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The Effects of Soy Consumption before Diagnosis on Breast Cancer Survival: the Multiethnic Cohort Study

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Abstract

This study tested the hypothesis that prediagnostic soy intake was inversely associated with all-cause and breast cancer-specific mortality. The analyses included 3,842 female in the Multiethnic Cohort (MEC) study of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Caucasians, who completed a quantitative food frequency questionnaire, aged 50 years at cohort entry, and diagnosed with primary invasive breast cancer following cohort entry (1993-2007). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated from Cox proportional hazards regression with adjustment for known clinical and lifestyle factors. During a mean follow-up after diagnosis of invasive breast cancer of 6.2±3.8 years, there were 804 deaths including 376 breast cancer-specific deaths. The HR (95%CI) for all-cause and breast cancer-specific mortality comparing the highest versus lowest tertiles were 1.03 (0.81-1.33) and 1.03 (0.71-1.50) for soy products and 0.99 (0.82-1.20) and 0.95 (0.71-1.28) for total isoflavones, respectively ($P_{trend} > 0.60$ for all). There was limited evidence of differences by hormone receptor status, tumor stage, or ethnic group. Prediagnostic soy intake was unrelated to mortality in postmenopausal women. Our findings are consistent with the literature that soy consumption does not adversely affect breast cancer survival in women.

Keywords

Breast neoplasms; ethnic groups; soy foods; isoflavones; survival; postmenopause

INTRODUCTION

Soy beans and soy based foods have received considerable attention as an alternative approach to treat symptoms of menopause (1, 2) and for promoting cardiovascular health (3, 4)); however, concerns have arisen on whether breast cancer survivors should consume soy because of the potential stimulatory effects on breast cancer cells (5). Soy isoflavones, such as genistein and daidzein, are structurally similar to 17 β -estradiol and, depending on the endogenous estrogen environment, may bind to estrogen receptors (ER) and stimulate cell proliferation (6, 7). In contrast, soy isoflavones possess anticarcinogenic effects [reviewed in: (8)] and epidemiologic data support a protective effect of lifelong or early life exposure

to high-soy intake on breast cancer risk (9-12). For instance, risk reductions of 29% have been reported with high (≥ 20 mg/d) vs. low (< 5 mg/d) soy intake in Asian populations where high-soy consumption is more common (9). With the recent advances in early detection and treatment, the number of breast cancer survivors has increased; the estimated prevalence for the US in 2010 was more than 3.4 million and projected to reach 4.5 million in 2020 (13). Obesity, at or before the time of diagnosis, represents one of the few potentially modifiable factors that may influence breast cancer outcomes (14, 15), with poor survival across ethnic groups (16, 17). In contrast, epidemiologic data for other modifiable factors (e.g., healthful diets) are less convincing (18, 19). Thus, studies evaluating whether soy isoflavone intake has beneficial or detrimental effects on breast cancer survival are of public health importance. To date, five individual studies have evaluated soy intake and breast cancer survival (20-24), three in American populations (21, 22, 24) and two in Chinese populations (20, 23). Of these studies, none has indicated adverse effects of soy on breast cancer outcomes and several of the studies observed lower mortality and/or recurrence in soy consumers (21-23). However, generalization across populations is challenging based on studies conducted within one ethnic group.

In addition to ethnical differences, we previously found obesity and diabetes to be positively associated with all-cause and breast cancer-specific mortality in the Multiethnic Cohort (MEC) for African American, Caucasian, Japanese American, Latino, and Native Hawaiian postmenopausal women (16). The present study examined the association between prediagnostic soy intake and breast cancer survival in the MEC. Specifically, we hypothesized that high-soy intake would predict better survival.

MATERIALS AND METHODS

Study Subjects

The design and implementation of the MEC study have been given elsewhere (25). Briefly, residents in Hawaii and California (primarily Los Angeles County) entered the cohort from 1993 to 1996 by completing a 26-page, self-administered mail questionnaire. The population-based sampling frames included drivers' license records in both states, supplemented with voter registration lists in Hawaii and Health Care Financing Administration (MEDICARE) files in California. The cohort included 96,382 men and 118,869 women aged 45-75 years at cohort creation and predominantly of five ethnic groups: African American, Caucasian, Japanese American, Latino, and Native Hawaiian. The Institutional Review Boards at the University of Hawaii and the University of Southern California approved the study protocol.

Women diagnosed with invasive breast cancer were identified by linkage with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the statewide Hawaii Tumor Registry. These tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (26) and provide data on tumor characteristics (i.e., stage, histology, hormone receptor status as defined by estrogen receptor [ER] and progesterone receptor [PR] expression) and first course of treatment (i.e., surgery, chemotherapy and/or radiotherapy) within the 6 months after diagnosis. Information on recurrence or comorbidities is not collected by the tumor registries. Linkages with the California and Hawaii death certificate files and the National Death Index provide information on vital status and dates and causes of death. For the present analysis, complete case and death ascertainment was available up to December 31, 2007. This analysis included women who were free of a previous breast cancer diagnosis (self-reported or registry-linked) at the time of cohort entry and were subsequently diagnosed with invasive breast cancer during follow-up. Excluded from the present analysis were women younger than 50 years old at cohort entry to remove most premenopausal and

perimenopausal women ($n = 612$) and women with missing ($n = 60$) or extreme values for height or weight that resulted in body mass index (BMI) outside of the 15–50 kg/m² range ($n = 11$). A total of 3,842 female breast cancer cases were included in the present analysis.

Data collection

Dietary intake was assessed at baseline by a self-administered quantitative food frequency questionnaire (QFFQ) that obtained frequency and quantity information on over 180 food items consumed during the preceding year. The items included on the questionnaire were the minimum set that yielded 85% of the intake of the major nutrients, as well as traditional foods of each particular ethnic group (25). The QFFQ was developed from three-day measured food records collected from men and women from each of the five ethnic groups (25) and was validated in a calibration study (27). Soy product intake was estimated from summing tofu, miso, and vegetarian meat. Total isoflavone intake, representing the sum of genistein, daidzein, and glycitein, was calculated from a wide range of foods including soy products (e.g., 3.06 mg isoflavones per g tofu; 0.036 mg isoflavones per g of miso soup, 0.095 mg isoflavones per g vegetarian meat), legumes other than soy, and foods with soy additives using the food composition table that has been developed and maintained by the University of Hawaii Cancer Center for the MEC study (25). In addition to diet, the baseline questionnaire included sections on demographic factors, anthropometric measures, history of prior medical conditions, reproductive history and use of hormone replacement therapy (HRT), family history of breast cancer, and personal behaviors. The presence of a cardiovascular comorbidity was defined in the present study as a self-reported history at baseline of hypertension, heart attack, angina, or stroke.

Statistical Methods

In the primary analyses, daily dietary intake was expressed as densities (intake per 1,000 kcal) because a calibration study within the MEC found a stronger correlation between the QFFQ and multiple 24-h recalls after energy adjustment than with absolute nutrient intakes (27). Tests for differences in dietary intake by ethnicity were based on the F-test from ANOVA models of log-transformed soy product or total isoflavone intakes. Statistical analysis was conducted using SAS version 9.2 (SAS Institute), with a two-sided P value of <0.05 considered to be statistically significant.

The time metric used in analyses was years from the date of diagnosis of invasive breast cancer to the date of death or the date of censoring. Women alive at the date of complete reporting (12/31/2007) were censored; in the breast cancer-specific models, women who died of other causes were also censored. Ethnic-specific Kaplan-Meier survival curves were compared using a log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression. Models were adjusted for BMI (< 22.5 , 22.5–24.9, 25.0–29.9, ≥ 30 kg/m²), age at breast cancer diagnosis (50–59, 60–69, ≥ 70 years), years between cohort entry and breast cancer diagnosis (continuous), hormone receptor status [ER+PR+, ER–PR–, mixed (ER+PR– or ER–PR+), other/unknown], SEER summary stage (local, regional, distant, unstaged/unknown), surgery (conserving, mastectomy, none/unknown), radiotherapy (yes, no/unknown), chemotherapy (yes, no/unknown), smoking status at baseline (never, former, current, missing), and diabetes (yes, no). The models were also adjusted for cardiovascular comorbidity (none, hypertension, heart attack/angina/stroke) because a previous study of the MEC cohort reported ethnic differences in cardiovascular disease mortality (28). Other confounders were considered, such as family history of breast cancer, age at menarche, age at first birth, number of children, HRT use, physical activity, and dietary intake of fruit, vegetables, fat, meat, calcium, vitamin D, or alcohol. However, the factors were not included in the models

because they were not associated with mortality and did not substantially alter the estimates for soy intake in the present analysis.

The proportional hazards assumptions were assessed by examining log (-log(survival function)) plots, testing the statistical significance of time-by-covariate interaction terms, and assessing the Schoenfeld residuals (29). Stage and hormone receptor status were found to become weaker predictors of mortality overtime and, thus, violate the proportional hazard assumption. Consequently, both were modeled as time-dependent variables by including cross-product terms with log-transformed continuous survival time. Non-linear relations between soy intake and mortality were examined non-parametrically with restricted cubic splines with knots at 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of intake and the 5th percentile of intake as the reference. The likelihood ratio test was used to test the non-linear component of the model (30) and the results support a linear model ($P_{non-linearity} = 0.50$ for all). Soy products and isoflavone intakes were categorized into tertiles based on intakes of all women in the cohort. However, for stratified analyses by ethnic group, ethnic-specific tertiles were used because the distribution of soy products and isoflavone intakes varied substantially across ethnic groups. Linear trends were tested by modeling continuous variables assigned the median value within the corresponding tertile level. Differences across ethnic groups were also evaluated for consumers compared to non-consumers [<2.4 vs. $2.4\text{g}/1,000\text{ kcal}$] of daily dietary intake of soy products. Subgroup analyses by ethnicity, hormone receptor status (ER+PR+, ER-PR-, mixed), stage (localized, regional, distant), and years between cohort entry and diagnosis (≤ 4.25 , > 4.25 years) were conducted to evaluate effect modification by these factors. Tests for multiplicative interactions were based on the likelihood ratio test, comparing global models that included cross-product terms of the subgroup variable and the trend for the soy intake to models with main effects only.

RESULTS

After following 3,842 women diagnosed with incident, invasive breast cancer for an average of 6.2 years (SD = 3.8), a total of 804 deaths were reported, with 376 of these deaths attributed to breast cancer and the remainder to other causes. The median daily intakes per 1,000 kcal at cohort entry were 0.7 g (range: 0-328) for soy products and 3.7 mg (range: 0-107) for total isoflavones, with significant differences across ethnic groups ($P < 0.001$; Table 1). Tofu was the major contributor to soy products, except in African American and Latino women. Japanese American women had a higher probability of 5-year survival from all-cause and breast cancer-specific deaths, tended to have lower BMI ($< 22.5\text{ kg/m}^2$), had the highest soy intake levels, and were more likely to be diagnosed with localized disease compared to the other ethnic groups. In contrast, African American women had a lower probability of survival, were less likely to consume any soy products, and were less likely to be diagnosed with ER+PR+ tumors compared to the other ethnic groups.

In multivariable-adjusted analyses (Table 2), soy intake, as measured by either soy products or total isoflavones, was not associated with all-cause or breast cancer-specific mortality. There was no evidence of a dose-response across increasing tertiles of intake ($P_{trend} > 0.60$ for all). Neither threshold nor non-linear effects were observed in nonparametric restricted spline models ($P_{non-linearity} = 0.50$ for all; Figure 1).

Similar null associations were observed in women with ER+PR+ breast cancer. In contrast, in women with ER-PR- breast cancer, a slightly higher, although non-statistically significant, risk for breast cancer-specific mortality was observed across increasing tertiles of intake of soy products ($P_{trend} = 0.15$), but not of total isoflavones ($P_{trend} = 0.69$). Furthermore there was limited evidence that hormone receptor status modified the

association between intake of soy products and breast-cancer specific mortality ($P_{interaction} = 0.19$). There was a suggestive lower risk associated with higher soy intake for those with distant and limited evidence of an association for those with localized or regional breast cancers at diagnosis. Although the average time between cohort entry, and, therefore, the assessment of dietary soy intake, and subsequent breast cancer diagnosis varied between women (average = 6.5; SD = 3.9 years; range: 0-14.6 years), time between cohort entry and diagnosis did not modify the association between intake of soy products or total isoflavones on all-cause or breast cancer-specific mortality ($P_{interaction} > 0.45$ for all).

In subgroup analyses by ethnicity (Table 3), weak ethnic-specific differences were suggested in the association between soy intake and mortality. Lower breast-cancer specific mortality was only observed in Native Hawaiian women with a marginally significant linear trend across tertiles of soy product intake ($P_{trend} = 0.09$) and total isoflavone intake ($P_{trend} = 0.18$). Caucasian women had a non-significant higher risk for breast-cancer specific mortality when comparing extreme tertiles: the HR (95% CI) was 1.53 (0.82-2.85) for soy products and 1.60 (0.90-2.83) for total isoflavones. Similarly, when comparing consumers to non-consumers of soy products, Caucasians had higher risk for all-cause mortality (HR = 1.35, 95% CI: 0.93-1.96) whereas suggestive protective effects were observed for African American (HR = 0.71, 95% CI: 0.35-1.43), Japanese American (HR = 0.74, 95% CI: 0.40-1.36) and Native Hawaiian (HR=0.86, 95% CI: 0.501.48) ($P_{interaction}=0.45$).

DISCUSSION

In this ethnically diverse cohort of postmenopausal women diagnosed with invasive breast cancer, prediagnostic soy intake as assessed by QFFQ was unrelated to all-cause and breast cancer-specific mortality with suggestive evidence for differential effects by tumor hormone receptor status or tumor stage. Significant differences in soy intake were observed across ethnic groups; for example, the median daily isoflavone intake per 1,000 kcal was 6.7 mg in Japanese American versus 2.2 mg in Caucasian women. There was an indication of ethnic differences in the effect of soy intake on all-cause or breast cancer-specific mortality; however, ethnic-specific analyses were not statistically powerful due to the smaller number of deaths. Suggestive trends for a reduced risk for breast cancer-specific mortality were observed with increasing tertiles of soy intake in Native Hawaiian women.

The mechanisms by which isoflavones may affect breast cancer survival are unclear. Concerns of detrimental effects in breast cancer survivors with hormone-sensitive cancers has arisen due to *in vivo* and *in vitro* data demonstrating estrogenic and proliferation-inducing activity of genistein on ER+ human breast cancer cells (MCF-7) (6, 7) and on breast cancer xenopants in ovariectomized athymic mice (6). Isoflavones appear to have dual functions depending on endogenous estrogen levels: estrogen agonists with low, postmenopausal levels or estrogen antagonists at high, premenopausal levels (7, 31). It appears that isoflavones are more likely to bind to ER and act as estrogen agonists when endogenous levels are low. In contrast, when endogenous levels are high, anti-estrogenic effect are attributed to the competition created between isoflavones and estradiol for ER binding sites, the weaker estrogenic potency of isoflavones, and the selective affinity of isoflavones for ER- α , in which may have anti-proliferative effects, over ER- β ligand binding sites (7, 32-35). Experimental data also suggest non-estrogen receptor-mediated pathways in which isoflavones may inhibit the proliferation, angiogenesis, and metastasis of neoplastic cells (36-39).

The findings from this study are consistent with previous studies that did not observe adverse effects of soy intake (20-23). On the contrary, the sparse data suggest a potential protective effect. Two population-based cohort studies examined prediagnostic soy intake

and breast cancer survival (20, 21). In a Chinese population ($n = 1,459$), usual soy intake was unrelated to breast cancer-specific mortality, with consistent null findings by menopausal status (20). In a primarily Caucasian US population, a statistically significant 48% lower risk of all-cause mortality for the highest compared to the lowest quintile of isoflavone intake (> 7.48 vs. 0.29 mg/d) was detected; the effect was more pronounced in postmenopausal women (21). Post-diagnostic soy intake was examined in three studies of cancer survivors: the Life After Cancer Epidemiology (LACE) Study in the US ($n=1,954$) (22), the Women's Healthy Eating and Living(WHEL) Study ($n = 3,088$) (24), and the Shanghai Breast Cancer Survival Study (SBCSS) in China ($n = 5,042$) (23). The LACE study observed a borderline statistically significant reduction in breast cancer recurrence with increasing quintiles of soy isoflavone intake (22) and the WHEL study found a suggested inverse trend of reduced risk of breast cancer-specific mortality with increased isoflavone intake (24). Furthermore, soy food intake (highest vs. lowest quartile) was significantly associated with a 32 % reduced risk of disease recurrence in the SBCSS (23). In a pooled analysis of these three studies, the daily consumption of ≥ 10 compared to < 4 mg isoflavone was associated with a non-significant 13% and 17% reduced risk of all cause and breast cancer specific mortality, respectively, and a statistically significant 25% reduced risk of recurrence (40). None of the reports found conclusive evidence of interaction effects by hormone receptor status.

The primary strength of the present study is the large number of ethnically diverse women. This is the first population-based study to examine soy intake and breast cancer survival across ethnic groups. Such studies are important for providing valuable information that may help to elucidate ethnic-specific differences in soy intake and their relation to breast cancer outcomes. For example, epidemiologic studies support a protective effect of lifelong or early life exposure to high-soy intake on breast cancer risk in Asian-American women (10, 12); the same mechanisms may also protect against recurrence (41). The detailed information collected at entry into the MEC permitted adjustment of several potential confounding factors for breast cancer survival, such as smoking and comorbidities. An additional strength is the ascertainment of incident breast cancer diagnoses through linkage with high-quality population-based tumor registries that provided detailed information on tumor characteristics and treatment within the first 6 months after diagnosis. Also, given the reliability of the National Death Index linkage (e.g., sensitivity $\geq 87\%$ compared to death certificates and/or cohort studies) (42), misclassification of vital status or differential loss-to-follow-up is unlikely.

Several limitations should be considered. Dietary modifications following cancer diagnosis have been reported (43, 44) and any effects due to post-diagnostic dietary change would not be captured by the present study. Limited data were available for post-diagnostic soy intake (only 7% of cases) and, therefore, these were not examined in this analysis. Soy is not the only source of isoflavones, as indicated by the relatively high isoflavone intake despite the low soy consumption in African American and Latino women. Thus, we found slight variability in the results obtained with soy products as compared to total isoflavones. Soy intake may have been underreported, especially for Japanese Americans, because the QFFQ only captured tofu, miso, and vegetarian meat as sources of soy and failed to capture other soy foods, such as soybean milk, cooked soybeans, and fried soybean curd. However, based on multiple 24-hr recalls on more than 3,200 MEC participants in a calibration study, tofu was consumed by 26% whereas soy milk was consumed by 0.7% of the Japanese American participants, supporting tofu as the major source of soy in Japanese Americans in this cohort (45). The net effect of this potential misclassification may in part explain the null findings. Although a wide range of soy intake was reported, the distribution was highly skewed with the median daily intake per 1,000 kcal of 3.7 mg (range: 0-107) for total isoflavones and, thus, inferences are only appropriate for low soy consumption. In particular, ethnic-specific

tertiles were necessary for subgroup analyses by ethnicity due to significant heterogeneity in soy intake across ethnic groups. The time from cohort entry when dietary intake was assessed to breast cancer diagnosis varied among women; however, models were adjusted for years between cohort entry and diagnosis, and no significant interaction was observed between this variable and soy intake on mortality. As we only had information on mortality and not breast cancer recurrence, our study was limited by the small number of deaths among Native Hawaiian and Japanese American women that affected the precision of our HR estimates. Data on hormone receptor status was incomplete for 31% of the women and data on Her2/*neu* expression was unavailable. Also, treatment data was only available for first course of treatment and not for any subsequent treatment.

Prediagnostic soy intake was unrelated to all-cause or breast cancer specific mortality in the present study comprised of a population-based cohort of ethnically diverse postmenopausal women. Our findings are consistent with the literature that soy consumption does not adversely affect breast cancer survival in women. Future studies with higher soy intakes and with post-diagnostic soy intake are needed to further assess the effects of soy consumption on breast cancer survival. Although there is some indication that women with high soy consumption experience better outcomes, the limited number of studies, conducted primarily in Chinese women, do not allow generalization to other populations, especially those with soy exposure in early life (9). Early life exposure is important to consider in future studies, because early life soy intake has been found to be associated with lower Her2/*neu* and proliferating cell nuclear antigen expression in malignant compared to benign breast tissue (46). Also, inter-individual differences in metabolism are important to consider in future studies. For example, the ability to produce the biologically active metabolite S(Y)-equol from daidzein varies across individuals and populations (47), and may modify the estrogenic potency of isoflavones (48, 49). Adding questionnaires about diet and supplement intake, in combination with treatment choices and lifestyle factors, to large clinical trials would be a suitable approach to studying the effect of phytoestrogens on breast cancer outcomes.

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A. Soy Products **B. Isoflavones** **Figure 1.**

Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality predicted by soy products (A) and isoflavones (B) using restricted cubic splines with knots at 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of intake and the 5th percentile of intake as the reference (the 5th, 10th, 25th and 50th percentiles of daily soy product intake were 0 mg/1,000 kcal). Models adjusted for body mass index, age at diagnosis, ethnicity, energy intake, stage, hormone receptor status, treatment, cardiovascular comorbidity, history of diabetes, smoking status, and years between cohort entry and diagnosis. Stage and hormone receptor status were included as time dependent variables.

Table 1

Characteristics of breast cancer cases in the Multiethnic Cohort Study diagnosed 1993-2007

	All women ^a	Ethnicity ^a					P-value ^b
		African American	Caucasian	Japanese American	Latino	Native Hawaiian	
<i>N</i>	3,842	748	991	1,141	623	339	
Deaths, <i>n</i>							
All-cause	804	226	226	141	135	76	
Cancer-specific	501	143	133	90	95	40	
Breast cancer-specific	376	115	93	65	72	31	
5-year survival ^c , %							
All-cause	84	77	81	92	82	86	<0.001
Breast cancer-specific	91	86	91	95	89	92	<0.001
Age at cohort entry, <i>y</i>	62.3 ± 7.1	63.3 ± 7.2	62.4 ± 7.3	62.7 ± 7.1	61.2 ± 6.5	59.9 ± 6.8	<0.001
Age at diagnosis, <i>y</i>	68.8 ± 7.7	70.1 ± 7.8	68.9 ± 7.8	69.1 ± 7.8	67.8 ± 7.0	66.2 ± 7.6	<0.001
Body mass index, <i>kg/m</i> ²	26.7 ± 5.3	29.2 ± 5.5	25.9 ± 5.1	24.2 ± 4.0	28.0 ± 5.2	29.2 ± 5.8	<0.001
Body mass index, <i>kg/m</i> ²							<0.001
<22.5	836 (22)	60 (8)	278 (28)	400 (35)	73 (12)	25 (7)	
22.5-24.9	807 (21)	116 (16)	205 (21)	314 (28)	112 (18)	60 (18)	
25.0 -29.9	1,298 (34)	277 (37)	319 (32)	342 (30)	242 (39)	118 (35)	
>30.0	901 (23)	295 (39)	189 (19)	85(7)	196 (31)	136 (40)	
Daily dietary intake							
Soy products ^d , <i>g/1,000 kcal</i>	0.7 (0.0-6.2)	0.0 (0.0-0.0)	0.0 (0.0-1.3)	8.4 (5.1-16.8)	0.0 (0.0- 0.3)	4.4 (1.8-8.1)	<0.001
Total isoflavones, <i>mg/1,000 kcal</i>	3.7 (1.9-6.8)	2.3 (1.2-4.2)	2.2 (1.1-4.0)	6.7 (4.4-10.5)	3.5 (1.9- 6.6)	4.5 (2.9-7.3)	<0.001
Total isoflavones, <i>mg/day</i>	6.9 (3.1- 13.5)	4.1 (1.8- 7.3)	3.8 (1.7- 7.4)	11.6 (7.4-19.3)	6.7 (3.0-14.3)	9.9 (6.4-17.4)	<0.001
Soy products ^d , <i>g/1,000 kcal</i>							<0.001
0	1,730 (45)	585 (78)	641 (65)	13 (1)	452 (73)	39 (12)	
0.1-<3.1	698 (18)	138 (18)	222 (22)	113 (10)	139 (22)	86 (25)	
3.1	1,414 (37)	25 (3)	128 (13)	1,015 (89)	32 (5)	214 (63)	
Total isoflavones, <i>mg/1,000 kcal</i>							<0.001
0-<2.5	1,308 (34)	409 (55)	550 (55)	63 (6)	230 (37)	56 (17)	
2.5-<5.5	1,254 (33)	229 (31)	304 (31)	371 (33)	201 (32)	149 (44)	
5.5	1,280 (33)	110 (15)	137 (14)	707 (62)	192 (31)	134 (40)	
Total isoflavones, <i>mg/day</i>							<0.001
0-<4.3	1,309 (34)	394 (55)	544 (55)	97 (9)	220 (35)	54 (16)	
4.3-<10.4	1,271 (33)	238 (31)	304 (31)	414 (36)	187 (30)	128 (38)	
10.4	1,262 (33)	116 (14)	143 (14)	630 (55)	216 (35)	157 (46)	
Contribution of soy products, %							<0.001
Tofu	68.7 ± 36.1	15.9 ± 35.2	61.5 ± 42.6	82.0 ± 18.5	21.0 ± 37.6	82.9 ± 24.3	

	All women ^a	Ethnicity ^a					P-value ^b
		African American	Caucasian	Japanese American	Latino	Native Hawaiian	
Miso	16.7 ± 25.8	24.3 ± 39.8	15.0 ± 30.7	16.1 ± 17.9	27.9 ± 41.2	10.5 ± 20.6	
Vegetarian meat	14.6 ± 31.8	59.8 ± 46.5	23.6 ± 38.6	1.9 ± 5.3	51.1 ± 46.9	6.5 ± 15.3	
Hormone receptor ^c							<0.001
ER+PR+	1,748 (45)	279 (37)	473 (48)	555 (49)	268 (43)	173 (51)	
ER-PR-	494 (13)	127 (17)	110 (11)	116 (10)	104 (17)	37 (11)	
ER+PR-/ER-PR+	395 (10)	81 (11)	107 (11)	120 (11)	65 (10)	22 (6)	
Other/unknown	1,205 (31)	261 (35)	301 (30)	350 (31)	186 (30)	107 (32)	
SEER stage ^e							<0.001
Local	2,713 (71)	484 (65)	693 (70)	893 (78)	417 (67)	226 (67)	
Regional	960 (25)	215 (29)	239 (24)	230 (20)	174 (28)	102 (30)	
Distant	108 (3)	33 (4)	35 (4)	14 (1)	19 (3)	7 (2)	
Unstaged/ unknown	61 (2)	16 (2)	24 (2)	4 (1)	13 (2)	4 (1)	

^aValues are mean ± SD, median (25th-75th percentiles), or n (%); percentages may not add to 100 because of rounding.

^bDifference between ethnic groups was tested using ANOVA for continuous variables, ² test with unknown category excluded for categorical variables, and ² for log-rank test for estimated 5-year survival across ethnic categories.

^cProduct-limit estimate for 5-year survival.

^dSoy product intake was calculated from tofu, miso, and vegetarian meat.

^eER, estrogen receptor; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

Table 2

Dietary soy intake and risk of all-cause and breast cancer-specific mortality for breast cancer cases in the Multiethnic Cohort study diagnosed 1993-2007

Daily dietary intake		Cases		All-cause mortality ^a		Breast cancer-specific mortality ^a		
		<i>n</i>	<i>n</i>	HR (95% CI)	<i>P</i> -trend ^b	<i>n</i>	HR (95% CI)	<i>P</i> -trend ^b
All participants								
Soy products ^c	<i>g/1,000 kcal</i>							
T1	0	1,730	422	1.00	0.89	200	1.00	0.93
T2	0.1-<3.1	698	166	1.04 (0.86-1.26)		81	1.04 (0.79-1.37)	
T3	3.1	1,414	216	1.03 (0.81-1.33)		95	1.03 (0.71-1.50)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	1,308	323	1.00	0.99	143	1.00	0.63
T2	2.5-<5.5	1,254	238	0.93 (0.78-1.11)		125	1.13 (0.88-1.46)	
T3	5.5	1,280	243	0.99 (0.82-1.20)		108	0.95 (0.71-1.28)	
Total Isoflavones	<i>mg/day</i>							
T1	0-<4.3	1,309	317	1.00	0.76	146	1.00	0.99
T2	4.3-<10.4	1,271	248	1.02 (0.85-1.22)		114	1.06 (0.74-1.39)	
T3	10.4	1,262	239	0.98 (0.79-1.21)		116	1.01 (0.74-1.39)	
Women with ER+PR+ breast cancer^d								
Soy products ^c	<i>g/1,000 kcal</i>							
T1	0	759	142	1.00	0.63	56	1.00	0.44
T2	0.1-<3.1	309	60	1.12 (0.80-1.55)		21	1.06 (0.61-1.86)	
T3	3.1	680	101	0.97 (0.66-1.42)		36	0.82 (0.43-1.56)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	582	116	1.00	0.44	41	1.00	0.89
T2	2.5-<5.5	596	91	0.80 (0.60-1.07)		36	0.90 (0.56-1.44)	
T3	5.5	570	96	1.03 (0.75-1.42)		36	1.01 (0.59-1.73)	
Women with ER-PR- breast cancer^d								
Soy products ^c	<i>g/1,000 kcal</i>							
T1	0	248	86	1.00	0.10	54	1.00	0.15
T2	0.1-<3.1	100	32	1.05 (0.68-1.64)		22	1.22 (0.71-2.10)	
T3	3.1	146	46	1.71 (0.89-3.26)		31	1.83 (0.86-3.93)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	175	58	1.00	0.89	35	1.00	0.69
T2	2.5-<5.5	156	52	1.22 (0.80-1.87)		39	1.22 (0.72-2.06)	
T3	5.5	163	54	1.08 (0.69-1.70)		33	0.96 (0.54-1.72)	
Women with localized breast cancer								
Soy products ^c	<i>g/1,000 kcal</i>							

Daily dietary intake		All-cause mortality ^a				Breast cancer-specific mortality ^a		
		Cases <i>n</i>	<i>n</i>	HR (95% CI)	<i>P</i> -trend ^b	<i>n</i>	HR (95% CI)	<i>P</i> -trend ^b
T1	0	1,165	220	1.00	0.63	62	1.00	0.30
T2	0.1-<3.1	472	82	1.03 (0.79-1.35)		26	1.10(0.67-1.80)	
T3	3.1	1,076	123	0.94 (0.66-1.33)		32	0.74 (0.36-1.53)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	884	167	1.00	0.20	44	1.00	0.56
T2	2.5-<5.5	874	112	0.86 (0.67, 1.10)		35	0.94 (0.59-1.50)	
T3	5.5	955	146	1.14 (0.88, 1.47)		41	1.13 (0.69-1.84)	
Women with regional breast cancer								
Soy products ^c	<i>g/1,000 kcal</i>							
T1	0	471	139	1.00	0.97	86	1.00	0.73
T2	0.1-<3.1	187	62	1.25 (0.90-1.73)		39	1.28 (0.85-1.92)	
T3	3.1	302	69	1.11 (0.70-1.77)		43	1.22 (0.67-2.24)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	356	114	1.00	0.30	68	1.00	0.50
T2	2.5-<5.5	328	90	0.98 (0.73, 1.32)		59	1.08 (0.74, 1.57)	
T3	5.5	276	66	0.84 (0.59, 1.19)		41	0.87 (0.55, 1.37)	
Women with distant breast cancer								
Soy products ^c	<i>g/1,000 kcal</i>							
T1	0	60	46	1.00	0.94	41	1.00	0.78
T2	0.1-<3.1	24	18	0.53 (0.26-1.09)		14	0.40 (0.18-0.90)	
T3	3.1	24	20	0.80 (0.38-1.72)		17	0.65 (0.27-1.54)	
Total Isoflavones	<i>mg/1,000 kcal</i>							
T1	0-<2.5	40	31	1.00	0.68	26	1.00	0.53
T2	2.5-<5.5	36	28	0.69 (0.35-1.39)		25	0.82 (0.39-1.73)	
T3	5.5	32	25	0.82(0.41-1.62)		21	0.77 (0.36-1.64)	

^aHazard ratio (HR) and 95% confidence interval (CI) from Cox proportional hazards models for soy products and total isoflavones in tertiles, with the lowest tertile as the referent, adjusted for BMI, age at diagnosis, ethnicity, energy intake, stage, hormone receptor status, treatment, cardiovascular comorbidity, history of diabetes, smoking status, and years between cohort entry and diagnosis. Stage and hormone receptor status were included as time dependent variables.

^bWald χ^2 test of a trend variable assigned the median values for each tertile level.

^cSoy product intake was calculated from tofu, miso, and vegetarian meat.

^dER, estrogen receptor; PR, progesterone receptor.

Table 3

All-cause and breast cancer-specific mortality by daily dietary soy intake and ethnicity for breast cancer cases in the Multiethnic Cohort study diagnosed 1993-2007

	African American ^a			Caucasian ^a			Japanese American ^a			Latino ^a			Native Hawaiian ^a		
	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)
All-cause mortality															
Soy products ^b															
	<i>g/1,000 kcal</i>														
T1	0	173	1.00	0	146	1.00	3.7	42	1.00	0	95	1.00	0.6	22	1.00
T2	0.6	26	0.77 (0.49-1.20)	1.3	47	1.08 (0.77-1.52)	8.2	41	0.81 (0.52-1.26)	0.4	16	1.20 (0.69-2.11)	3.7	23	0.78 (0.41-1.46)
T3	2.0	27	1.05 (0.69-1.60)	5.3	33	1.31 (0.89-1.95)	21.5	58	1.23 (0.81-1.87)	1.7	24	1.08 (0.67-1.72)	10.2	31	0.89 (0.47-1.68)
<i>P</i> -trend ^c			0.91			0.17			0.13			0.75			0.89
Total isoflavones															
	<i>mg/1,000 kcal</i>														
T1	0.8	81	1.00	0.8	82	1.00	3.7	38	1.00	1.5	46	1.00	2.4	28	1.00
T2	2.4	68	1.04 (0.74-1.46)	2.3	80	1.03 (0.74-1.42)	6.7	48	1.28 (0.83-1.97)	3.7	38	0.97 (0.62-1.51)	4.3	20	0.63 (0.33-1.20)
T3	5.3	77	1.05 (0.76-1.46)	5.2	64	0.87 (0.61-1.23)	12.2	55	1.23 (0.80-1.88)	8.2	51	0.97 (0.63-1.50)	8.7	28	0.89 (0.49-1.61)
<i>P</i> -trend ^c			0.78			0.40			0.44			0.92			0.89
Breast cancer specific mortality															
Soy products ^b															
	<i>g/1,000 kcal</i>														
T1	0	88	1.00	0	57	1.00	3.7	24	1.00	0	51	1.00	0.6	10	1.00
T2	0.6	15	0.66 (0.35-1.25)	1.3	21	1.05 (0.60-1.82)	8.2	15	0.55 (0.28-1.09)	0.4	7	1.27 (0.54-2.97)	3.7	9	0.53 (0.18-1.59)
T3	2.0	12	0.87 (0.46-1.64)	5.3	15	1.53 (0.82-2.85)	21.5	26	1.07 (0.59-1.96)	1.7	14	1.29 (0.69-2.41)	10.2	12	0.34 (0.11-1.06)
<i>P</i> -trend ^c			0.60			0.18			0.37			0.42			0.09
Total isoflavones															
	<i>mg/1,000 kcal</i>														
T1	0.8	45	1.00	0.8	25	1.00	3.7	19	1.00	1.5	27	1.00	2.4	12	1.00
T2	2.4	35	0.83 (0.52-1.34)	2.3	32	1.27 (0.72-2.26)	6.7	23	1.31 (0.70-2.45)	3.7	16	0.73 (0.38-1.40)	4.3	9	0.46 (0.15-1.35)

	African American ^a			Caucasian ^a			Japanese American ^a			Latino ^a			Native Hawaiian ^a		
	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)	Median	n	HR (95% CI)
T3	5.3	35	0.89 (0.55-1.43)	5.2	36	1.60 (0.90-2.83)	12.2	23	0.97 (0.51-1.84)	8.2	29	0.92 (0.51-1.66)	8.7	10	0.44 (0.14-1.35)
<i>P</i> -trend ^c	0.68			0.11			0.76			0.92			0.18		

^aHazard ratio (HR) and 95% confidence interval (CI) for ethnic-specific tertiles of soy intake from Cox proportional hazards models adjusted for BMI, age at diagnosis, energy intake, stage, hormone receptor status, treatment, cardiovascular comorbidity, history of diabetes, smoking status, and years between cohort entry and diagnosis. Stage and hormone receptor status were included as time dependent variables.

^bSoy product intake was calculated from tofu, miso, and vegetarian meat.

^cWald ² test of a trend variable assigned the ethnic-specific median values for each tertile level.