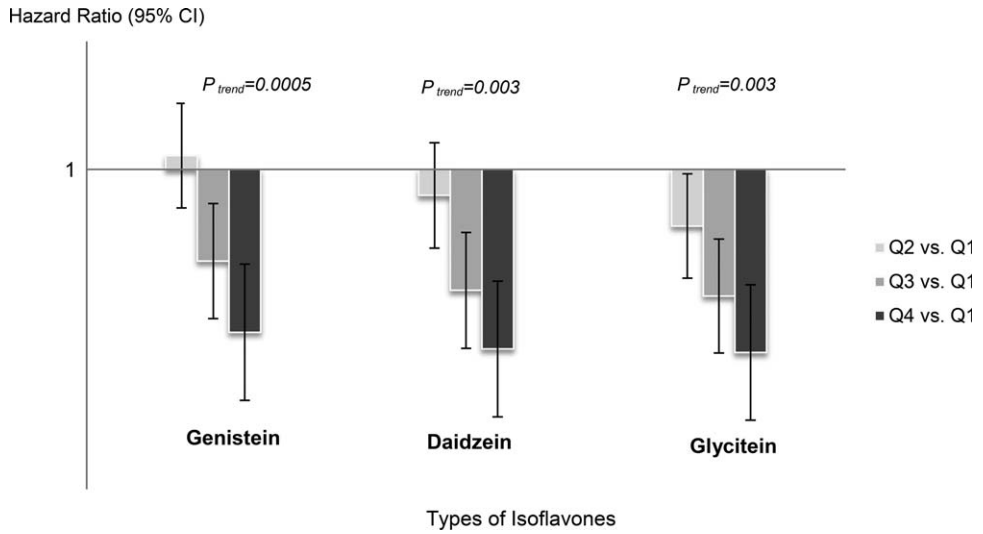

Figure 1. Types of isoflavone intake and all-cause mortality are illustrated in women with breast cancer from the Breast Cancer Family Registry. The 3 bars with different gray shading correspond to the hazard ratios (HRs) comparing the highest quartile (Q4), the third quartile (Q3), and the second quartile (Q2) with the lowest quartile (Q1) for different types of isoflavone intake. The 3 lines correspond to the 95% confidence intervals (CIs).

TABLE 4. Associations Between Dietary Intake of Isoflavone and All-Cause Mortality in Women With Breast Cancer by Patient and Treatment Characteristics: The Breast Cancer Family Registry

Isoflavone Dose, mg/d	No. of Deaths	Person-Years	HR (95% CI)[a]	HR (95% CI)[b]
By tumor hormone receptor status				
Tumor hormone receptor positive: ER+PR+, ER+PR−, ER−PR+, n = 3348				
Q1, < 0.342	192	7665	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	190	7966	1.00 (0.81-1.24)	1.06 (0.85-1.31)
Q3, 0.675-1.493	168	8209	0.85 (0.68-1.06)	0.96 (0.76-1.22)
Q4, ≥ 1.494	146	8067	0.72 (0.57-0.91)	0.90 (0.69-1.19)
P_{trend}			.002	.41
Tumor hormone receptor negative: ER−PR−, n = 1167				
Q1, < 0.342	65	2554	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	61	2463	0.92 (0.63-1.34)	0.95 (0.64-1.41)
Q3, 0.675-1.493	44	2177	0.69 (0.45-1.04)	0.69 (0.44-1.08)
Q4, ≥ 1.494	37	2349	0.49 (0.31-0.76)	0.49 (0.29-0.83)
P_{trend}			.001	.005
$P_{interaction}$			.55	.53
By breast cancer treatment with hormone therapy				
Received hormone therapy, n = 2862				
Q1, < 0.342	153	6266	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	158	6487	0.99 (0.78-1.24)	0.99 (0.78-1.26)
Q3, 0.675-1.493	123	6904	0.72 (0.56-0.93)	0.78 (0.60-1.02)
Q4, ≥ 1.494	123	6476	0.75 (0.58-0.97)	0.90 (0.66-1.22)
P_{trend}			.005	.19
Did not receive hormone therapy, n = 3373				
Q1, < 0.342	206	7672	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	185	7585	0.93 (0.76-1.15)	1.03 (0.83-1.28)
Q3, 0.675-1.493	168	7323	0.88 (0.71-1.10)	0.95 (0.75-1.20)
Q4, ≥ 1.494	108	7083	0.58 (0.45-0.75)	0.68 (0.51-0.91)
P_{trend}			< .0001	.02
$P_{interaction}$			.08	.20
By race/ethnicity				
Non-Hispanic whites, n = 3647				
Q1, < 0.342	232	9844	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	260	10,885	1.03 (0.85-1.24)	1.07 (0.88-1.29)
Q3, 0.675-1.493	206	10,268	0.88 (0.72-1.08)	0.97 (0.78-1.19)

TABLE 4. *Continued*

Isoflavone Dose, mg/d	No. of Deaths	Person-Years	HR (95% CI)[a]	HR (95% CI)[b]
Q4, ≥ 1.494	104	6617	0.73 (0.57-0.94)	0.86 (0.66-1.12)
P_{trend}			.008	.25
Blacks, n = 751				
Q1, < 0.342	92	2342	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	31	869	0.85 (0.55-1.29)	0.82 (0.52-1.27)
Q3, 0.675-1.493	26	1040	0.53 (0.33-0.87)	0.52 (0.31-0.87)
Q4, ≥ 1.494	23	642	0.82 (0.49-1.37)	0.76 (0.42-1.39)
P_{trend}			.10	.08
Hispanics, n = 1033				
Q1, < 0.342	28	1380	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	40	1710	1.23 (0.73-2.07)	1.24 (0.71-2.16)
Q3, 0.675-1.493	39	2092	0.92 (0.54-1.57)	0.82 (0.45-1.47)
Q4, ≥ 1.494	27	1854	0.71 (0.39-1.28)	0.62 (0.32-1.21)
P_{trend}			.11	.05
Asians, n = 690[c]				
Q1, < 1.677	29	1380	1.0 (Ref)	1.0 (Ref)
Q2, 1.678-3.699	22	1373	0.74 (0.42-.30)	0.83 (0.46-1.49)
Q3, 3.700-7.999	19	1384	0.61 (0.34-1.11)	0.56 (0.30-1.03)
Q4, ≥ 8.000	27	1424	0.90 (0.52-1.58)	0.81 (0.44-1.46)
P_{trend}			.59	.26
$P_{interaction}$			.52	.52
By menopausal status				
Premenopausal women, n = 3056				
Q1, < 0.342	126	5838	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	156	6650	1.06 (0.83-1.35)	1.17 (0.91-1.51)
Q3, 0.675-1.493	146	7700	0.86 (0.67-1.11)	0.99 (0.75-1.29)
Q4, ≥ 1.494	123	7295	0.77 (0.59-1.01)	0.93 (0.68-1.27)
P_{trend}			.02	.46
Postmenopausal women, n = 3176				
Q1, < 0.342	231	8080	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	187	7423	0.94 (0.77-1.15)	0.96 (0.78-1.18)
Q3, 0.675-1.493	145	6527	0.83 (0.66-1.04)	0.88 (0.69-1.11)
Q4, ≥ 1.494	108	6265	0.65 (0.50-0.83)	0.78 (0.59-1.05)
P_{trend}			.001	.09
$P_{interaction}$			.49	.45
By BMI status				
Normal weight: BMI < 25 kg/m^2, n = 2991				
Q1, < 0.342	150	6520	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	146	6858	0.94 (0.74-1.19)	0.97 (0.76-1.24)
Q3, 0.675-1.493	120	6828	0.78 (0.61-1.01)	0.86 (0.66-1.13)
Q4, ≥ 1.494	122	8147	0.67 (0.52-0.87)	0.74 (0.54-1.01)
P_{trend}			.001	.05
Overweight: BMI 25-29.9 kg/m^2, n = 1723				
Q1, < 0.342	104	4006	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	81	3636	0.93 (0.68-1.26)	1.01 (0.74-1.39)
Q3, 0.675-1.493	93	4247	0.93 (0.68-1.26)	0.95 (0.69-1.30)
Q4, ≥ 1.494	68	3342	0.89 (0.64-1.24)	0.97 (0.66-1.41)
P_{trend}			.51	.75
Obese: BMI ≥ 30 kg/m^2, n = 1336				
Q1, < 0.342	91	2992	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	103	3014	1.06 (0.79-1.44)	1.17 (0.86-1.60)
Q3, 0.675-1.493	70	2741	0.74 (0.53-1.05)	0.83 (0.58-1.20)
Q4, ≥ 1.494	38	1767	0.59 (0.39-0.90)	0.76 (0.48-1.19)
P_{trend}			.005	.13
$P_{interaction}$			.76	.77
By levels of recreational physical activity				
Physically inactive, n = 3262				
Q1, < 0.342	170	6457	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	155	6357	0.88 (0.71-1.12)	0.94 (0.74-1.18)
Q3, 0.675-1.493	127	5809	0.78 (0.61-1.00)	0.84 (0.64-1.08)
Q4, ≥ 1.494	107	5321	0.70 (0.54-0.91)	0.85 (0.62-1.15)
P_{trend}			.005	.19
Physically active, n = 2725				
Q1, < 0.342	171	6850	1.0 (Ref)	1.0 (Ref)
Q2, 0.343-0.674	167	7110	1.01 (0.81-1.27)	1.09 (0.86-1.38)

TABLE 4. *Continued*

Isoflavone Dose, mg/d	No. of Deaths	Person-Years	HR (95% CI)[a]	HR (95% CI)[b]
Q3, 0.675-1.493	153	7839	0.86 (0.68-1.08)	0.93 (0.73-1.20)
Q4, ≥ 1.494	118	7815	0.66 (0.51-0.85)	0.75 (0.56-1.01)
P_{trend}			.001	.04
$P_{interaction}$			.62	.64

Abbreviations: −, negative; +, positive; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; Q, quartile; PR, progesterone receptor; Ref, reference category.

[a] The analysis was adjusted for age (continuous), study site, and total caloric intake (quartiles).

[b] The analysis was also adjusted for race/ethnicity (non-Hispanic white, black, Hispanic, and Asian Americans), education (high school or less, some college or bachelor's degree, or graduate degree), total fiber intake (quartiles), Health Eating Index-2010 (quartiles), treatment type (surgery, radiation, chemotherapy, and hormone therapy), physical activity (active, inactive), BMI (categorical: < 25, 25-29.9, ≥ 30 kg/m^2), alcohol use (never, < 7 drinks/wk, ≥ 7 drinks/wk), smoking status (never, ever), and pack-years (continuous).

[c] Quartiles were based on the distribution of dietary intake of isoflavone among Asian Americans.

smoking, and alcohol consumption. To minimize the chance of residual confounding, we carefully adjusted for all of these factors in the multivariable models.

Third, information on treatment was based on women's self-reports, and we lacked information on type and length of hormone therapy, preventing a more in-depth analysis of potential different effects in women who received different types and lengths of hormone therapy. However, previous validation studies in the BCFR have indicated high agreement between self-reported treatment information and medical records.[22,23]

Fourth, tumor hormone receptor status was not available for approximately 28% of the women; the mean intake of dietary isoflavone, however, was similar for women with and without information on tumor hormone receptor status (1.9 vs 1.8 mg daily, respectively; $P = .49$). Finally, our study outcome was limited to all-cause mortality, which prevented us from evaluating breast cancer-specific mortality, recurrence, and other prognostic endpoints. Prior studies of women with breast cancer have indicated that from 48% to 70% of all deaths caused by breast cancer. We also lacked information on comorbidities, which could influence all-cause mortality. Although prior studies suggested that lifestyle risk factors may impact all-cause mortality through effects on deaths unrelated to breast cancer, a pooled analysis of 2 US cohorts reported that women who consumed high levels of dietary isoflavone had a significantly reduced breast cancer recurrence, which is a surrogate for breast cancer-specific survival.

The strengths of this study include a large number of women from racial/ethnic minority populations, which allowed us to evaluate the potential heterogeneous effect by race/ethnicity groups, and the availability of clinical and interview data, which allowed us to consider different subtypes of breast cancer and subgroups of patients and to adjust for confounders to minimize confounding. Bias because of differential follow-up was minimized by the use of linkages to population-based cancer registries and death registry record outcomes of all patients. We adjusted for any survival bias by left-truncating all patients at the time of recruitment.

In conclusion, in this large, ethnically diverse cohort of women with breast cancer, higher dietary intake of isoflavone was associated with reduced total mortality. High isoflavone intake may be associated with lower mortality only for women with ER-negative/PR-negative tumors or those who do not receive hormone therapy as part of their cancer treatment.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Fang Fang Zhang: Conceptualization, methodology, software, validation, formal analysis, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Danielle E. Haslam**: Software and formal analysis. **Mary Beth Terry**: Investigation, resources, data curation, and funding acquisition. **Julia A. Knight**: Investigation, resources, data curation, and funding acquisition. **Irene L. Andrulis**: Investigation, resources, data curation, and funding acquisition. **Mary B. Daly**: Investigation, resources, data curation, and funding acquisition. **Saundra S. Buys**: Investigation, resources, data curation, and funding acquisition. **Esther M. John**: Conceptualization, methodology, validation, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, project administration, and funding acquisition.

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