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Soy Isoflavone Intake and Bone Mineral Density in Breast Cancer Survivors

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Abstract

Purpose—Low bone mineral density is common among breast cancer survivors due to acute estrogen deprivation. Soy food is a rich source of phytoestrogens, namely isoflavones known to have both estrogenic and anti-estrogenic effects. The objective of the study was to assess the association between soy consumption and bone mineral density in breast cancer survivors, which has not previously been evaluated.

Methods—Forearm bone mineral density was evaluated using dual energy x-ray absorptiometry at 60 months post-diagnosis for 1,587 participants of the Shanghai Breast Cancer Survival Study. Soy intakes collected at 6, 18, and 36 months post-diagnosis were averaged and the association with bone mineral density, osteopenia, and osteoporosis was evaluated using linear and logistic regression.

Results—The mean (standard deviation) intake of isoflavones was 48.1 (28.0) mg/day. Soy intake was inversely associated with bone mineral density and positively associated with osteoporosis. Compared with the lowest quartile, the highest quartile of soy isoflavone intake, 62.64mg/day, was associated with a reduction of bone mineral density by 1.95% (95% confidence interval (CI): −3.54%, −0.36%) and an increased odds ratio of 1.69 for osteoporosis (95% CI: 1.09, 2.61). The inverse association was predominantly seen among women who recently entered menopause (< 5 years).

Conclusion—In contrast to observations from general populations, high soy intake (> 62.64 mg of soy isoflavone/day) was associated with lower proximal forearm bone mineral density among breast cancer survivors, particularly during the early years of menopause. Our finding needs to be replicated, particularly in studies with more comprehensive bone density evaluation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Keywords

breast cancer; survivors; bone mineral density; soy food intake; epidemiology

INTRODUCTION

Breast cancer is the most common cancer diagnosis in women worldwide [1]. Due to advances in early detection and treatment, the population of breast cancer survivors is rapidly increasing [2]. Current estimates indicate that there are more than 2.9 million breast cancer survivors in the United States and more than 5 million worldwide [3, 4]. Breast cancer survivors are at an increased risk for adverse health conditions stemming from long-term or late effects of cancer treatment, including decreased bone mineral density (BMD) [5–7]. Low BMD is common in breast cancer survivors; [6, 8] in the Women's Health Initiative Observational Study, breast cancer survivors had a 15% increased risk of bone fracture as compared with women without cancer [9].

Estrogen plays a critical role in maintaining BMD and hormone replacement therapy has been shown to prevent bone loss [10, 11]. Breast cancer patients often have acute estrogen deprivation, due to premature ovarian failure following adjuvant chemotherapy, which increases risk of rapid bone loss and fracture [6, 12, 13]. Additionally, anti-estrogenic endocrine therapies contribute to bone health issues; aromatase inhibitors exert negative effects on bone health due to estrogen depletion, and tamoxifen negatively affects BMD in premenopausal women [6].

Soy foods contain high levels of phytoestrogens, mainly isoflavones, whose chemical structures mimic 17 β -estradiol and compete with endogenous estrogen to bind estrogen receptors [14]. Because of their weak estrogenic potency, it has been suggested that soy isoflavones act as an estrogen antagonist when the endogenous estrogen level is high [15]. However, in an estrogen-deprived environment isoflavones may exert estrogen-like effects, serving as estrogen agonists [16]. Soy food intake has been shown to be associated with increased BMD and reduced risk of fracture in postmenopausal women in the general population [17–22]. However, randomized clinical trials have failed to substantiate a protective effect [23, 24]. The influence of soy consumption on the bone health of breast cancer survivors has never been evaluated.

We report here a comprehensive evaluation of the association between soy isoflavone intake and BMD in a cohort of breast cancer survivors recruited into the Shanghai Breast Cancer Survival Study (SBCSS).

MATERIAL AND METHODS

Study population

The study population consisted of 1,699 members of the SBCSS cohort who had BMD measured at approximately five years after breast cancer diagnosis. The SBCSS, previously described elsewhere, is a longitudinal, population-based cohort study of 5,042 breast cancer patients in Shanghai, China [25]. Patients diagnosed with incident breast cancer between

March 2002 and April 2006 were identified from the population-based Shanghai Cancer Registry and recruited approximately 6 months after breast cancer diagnosis to participate in the study. Additional eligibility criteria included age between 20 and 75 years at cancer diagnosis and permanent residency in Shanghai. Participants were followed through in person surveys at 18, 36, and 60 months post-diagnosis. Approximately 42.7% of surviving cohort members (n=3,976 available at 60-month interview) participated in the ancillary BMD study. All participants provided written informed consent, and the study protocol was approved by the institutional review boards of Vanderbilt University and the Shanghai Municipal Center for Disease Control and Prevention.

Dietary assessment

Habitual dietary intake was assessed in the SBCSS using a culturally-appropriate validated food frequency questionnaire designed to capture the consumption of commonly consumed soy foods in Shanghai, including soymilk, tofu, fresh soy beans, and other soy foods, as well as intakes of cruciferous vegetables, meat, and fish [26]. Dietary intakes after cancer diagnosis were measured at the baseline (for the preceding 6 months), 18-month (for the preceding 12 months), and 36-month interviews (for the preceding 18 months). Estimated nutrient intakes, including soy and isoflavones, were calculated by summing the product of food intake and the nutrient content of the specific food item based on the Chinese Food Composition Tables 2002 [27]. Average nutrient intake over the 3-year period was calculated by averaging the intakes from each questionnaire weighted according to the assessment time interval. Data for soy food consumption were available for all study participants at the baseline survey, but missing at the 18-month or 36-month surveys for some participants (4.3%).

BMD measurement

Forearm BMD was measured by peripheral dual energy x-ray absorptiometry (pDEXA, Norland Medical Systems) at the 60-month, post-diagnosis survey. Three measurements were taken: proximal forearm (radius), proximal forearm (radius and ulna), and distal forearm (radius and ulna). T-scores, indicating the number of standard deviations below the average, for the proximal (radius and ulna) forearm and distal forearm were calculated using a young adult reference mean [28]. Using cut-points based on standard definitions from the World Health Organization, normal BMD was defined as T-score ≥ -1 , osteopenia as T-score between -1 and -2.5 , and osteoporosis as T-score ≤ -2.5 .

Statistical methods

The primary outcomes of this study were BMD, osteoporosis, and osteopenia at 60-months after breast cancer diagnosis, and the exposure of interest was averaged soy isoflavone intake during the 36 months following diagnosis. A total of 112 participants were excluded from the analyses due to missing soy food intake data for at least one follow-up survey (n=89) or missing progesterone receptor status (n=23), resulting in a sample size of 1,587 for the current analysis.

Selected demographic and clinical factors were analyzed for their association with BMD using age-adjusted generalized linear models. Hormonal and patient factors were analyzed

for their association with BMD using generalized linear models controlling for age, progesterone receptor status, and tamoxifen use. Relevant demographic, clinical, and hormonal factors were analyzed for their association with soy isoflavone intake using age-adjusted generalized linear models for continuous variables and were rate-adjusted (using three categories of age: <50, 50–60, >60) for categorical variables. These factors were further evaluated as potential confounders based on their influence on the coefficient estimate for soy isoflavones using a change of 10% as the definition of a confounder. Covariates chosen for final adjustment in the multivariate analyses included age, body mass index (BMI) at the 60-month interview, education level (elementary school or less, middle school, high school or vocational school, or more than high school), radiotherapy (yes/no), chemotherapy (yes/no), progesterone receptor status, tamoxifen use (ever/never), and years since diagnosis at BMD measurement.

Generalized linear models were applied to evaluate the association between BMD and soy isoflavone intake; the latter was analyzed as a categorical variable defined by quartiles of intake. Percent difference in BMD associated with the 2nd to 4th quartile of soy intake was calculated by referencing to the lowest quartile of intake. Multivariate logistic regression was used to assess the association between soy isoflavone intake and osteoporosis alone, as well as osteopenia or osteoporosis.

Analyses were stratified by menopausal status at the time of the BMD measurement to assess whether this modified the association between soy isoflavone intake and BMD, as well as osteopenia or osteoporosis. As the years immediately following menopause are a critical period of rapid bone loss due to estrogen depletion, [29] we stratified our analyses by menopausal status—premenopausal, early postmenopausal (< 5 years), and late postmenopausal (>5 years). This stratified analysis was not performed when osteoporosis was the outcome due to a small number of women with osteoporosis. Additionally, analyses stratified by tamoxifen use and BMI were performed.

The same analyses were performed for soy protein intake and the results were remarkably similar to those observed for soy isoflavone intake; therefore, only the latter are presented in this report. Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC).

RESULTS

The mean (standard deviation (SD)) BMD for each of the three measurement sites (proximal radius, proximal radius and ulna, and distal radius and ulna) were 0.69 (0.11) grams/centimeter² (g/cm²), 0.74 (0.10) g/cm², and 0.30 (0.06) g/cm², respectively. As expected, all BMD measurements decreased as age increased. After adjustment for age, progesterone receptor status and tamoxifen use appeared to be the only demographic or clinical factors associated with proximal forearm BMD; none of these factors were associated with distal forearm BMD (Table 1). Higher levels of estrogen exposure as measured by various reproductive factors, including age at menarche and menopause, and higher BMI, were related to higher BMD after adjusting for age, progesterone receptor status, and tamoxifen use (Table 2).

Participants' mean (SD) intakes of soy protein and soy isoflavones were 12.1 (6.5) g/day and 48.2 (28.1) mg/day, respectively, over the 3-year assessment period. The median soy isoflavone intakes by quartile were 20.0 mg/day, 36.0 mg/day, 52.2 mg/day, and 79.7 mg/day. Age-adjusted isoflavone intake was marginally significantly associated with chemotherapy ($P=0.09$), radiotherapy ($P=0.06$), and exercise (MET-hours/week) at 60 months ($P=0.06$) (Table 3). Age-adjusted isoflavone intake did not differ by other demographic, patient, or disease/treatment factors.

Soy isoflavone intake was significantly associated with decreased BMD of the proximal, but not the distal, forearm. Women in the highest quartile of soy isoflavone intake had significantly lower BMD at the proximal forearm compared with those in the lowest quartile (radius: difference in BMD=-2.47%, 95% CI: -4.24%, -0.70%, P for trend=0.02; radius and ulna: difference in BMD=-1.95%, 95% CI: -3.54%, -0.36%, P for trend=0.05).

When stratified by menopausal status, the inverse association was only significant in the early postmenopausal group. Early postmenopausal women in the highest quartile of soy isoflavone intake had significantly lower BMD in the proximal forearm at the radius compared with those in the lowest quartile although the trend was only borderline significant (difference in BMD=-3.70%, 95% CI: -7.19%, -0.20%, P for trend=0.06).

Using T-scores for the proximal and distal forearm, the prevalence of osteopenia was 28.3% and 42.3%, respectively, and the prevalence of osteoporosis was 16.0% and 9.4%, respectively. Overall, the prevalence of osteopenia plus osteoporosis was not significantly associated with soy isoflavone intake (Table 4). However, when stratified by menopausal status, early postmenopausal women in the highest quartile of soy isoflavone intake were 1.90 (95% CI: 0.96, 3.75) times as likely to have osteopenia or osteoporosis as compared with the lowest quartile at the proximal site (P for trend=0.05). Overall, women in the highest quartile of soy isoflavone intake were 1.69 (95% CI: 1.09, 2.61) times as likely to have osteoporosis, using proximal forearm BMD, as compared with the lowest quartile (P for trend=0.03). The small number of women with osteoporosis in the study prohibited further analysis by menopausal status.

Analyses stratified by tamoxifen use and BMI showed no interactions. Additionally, total meat and vegetable intake adjustment did not materially change the results (data not shown).

DISCUSSION

In this large study of breast cancer survivors, we found that soy isoflavone intake was inversely associated with BMD at the proximal forearm. This inverse association was stronger and reached statistical significance for breast cancer survivors during the early postmenopausal period. Soy isoflavone intake was marginally significantly associated with prevalence of osteopenia or osteoporosis among women in the first 5 years following menopause and significantly associated with prevalence of osteoporosis among all survivors.

The protective effect of estrogen on BMD is well-known; rapid bone loss and increased bone resorption occur in estrogen-deplete environments [6]. Though not fully understood, estrogen potentially acts through mechanisms related to inhibition of bone resorption and

regulation of bone remodeling [30]. Although hormone replacement therapy has been shown to increase BMD and decrease bone loss in menopausal women, [12] its benefits for bone health are eclipsed by potentially associated risks, including increased risk of cardiovascular disease and breast cancer [31].

Isoflavones, the most abundant form of phytoestrogens found in soy foods, have drawn substantial interest as a beneficial nutritional alternative to hormone replacement therapy for postmenopausal women because of their potential ability to decrease adverse symptoms associated with menopause without the adverse effects associated with hormone replacement therapy. Isoflavones bind to estrogen receptors and activate estrogen response genes, although their estrogenic potency is much weaker than endogenous estrogen [32]. It has been postulated that isoflavones act as an estrogen agonist in environments where estrogen levels are low while exerting an anti-estrogenic effect when estrogen level is high [15, 16, 33].

Previous studies of soy food intake and BMD in healthy postmenopausal women have shown that soy food consumption was associated with increased BMD measured at the lumbar spine, [17–20] hip, [17] Ward's triangle, [18] and total body, [17] although the evidence is not entirely consistent [34]. Randomized clinical trials assessing the effects of soy constituents on BMD and fracture risk have shown inconsistent results which may be due to the small sample size of previous studies or to differences in experimental design, BMD measurement site, or study duration [35]. To our knowledge, no study has evaluated the association between soy food intake and BMD among breast cancer survivors.

Breast cancer patients often suffer acute estrogen deprivation due to anti-estrogen therapy or premature ovarian failure related to cancer treatment. We have previously reported that soy food intake was associated with a decreased risk of recurrence among breast cancer survivors [25, 36] and that women in the highest quartile of soy intake had an increased risk of hot flashes compared with women in the lowest quartile [37]. In the current study, we found women in the highest quartile of soy intake had a reduced proximal forearm BMD and increased prevalence of osteoporosis. The totality of evidence appears to suggest that soy isoflavones derived from the traditional Chinese diet may primarily act as estrogen antagonists in breast cancer survivors. The lack of an apparent dose-response relationship may suggest a threshold effect. These findings need to be validated in independent studies.

The most prominent association of soy isoflavones and BMD in our study was seen in the early postmenopausal group. It is well recognized that the years immediately following menopause are a critical period of rapid bone loss due to the sudden depletion of estrogen [29]. Adjuvant chemotherapy, which occurred in 93.8% of breast cancer patients in the current study, may have resulted in ovarian failure and a sudden drop in estrogen level [6]. Therefore, it is possible that the association between moderate soy isoflavone intake and BMD is more easily detected when bone loss is greatest. In our earlier study of general population, we found that soy food intake was associated with a decreased risk of fracture only among women in the early years of menopause [22], supporting the notion that soy food may primarily be relevant to bone density during the susceptible window.

In studies of soy intake and BMD, the forearm is not a typical BMD assessment site. Typically, BMD is measured in the spine, hip, and total body using DEXA. However, BMD measured at peripheral sites such as the forearm have demonstrated an association with fracture risk.[38] Furthermore, we found that forearm BMD decreased with age, menopausal status, and years since menopause and increased with BMI, consistent with findings from studies that measured BMD at other sites. Additionally, in a subset of study participants (n=304) in whom we measured circulating 25-hydroxyvitamin D levels, we found that the vitamin D level was positively associated with BMD. Furthermore, we found that low forearm BMD was associated with fracture risk in our study (proximal forearm: OR=1.67, 95% CI: 1.17, 2.38; distal forearm: OR=1.91, 95% CI=1.32, 2.77). These results support the validity of using forearm BMD in evaluating the relationship between BMD and soy intake. However, we don't have a clear explanation on why the association is only significant for proximal but not for distal forearm bone density. Clearly, more studies, particularly those with improved bone density measurements, are needed to replicate the finding of our study. The number of breast cancer survivors who developed a bone fracture is too small to allow a stable estimate of the association between soy food and bone fracture. We did not find a significant association between hormone replacement therapy and BMD. This is likely due to the low percentage of hormone replacement therapy use in our study population.

While soy intake was assessed before the BMD measurements in our study, the causality of the observed association cannot be directly established due to lack of a baseline BMD measurement. To further evaluate the direction of the association between soy intake and BMD in our population, additional analyses were performed in which we excluded women with a prior history of bone fracture or previous diagnosis of osteoporosis. We found that the inverse association between soy intake and BMD persisted (data not shown) suggesting that the inverse association observed in our study is unlikely to be due to reverse causality, i.e., low BMD causes high soy consumption.

Soy intake is associated with several lifestyle and demographic factors. While we have carefully evaluated and adjusted for a wide range of potential confounders in our analyses, residual confounding due to imperfectly measured or unmeasured variables (e.g. calcium intake, vitamin D exposure, bisphosphonate use) cannot be completely ruled out. Calcium intake data was available for a subset of study participants (n=553) and was positively associated with soy intake, but when adjusted for, did not alter the association between soy intake and BMD (data not shown). Additionally, we could not adjust for total energy intake because these data were not available for the first 3 surveys of our study. However, we found that further adjustment for cruciferous vegetables and/or meat/fish intake did not change the association between soy intake and BMD (data not shown).

It should be noted that only a subset (42.7%) of SBCSS participants took part in the ancillary BMD study. Women who participated in the BMD study were more likely to be younger, have higher education, be physically active, have higher BMI, and have higher soy intake than non-participants. Participants were also less likely to have undergone radiotherapy treatment and had fewer advanced-stage tumors compared with non-participants. These factors were adjusted for in our analyses. It is worth mentioning that although selective participation may affect the generalizability of the results, it should not

affect the validity of the findings of this study. We excluded 89 women who were missing soy food intake information at either the 18-month or 36-month survey. Additional analyses in which these women were included by using imputed soy intake information provided results that were very similar to the findings reported here (data not shown).

Our study also has several strengths worth mentioning. First, the prospective study design and repeated dietary surveys minimized measurement error and captured dietary intake changes following breast cancer diagnosis. Use of a validated dietary questionnaire specifically designed to capture soy food intake in our study population further enhanced the quality of the exposure information collected. Secondly, BMD was assessed at a designated study clinic by trained study staff according to a standard protocol ensuring the quality of the outcome measurement. Finally, the large sample size and detailed covariate information allowed for a comprehensive evaluation of the association between soy food intake and BMD among breast cancer survivors.

In summary, this large population-based study provides no support that soy food intake is associated with increased bone density among breast cancer survivors. Instead, we found that high soy isoflavone intake may be associated with decreased BMD and increased risk of osteoporosis for breast cancer survivors during the period immediately following menopause. Breast cancer survivors on a high soy diet may need to take additional measures to prevent bone loss.

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Age-Adjusted Bone Mineral Density by Selected Demographic and Clinical Factors, Shanghai Breast Cancer Survival Study, 2002–2011

Table 1

	N	Bone Mineral Density (g/cm ²)									
		Proximal (Radius)					Proximal (Radius and Ulna)				
		Mean	SE	P	Mean	SE	Mean	SE	P	Mean	SE
Age		<.0001					<.0001				
<40	51	0.785	0.009		0.811	0.009	0.354	0.008		0.354	0.008
40–49	713	0.739	0.003		0.782	0.003	0.323	0.002		0.323	0.002
50–59	564	0.668	0.004		0.711	0.004	0.285	0.002		0.285	0.002
60–69	229	0.611	0.006		0.655	0.006	0.259	0.003		0.259	0.003
70–79	30	0.557	0.017		0.601	0.017	0.235	0.008		0.235	0.008
Education		0.34					0.05				
Elementary school or less	67	0.693	0.012		0.729	0.011	0.300	0.007		0.300	0.007
Middle school	612	0.697	0.004		0.741	0.003	0.299	0.002		0.299	0.002
High school or vocational school	688	0.694	0.003		0.736	0.003	0.301	0.002		0.301	0.002
College or more	220	0.684	0.006		0.723	0.006	0.297	0.004		0.297	0.004
Income (yuan per month per person)		0.89					0.85				
<500	209	0.697	0.006		0.741	0.006	0.300	0.004		0.300	0.004
500 – <700	277	0.691	0.005		0.736	0.005	0.301	0.003		0.301	0.003
700 – <1,000	419	0.692	0.004		0.736	0.004	0.300	0.003		0.300	0.003
1,000 – <2,000	505	0.696	0.004		0.736	0.004	0.299	0.002		0.299	0.002
2,000	177	0.689	0.007		0.731	0.006	0.296	0.004		0.296	0.004
TMN Stage		0.85					0.73				
0 – I	664	0.694	0.003		0.737	0.003	0.301	0.002		0.301	0.002
IIA	541	0.692	0.004		0.733	0.004	0.299	0.002		0.299	0.002
IIB	235	0.698	0.006		0.740	0.006	0.299	0.003		0.299	0.003
III – IV	81	0.689	0.010		0.734	0.010	0.296	0.006		0.296	0.006
Unknown	66	0.688	0.011		0.728	0.011	0.295	0.007		0.295	0.007
Estrogen Receptor Status		0.13					0.40				
+	1049	0.696	0.003		0.737	0.003	0.299	0.002		0.299	0.002
–	538	0.689	0.004		0.733	0.004	0.301	0.002		0.301	0.002

Bone Mineral Density (g/cm ²)										
	N	Proximal (Radius)			Proximal (Radius and Ulna)			Distal (Radius and Ulna)		
		Mean	SE	P	Mean	SE	P	Mean	SE	P
Progesterone Receptor Status				0.03			0.08			0.78
+	940	0.698	0.003		0.739	0.003		0.299	0.002	
-	647	0.687	0.004		0.731	0.003		0.300	0.002	
Chemotherapy				0.40			0.45			0.48
Yes	1488	0.693	0.002		0.735	0.002		0.299	0.001	
No	99	0.701	0.009		0.742	0.009		0.303	0.005	
Radiotherapy				0.28			0.37			0.74
Yes	497	0.697	0.004		0.739	0.004		0.299	0.002	
No	1090	0.692	0.003		0.735	0.003		0.300	0.002	
Tamoxifen				0.01			0.02			0.62
Yes	1124	0.697	0.003		0.739	0.003		0.299	0.002	
No	463	0.684	0.004		0.728	0.004		0.301	0.002	

Abbreviations: g/cm², grams per centimeter squared; SE, standard error

Table 2

Bone Mineral Density by Selected Hormonal and Patient Characteristics

	Bone Mineral Density (g/cm ²)									
	Proximal (Radius)					Proximal (Radius and Ulna)				
	N	Mean ^a	SE	P		Mean ^a	SE	P	Mean ^a	P
Hormone Therapy Use^b				0.14				0.21		0.55
Yes	70	0.625	0.011			0.671	0.011		0.276	0.006
No	613	0.643	0.004			0.686	0.004		0.273	0.002
Menopausal Status at 60 months post-diagnosis				<.0001				<.0001		<.0001
Premenopausal	222	0.723	0.007			0.761	0.006		0.330	0.004
Postmenopausal	1365	0.689	0.002			0.732	0.002		0.295	0.001
Years Since Menopause^c				0.02				0.01		<0.01
5 years	334	0.689	0.006			0.734	0.006		0.299	0.003
>5 – 10 years	546	0.686	0.004			0.728	0.004		0.293	0.002
>10 years	485	0.665	0.006			0.708	0.005		0.281	0.003
Reproductive Years				0.05				0.03		0.01
32 years	383	0.681	0.005			0.724	0.005		0.293	0.003
>32 – 35 years	473	0.692	0.004			0.734	0.004		0.297	0.002
>35 – 38 years	437	0.698	0.004			0.740	0.004		0.301	0.003
>38 years	259	0.699	0.006			0.742	0.005		0.307	0.003
BMI at 60 months post-diagnosis				<.0001				<.0001		<.0001
<18.5	37	0.626	0.015			0.674	0.014		0.263	0.009
18.5 – 25	928	0.691	0.003			0.733	0.003		0.296	0.002
>25 – 30	534	0.698	0.004			0.740	0.004		0.305	0.002
>30	88	0.722	0.010			0.764	0.009		0.315	0.006
Waist-to-Hip Ratio				0.06				0.13		0.23
0.79	425	0.687	0.004			0.732	0.004		0.297	0.003
>0.79 – 0.83	452	0.688	0.004			0.731	0.004		0.297	0.003
>0.83 – 0.86	322	0.699	0.005			0.741	0.005		0.303	0.003
>0.86	388	0.701	0.005			0.742	0.004		0.303	0.003

Bone Mineral Density (g/cm ²)										
	Proximal (Radius)			Proximal (Radius and Ulna)			Distal (Radius and Ulna)			<i>P</i>
	<i>N</i>	Mean ^a	SE	<i>P</i>	Mean ^a	SE	Mean ^a	SE	<i>P</i>	
Smoker				0.93					0.45	0.15
Yes	34	0.692	0.015		0.725	0.015	0.286	0.009		
No	1553	0.693	0.002		0.736	0.002	0.300	0.001		
Exercise (hours/week; %)				0.17					0.22	0.17
0	525	0.697	0.004		0.739	0.004	0.301	0.002		
>0 – < 11.08	265	0.691	0.006		0.733	0.005	0.292	0.003		
11.08 – < 18.33	263	0.701	0.006		0.742	0.005	0.301	0.003		
18.33 – < 26.78	272	0.684	0.005		0.726	0.005	0.300	0.003		
26.78	261	0.691	0.006		0.735	0.005	0.302	0.003		

Abbreviations: g/cm², grams per centimeter squared; SE, standard error

^a Adjusted for age (continuous), tamoxifen use, and progesterone receptor status

^b Information on hormone replacement therapy use was collected at the baseline interview, thus, only women who reported menopause at baseline were included

^c Only includes participants who reported menopause at the 60-month, post-diagnosis survey

Table 3

Baseline Characteristics and Soy Isoflavone Intake by Quartile

	Soy Isoflavone Intake ^d (mg/day) (N=1,587)				
	Quartile 1 (<28.96)	Quartile 2 (28.96–43.23)	Quartile 3 (43.23–62.64)	Quartile 4 (>62.64)	P
Age (mean(se))	51.7 (0.38)	52.1 (0.38)	51.6 (0.41)	52.2 (0.39)	0.50
Education (%)					0.26
Elementary school or less	5.01	2.65	4.31	4.99	
Middle school	37.45	40.96	36.22	39.11	
High school or vocational school	42.20	42.12	43.91	45.73	
College or more	15.34	14.27	15.57	10.16	
Income (%; yuan per month per person)					0.28
<500	11.67	14.34	13.06	13.51	
500 – <700	18.77	15.50	17.55	18.13	
700 – <1,000	26.00	29.06	25.91	24.09	
1,000 – <2,000	31.17	29.08	30.82	36.43	
>2,000	12.37	12.03	12.67	7.83	
TMN Stage (%)					0.81
0–I	43.58	43.39	38.19	42.13	
IIA	35.11	31.22	36.16	33.99	
IIB	12.28	14.76	16.74	15.30	
III – IV	5.02	6.06	4.63	4.80	
Unknown	4.02	4.56	4.27	3.78	
Estrogen Receptor Status (%)					0.40
+	67.42	68.09	63.06	65.66	
–	32.58	31.91	36.94	34.34	
Progesterone Receptor Status (%)					0.20
+	62.07	60.30	55.08	59.26	
–	37.93	39.70	44.92	40.74	
Chemotherapy (%)	91.41	94.13	95.50	94.26	0.09
Radiotherapy (%)	35.45	30.80	32.51	26.80	0.06

Soy Isoflavone Intake ^d (mg/day) (N=1,587)					
	Quartile 1 (<28.96)	Quartile 2 (28.96–43.23)	Quartile 3 (43.23–62.64)	Quartile 4 (>62.64)	P
Tamoxifen (%)	72.28	71.13	68.68	71.32	0.70
Hormone replacement therapy use ^b (%)	6.52	12.84	12.30	9.06	0.27
Menopause at 60 months post-diagnosis (%)	84.15	87.39	86.42	86.17	0.55
Years Since Menopause ^c	9.4 (0.20)	9.6 (0.19)	9.5 (0.19)	10.0 (0.19)	0.25
Reproductive Years	34.6 (0.19)	34.3 (0.19)	34.2 (0.19)	33.9 (0.19)	0.12
BMI at 60 months post-diagnosis (mean (se))	24.1 (0.17)	24.2 (0.17)	24.4 (0.17)	24.6 (0.17)	0.19
Waist-to-Hip Ratio (mean (se))	0.83 (0.003)	0.83 (0.003)	0.83 (0.003)	0.83 (0.003)	0.23
Smoker (%)	1.96	2.75	1.50	2.30	0.65
Exercise (hours/week; %)					0.06
0	38.55	34.40	29.99	29.43	
<11	14.26	18.18	18.94	15.65	
11 – <18	16.27	14.87	19.12	15.70	
18 – <26.6	13.91	18.39	16.71	19.47	
26.6	17.02	14.17	15.24	19.76	

Abbreviations: BMI, body mass index; mg, milligrams; se, standard error

^a Age adjusted values (age adjustment for categorical variables used 3 categories: <50, 50–60, >60)

^b Information on hormone replacement therapy use collected at baseline; only women who reported menopause at baseline were included

^c Only includes participants who reported menopause at the 60-month, post-diagnosis survey

Table 4

Soy Isoflavone Intake in Association with Osteopenia and Osteoporosis

Soy Intake ^a	Proximal T-score			Distal T-score		
	Osteopenia/ Osteoporosis	Normal BMD	Adj OR ^b (95% CI)	Osteopenia/ Osteoporosis	Normal BMD	Adj OR ^b (95% CI)
Overall (n=1587)						
Quartile 1	170	226	1.00 (reference)	210	186	1.00 (reference)
Quartile 2	185	213	1.05 (0.76, 1.45)	203	195	0.81 (0.59, 1.10)
Quartile 3	155	242	0.78 (0.56, 1.09)	200	197	0.86 (0.63, 1.18)
Quartile 4	193	203	1.25 (0.90, 1.73)	208	188	0.92 (0.67, 1.25)
P _{trend}			0.28			0.83
Overall^c (n=1587)						
Quartile 1	53	343	1.00 (reference)	35	361	1.00 (reference)
Quartile 2	68	330	1.28 (0.82, 1.99)	40	358	1.10 (0.66, 1.85)
Quartile 3	54	343	0.95 (0.60, 1.51)	28	369	0.71 (0.40, 1.25)
Quartile 4	79	317	1.69 (1.09, 2.61)	46	350	1.41 (0.85, 2.36)
P _{trend}			0.03			0.27
Premenopausal (n=222)						
Quartile 1	5	61	1.00 (reference)	9	57	1.00 (reference)
Quartile 2	5	42	1.63 (0.41, 6.38)	10	37	1.75 (0.59, 5.17)
Quartile 3	3	54	1.00 (0.21, 4.85)	5	52	0.70 (0.19, 2.58)
Quartile 4	4	48	1.24 (0.30, 5.16)	9	43	1.34 (0.45, 3.98)
P _{trend}			0.91			0.88
Early Postmenopausal 5 years (n=334)						
Quartile 1	23	65	1.00 (reference)	43	45	1.00 (reference)
Quartile 2	22	58	1.22 (0.60, 2.48)	29	51	0.64 (0.33, 1.21)
Quartile 3	26	55	1.44 (0.72, 2.90)	29	52	0.60 (0.31, 1.14)
Quartile 4	31	54	1.90 (0.96, 3.75)	39	46	1.00 (0.53, 1.86)
P _{trend}			0.05			0.83
Late Postmenopausal >5 years (n=1,031)						
Quartile 1	142	100	1.00 (reference)	158	84	1.00 (reference)

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Soy Intake ^a	Proximal T-score			Distal T-score		
	Osteopenia/ Osteoporosis	Normal BMD	Adj OR ^b (95% CI)	Osteopenia/ Osteoporosis	Normal BMD	Adj OR ^b (95% CI)
Quartile 2	158	113	0.95 (0.64, 1.39)	164	107	0.80 (0.54, 1.16)
Quartile 3	126	133	0.64 (0.43, 0.95)	166	93	0.99 (0.67, 1.46)
Quartile 4	158	101	1.08 (0.73, 1.61)	160	99	0.85 (0.58, 1.26)
P _{trend}	0.90			0.69		

Abbreviations: BMD, bone mineral density; OR, odds ratio; CI, confidence interval; mg, milligrams

^a Soy quartile ranges (mg/day) - Quartile 1: <28.96; Quartile 2: 28.96–43.23, Quartile 3: 43.23–62.64, Quartile 4: >62.64

^b OR adjusted for age, body mass index, education, radiotherapy, chemotherapy, progesterone receptor status, tamoxifen use, menopause, and years since diagnosis at the time of BMD measurement

^c Outcome is osteoporosis only vs normal and osteopenia