Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

Dietary Isoflavone Intake and Breast Cancer Prognosis: A Prospective Analysis and Meta-Analysis

Sihan Song, Jong-Ho Cheun, Hyeong-Gon Moon, Dong-Young Noh, So-Youn Jung, Eun Sook Lee, Zisun Kim, Hyun Jo Youn, Jihyoung Cho, Young Bum Yoo, Shinyoung Jun, Hyojee Joung & Jung Eun Lee

To cite this article: Sihan Song, Jong-Ho Cheun, Hyeong-Gon Moon, Dong-Young Noh, So-Youn Jung, Eun Sook Lee, Zisun Kim, Hyun Jo Youn, Jihyoung Cho, Young Bum Yoo, Shinyoung Jun, Hyojee Joung & Jung Eun Lee (09 Nov 2023): Dietary Isoflavone Intake and Breast Cancer Prognosis: A Prospective Analysis and Meta-Analysis, Nutrition and Cancer, DOI: 10.1080/01635581.2023.2279220

To link to this article: https://doi.org/10.1080/01635581.2023.2279220

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2023.2279220

Dietary Isoflavone Intake and Breast Cancer Prognosis: A Prospective Analysis and Meta-Analysis

Sihan Song[a,b], Jong-Ho Cheun[c], Hyeong-Gon Moon[d], Dong-Young Noh[d], So-Youn Jung[e], Eun Sook Lee[e], Zisun Kim[f], Hyun Jo Youn[g], Jihyoung Cho[h], Young Bum Yoo[i], Shinyoung Jun[j], Hyojee Joung[k] and Jung Eun Lee[a,l]

[a]Department of Food and Nutrition, Seoul National University, Seoul, Republic of Korea; [b]Division of Population Health Research, Department of Precision Medicine, Korea National Institute of Health, Cheongju, Republic of Korea; [c]Department of Surgery, Seoul Metropolitan Government Seoul National University, Boramae Medical Center, Seoul, Republic of Korea; [d]Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [e]Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea; [f]Department of Surgery, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea; [g]Department of Surgery, Jeonbuk National University Medical School, Jeonju, Republic of Korea; [h]Department of Surgery, Keimyung University School of Medicine, Daegu, Republic of Korea; [i]Department of Surgery, Konkuk University Medical Center, Seoul, Republic of Korea; [j]Department of Food Science and Nutrition, Soonchunhyang University, Asan, Republic of Korea; [k]Department of Public Health, Graduate School of Public Health, Seoul National University, Seoul, Republic of Republic of Korea; [l]Research Institute of Human Ecology, Seoul National University, Seoul, Republic of Korea

ABSTRACT

We aimed to examine the association between dietary isoflavone intake and the risk of breast cancer recurrence and summarize evidence on the role of dietary isoflavone intake in breast cancer prognosis. This prospective study included 592 breast cancer survivors who completed a dietary assessment. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Of the studies published until May 31, 2023, that were searched in PUBMED and EMBASE databases, 14 studies were selected. Adjusted HRs were combined using fixed- or random-effects models. During the median follow-up of 4.3 years, 47 recurrences were identified. The HR (95% CI) for recurrence comparing the highest versus the lowest tertile of isoflavones intake was 1.29 (0.60–2.78). In a meta-analysis of previously published data and ours, dietary isoflavone intake was associated with a better breast cancer prognosis. The combined HRs (95% CIs) comparing the extreme categories were 0.81 (0.67–0.98) for recurrence and 0.85 (0.76–0.96) for all-cause mortality. A nonlinear inverse association was observed between isoflavone intake and the risk of recurrence and all-cause mortality. Our study suggests that dietary isoflavone intake is associated with a favorable prognosis in breast cancer survivors and warrants further investigation.

ARTICLE HISTORY
Received 6 July 2023
Accepted 30 October 2023

Introduction

Female breast cancer is the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases in 2020, and is the leading cause of cancer-related deaths in women (1). In Korea, there was a continuously increasing incidence rate of breast cancer between 1999 and 2019, and it was the most common incident and second most prevalent cancer among women in 2019 (2). The 5-year relative survival rate in patients with breast cancer in Korea improved from 79.3% in 1993–95 to 93.6% in 2015–19 (2). To reduce the global burden of breast cancer, more research is needed on modifiable lifestyle factors contributing to improvements in treatment responses, quality of life, and long-term outcomes in patients with breast cancer (3). Research on breast cancer survivorship has grown with an increased number of survivors; however, evidence remains inadequate for making lifestyle recommendations for breast cancer survivors (4).

Isoflavones, mainly found in soy, are plant-derived compounds with a structure similar to that of estradiol-17β (5). Isoflavones may act as selective estrogen receptor (ER) modulators with both estrogenic and antiestrogenic activities (6,7). A suggestive inverse association between dietary isoflavone intake and breast cancer prognosis has been reported in a

CONTACT Jung Eun Lee jungelee@snu.ac.kr Department of Food and Nutrition, Seoul National University, Seoul 08826, Republic of Korea
Supplemental data for this article can be accessed online at https://doi.org/10.1080/01635581.2023.2279220.

few cohort studies that were mainly conducted in US and Chinese women (8,9). No significant associations were observed between dietary isoflavone intake and breast cancer recurrence in a previous Korean study with a small sample size and short follow-up period (10). Evidence from epidemiological studies does not suggest any adverse effects of isoflavones on breast cancer progression or treatment response. In *in vitro* and *in vivo* studies, however, conflicting results exist regarding the effects of isoflavone on hormone-sensitive breast cancer and on the therapeutic agents for treating breast cancer (11). Therefore, additional evidence is needed to gain a better understanding of the role of isoflavones in breast cancer prognosis among different populations, and by breast cancer subtypes.

In this study, we aimed to investigate the association between dietary isoflavone intake and the risk of breast cancer recurrence in Korean women whose soy consumption is generally high. Furthermore, we summarized the data from previous studies and ours, on the role of dietary isoflavone intake in the risk of breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality, using a meta-analysis.

Materials and Methods

Study Population

In this prospective study, female breast cancer survivors were recruited from six hospitals in Korea between September 2012 and November 2017. Women who underwent breast cancer surgery at least 6 months before study entry and had histologically confirmed *in situ* or invasive breast cancer were eligible. Among the 821 enrolled women, 675 completed a dietary assessment and structured questionnaire survey. No significant differences were observed in clinical characteristics between women with and without dietary data. We further excluded women who reported duplicate meals ($n = 4$) or consumed implausible extreme energy intake values (at least three SDs above or below the mean log-transformed energy intake, $n = 1$). We included participants who had been diagnosed with American Joint Committee on Cancer (AJCC) stages 0–III breast cancer and did not have recurrence or any other cancer before enrollment. Consequently, 597 participants were eligible for analysis. We excluded five women who were not followed-up after the initial survey. This study was approved by the Institutional Review Boards of Seoul National University Hospital (H-1111-080-387 and H-2010-019-1161), National Cancer Center, Korea (NCC2014-0101), Soonchunhyang University Hospital (SCHBC2014-12-004-001), Jeonbuk National University Hospital (CUH2014-05-002-005), Keimyung University Dongsan Medical Center (DSMC2015-03-026), and Konkuk University Medical Center (KUH1020068). All the participants provided written informed consent.

Data Collection

Post-diagnosis diet was assessed using a 3-day dietary record ($n = 571$) or food frequency questionnaires (FFQs) ($n = 21$). For the 3-day dietary record, participants were asked to record all food and beverages consumed over 3 days, including two weekdays and one weekend day, and dietary data were analyzed using the Computer-Aided Nutritional Analysis Program (CAN-pro) version 4.0, developed by the Korean Nutrition Society (12). Participants were asked to report their average frequency of consumption of each food item over the past year and their usual portion size using the semi-quantitative FFQ developed for Korean breast cancer survivors (13). The FFQ used in our study had acceptable reproducibility and validity (14). Total isoflavone intake (mg/day) was estimated using the flavonoid database of common Korean foods (KFDB) (15), and protein intake from soy foods (g/day) and the mean daily intake of energy and nutrients were estimated using the nutrient database of the Korean Nutrition Society (16) and the Rural Development Administration of Korea (17,18).

Using a structured questionnaire, the participants' information on age, educational level, and lifestyle and reproductive factors was collected. Body mass index (BMI) at baseline was calculated by dividing body weight (kg) by the square of height (m^2); BMI at diagnosis was used when the baseline data were unavailable. The time spent performing physical activities (per week) was obtained from participants and a metabolic equivalent (MET) value was assigned to each physical activity based on the classification by Ainsworth et al. (19,20). Total physical activity (MET-hours/week) was calculated by summing the weighted values. Adherence scores to the American Cancer Society (ACS) guidelines on diet for cancer prevention, which are also recommended for cancer survivors, were calculated (21). The highest quartile of dietary intakes of vegetables/fruits and whole grains or the lowest quartile of dietary intake of red/processed meat was assigned a value of 4. The overall adherence scores to the ACS guidelines ranged from 3 to 12, with higher scores indicating higher adherence to the guidelines. Data on dietary supplement use in the past year, including the supplement type, product name, amount, and frequency, were collected.

No one reported the use of either soy or isoflavone supplements. Clinical information, including stage, time since surgery, hormone receptor status, disease history, and menopausal status at diagnosis, was obtained from the medical records of each hospital.

The primary endpoint was the risk of recurrence, defined as any ipsilateral, contralateral, local, regional, or distant recurrence and a second cancer. Outcome information was obtained during active follow-up and from medical records of each hospital between December 2019 and November 2020. The clinical outcome information was obtained for 592 women. Five women died before November 2020 but had either developed distant recurrence or a second cancer; therefore, the dates of these endpoints were considered as the case occurrence time points. Person-years were calculated from the date of study entry to the date of recurrence. Breast cancer survivors without recurrence were censored either at the end of follow-up or on the date of last contact (1.7%, $n = 10$).

Statistical Analysis

Dietary soy and isoflavone intakes data were log-transformed and adjusted for total energy intake using the residual method (22). Participant characteristics are described according to tertiles of isoflavone intake. Hazard ratios (HRs) and 95% confidence intervals (CIs) for recurrence were estimated using Cox proportional hazards models. Dietary intakes of isoflavone, soy protein, and soy food were analyzed both in tertiles (with the lowest tertile as a reference) and continuously (per 10-unit increment for isoflavone and soy food and 5 g/d increment for soy protein). The proportional hazard assumption was tested using interaction terms between follow-up time and tertiles of exposure. The proportional hazard assumption was not violated. Multivariable models were adjusted for age at baseline (years, continuous), energy intake (kcal/day, continuous), center (A or others), breast cancer stage (0–I, II, or III), ER status (positive or negative), time since surgery (<2, ≥ 2 years), menopausal status at diagnosis (pre- and postmenopausal), and history of hypertension, type 2 diabetes, or cardiovascular disease (CVD) (no, yes). Models were additionally adjusted for BMI (<23, 23–<25, and ≥25 kg/m^2), physical activity (tertiles of METs-hours/week), ACS diet guidelines score (tertiles), alcohol drinking (never, ever), dietary supplement use (no, yes), and educational levels (high school or below, college or above). *P*-values for the trends were calculated by assigning the median value to each category of dietary exposure, as a continuous variable, in the model. Sensitivity analyses were restricted to women with ER-positive tumors or those who were post-menopausal at baseline. We conducted an analysis by excluding participants who experienced recurrence within the first year of follow-up to consider the possibility of reverse causation. Sensitivity analyses were also conducted by excluding those who had been diagnosed with breast cancer stage 0. All statistical tests and corresponding *P* values were two-sided, and *P* values < 0.05 were considered statistically significant. All statistical analyses were conducted using the SAS statistical software package, version 9.4 (SAS Institute, Inc., Cary, NC).

Meta-Analysis

A literature search was conducted by the first author (SS) in the PUBMED and EMBASE databases on May 31, 2023. The following search terms were used: "((polyphenol* OR flavonoid* OR phytoestrogen* OR isoflavone* OR isoflavonoid* OR soy OR soybean OR genistein OR daidzein OR glycitein OR equol) AND (breast cancer OR breast neoplasm OR breast carcinoma) AND (prognosis OR recurrence OR survival OR mortality OR death OR outcome))." The search was restricted to original articles involving human participants published in English. After screening the articles' titles and abstracts, the full texts of eligible articles were assessed. Articles were retained if they met the following inclusion criteria: (1) cohort studies (either prospective or retrospective); (2) women with breast cancer; (3) investigated the associations between dietary soy (foods, protein) or isoflavone intake and the risk of breast cancer recurrence, breast cancer-specific mortality, or all-cause mortality; and (4) reported HRs and corresponding 95% CIs. If multiple published reports from the same study were available, only the one with the most detailed information on exposure and outcomes was included in the analysis. Any uncertainties were discussed with the last author (JEL). This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23). The following information was extracted from each article: first author, year of publication, study name, country, study design, follow-up period, age of participants, dietary assessment method, timing of dietary assessment (pre- or post-diagnostic), sample size, number of events, range of exposure, association measure of the highest to the lowest category, and adjustment variables. For the dose-response meta-analysis, we further retrieved the midpoint of the dose, number of participants and events, and association measures

for each exposure level (≥ 3 categories). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the risk estimates of breast cancer-specific mortality and all-cause mortality were expressed as $\log_2$-transformed pre-diagnostic isoflavone intakes' values (24). Therefore, unpublished risk estimates for each quartile compared to the lowest quartile of raw dietary isoflavone intake were obtained from the first author.

We estimated the pooled effect sizes to summarize the evidence from published studies and the current analysis of dietary isoflavone or soy intake with breast cancer prognosis. Log-transformed relative risks and their standard errors were calculated using HRs and their 95% CIs. Pooled estimates were calculated from the effect estimates of at least two studies using fixed-effects (25,26) and random-effects models (27). Summary estimates were visualized using forest plots, and the weight of each study was calculated as the inverse of the variance of the risk estimate (28). Categorical meta-analysis was conducted using the estimates of the highest compared to the lowest categories. A dose-response meta-analysis was conducted based on the methods suggested by Greenland and Longneker (29) and Orinsini et al. (30). The dose-response association of a 5- or 10-unit increment between dietary exposure and breast cancer prognosis was examined. The midpoint value or median of each category was assigned to the exposure level and considered as the corresponding HR estimates. When the lowest or highest category was open-ended, the lowest category was set at half the upper limit, while the highest category was assumed to have the same interval as the preceding category. When studies examined the association using nutrient density intake (per 1,000 kcal), the median value of isoflavone intake (mg/day) for each category was used (9), or the density value was multiplied by the estimated median energy intake and divided by 1,000 (31). A restricted cubic spline dose-response model was fitted with three knots (10th, 50th, and 90th percentiles) (32,33). In the EPIC study, dietary isoflavone intake was estimated as the sum of the available forms (aglycones, glycosides, or esters), depending on the form in which they occur in foods, based on the Phenol-Explorer database (24). Therefore, we also conducted a sensitivity analysis by excluding the EPIC study to examine the dose-response relationship between breast cancer outcomes and isoflavone intake as aglycones. Subgroup analyses were conducted to examine potential interactions by the timing of dietary assessment, menopausal status, ER status, geographic location, and sources of isoflavones. The *Q*-test was used to test for subgroup differences (34). Heterogeneity was analyzed using the I^2 index (35,36) and possible publication bias was examined using funnel plots and Egger's test (37,38). The "meta" (39), "dmetar" (34), "dosresmeta," and "rms" (32) packages in R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) were used to conduct the meta-analyses. P values < 0.05 were considered statistically significant.

Results

Prospective Study Results

The mean age of the 592 participants was 51.57 years (SD, 7.96), and the mean time interval between dietary assessment and breast cancer surgery was 3.32 years (SD, 2.69) (Table 1). The mean daily intakes of isoflavone, soy protein, and soy foods were 22.83 mg/day, 7.93 g/day, and 76.22 g/day, respectively. Women with a higher isoflavone intake were more likely to be older than those with a lower isoflavone intake. In addition, levels of physical activity, adherence score to the ACS guidelines on diet, the proportions of postmenopausal women at enrollment and women who had ever had chronic diseases increased with increasing levels of isoflavone intake. There were no significant differences in the clinical characteristics of patients with breast cancer across the tertiles of isoflavone intake. During a median follow-up of 4.3 years, 47 recurrences were identified. Overall, no significant association was observed between soy or isoflavone intake and the risk of recurrence among Korean breast cancer survivors (Table 2). The HRs (95% CIs) for comparing extreme tertiles for isoflavone, soy protein, and soy food were 1.29 (0.60–2.78), 0.87 (0.40–1.89), and 1.03 (0.48–2.19), respectively. Each 10 mg/day increment in isoflavone intake was not associated with recurrence (HR: 0.97, 95% CI 0.82–1.15). The HRs (95% CIs) for each 5 g/d and 10 g/d increment in soy protein and soy food were 0.89 (0.67–1.17) and 0.99 (0.94–1.05), respectively. Similar results were found among women with ER-positive breast cancer or post-menopausal status (Supplementary Table 1). When we excluded women whose breast cancer recurred within the first year of follow-up ($n = 12$), we found similar results to those in the main analysis. The HRs (95% CIs) for comparing extreme tertiles for isoflavone, soy protein, and soy food were 1.48 (0.59–3.71), 0.85 (0.35–2.09), and 1.47 (0.58–3.72), respectively. In the sensitivity analysis after excluding women who had been diagnosed with breast cancer stage 0 ($n = 13$), the HRs (95% CIs) for

Table 1. Baseline characteristics of breast cancer survivors according to tertiles of dietary isoflavone intake: Korean breast cancer survivor study.

Characteristics	All ($n=592$)	T1 ($n=197$)	T2 ($n=198$)	T3 ($n=197$)
Age at baseline, years	51.57 ± 7.96	49.96 ± 8.02	52.12 ± 8.07	52.63 ± 7.58
Time since surgery, years	3.32 ± 2.69	3.22 ± 2.26	3.39 ± 2.70	3.35 ± 3.07
Dietary intake				
Energy, kcal/day	1735 ± 458	1693 ± 388	1751 ± 510	1761 ± 467
Isoflavone, mg/day	22.83 ± 20.83	6.88 ± 3.90	18.31 ± 7.46	43.31 ± 23.21
Soy protein, g/day	7.93 ± 6.45	3.04 ± 1.93	6.97 ± 3.00	13.78 ± 7.29
Soy food, g/day	76.22 ± 68.72	29.21 ± 18.25	65.57 ± 33.17	133.9 ± 84.37
Body mass index, kg/m^2	23.08 ± 2.77	23.28 ± 2.97	23.23 ± 2.64	22.74 ± 2.67
Physical activity, METs-hr/wk	36.20 ± 36.37	31.50 ± 30.10	36.71 ± 41.47	40.39 ± 36.25
ACS diet guidelines score	7.52 ± 2.21	7.04 ± 2.17	7.40 ± 2.26	8.13 ± 2.05
Dietary supplement use				
No	193 (33.10)	62 (31.79)	62 (32.29)	69 (35.20)
Yes	390 (66.90)	133 (68.21)	130 (67.71)	127 (64.80)
Alcohol consumption				
Never	248 (42.11)	71 (36.22)	89 (44.95)	88 (45.13)
Ever	341 (57.89)	125 (63.78)	109 (55.05)	107 (54.87)
Smoking status				
Never	504 (92.65)	163 (91.06)	176 (94.62)	165 (92.18)
Ever	40 (7.35)	16 (8.94)	10 (5.38)	14 (7.82)
Educational level				
High school or below	404 (68.59)	121 (62.37)	141 (71.21)	142 (72.08)
College or above	185 (31.41)	73 (37.63)	57 (28.79)	55 (27.92)
Menopausal status at diagnosis				
Premenopause	375 (63.45)	134 (68.02)	127 (64.14)	114 (58.16)
Postmenopause	216 (36.55)	63 (31.98)	71 (35.86)	82 (41.84)
Menopausal status at enrollment				
Premenopause	75 (12.69)	35 (17.77)	22 (11.11)	18 (9.18)
Postmenopause	516 (87.31)	162 (82.23)	176 (88.89)	178 (90.82)
History of chronic diseases[a]				
No	466 (78.72)	169 (85.79)	153 (77.27)	144 (73.10)
Yes	126 (21.28)	28 (14.21)	45 (22.73)	53 (26.90)
AJCC Stage				
0	13 (2.22)	4 (2.06)	5 (2.55)	4 (2.04)
I	276 (47.10)	92 (47.42)	93 (47.45)	91 (46.43)
II	233 (39.76)	75 (38.66)	75 (38.27)	83 (42.35)
III	64 (10.92)	23 (11.86)	23 (11.73)	18 (9.18)
PR status				
Negative	222 (38.01)	82 (42.05)	68 (34.69)	72 (37.31)
Positive	362 (61.99)	113 (57.95)	128 (65.31)	121 (62.69)
ER status				
Negative	151 (25.81)	55 (28.21)	52 (26.40)	44 (22.80)
Positive	434 (74.19)	140 (71.79)	145 (73.60)	149 (77.20)
Current hormone therapy use[b]				
No	64 (14.78)	21 (15.00)	19 (13.10)	24 (16.22)
Yes	369 (85.22)	119 (85.00)	126 (86.90)	124 (83.78)

Data are expressed as mean ± SD or number (%).
ACS, American Cancer Society; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; METs-hr/wk, metabolic equivalent tasks-hours/week; PR, progesterone receptor.
[a]History of hypertension, type 2 diabetes, or cardiovascular disease.
[b]Analysis was limited to women with ER + breast cancer.
The number of participants did not sum up to the total because information was unavailable for some variables.

comparing extreme tertiles were 1.39 (0.63–3.05) for isoflavone, 0.92 (0.41–2.03) for soy protein, and 1.09 (0.50–2.35) for soy food.

Meta-analysis Results

The flow of the study inclusion process is illustrated in Figure 1. The titles and abstracts of potentially relevant articles were screened, and 17 full-text articles were assessed for eligibility. Consequently, three articles (40–42) that did not meet the inclusion criteria were excluded. Fifteen studies (14 from the literature and the present study) were included in the meta-analysis. The After Breast Cancer Pooling Project (ABCPP) included pooled data on isoflavone intake and breast cancer prognosis from the following three prospective cohort studies (43): the Shanghai Breast Cancer Survival Study (SBCSS) (44), Life After Cancer Epidemiology (LACE) Study (41), and the Women's Healthy Eating and Living (WHEL) Study (45). The estimates from the ABCPP were included in the meta-analysis of isoflavone intake and the risk of recurrence, breast cancer-specific mortality, and all-cause mortality (43). When specific estimates were not reported in the pooled study, we used the available estimates from individual studies. The summary

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer recurrence according to dietary isoflavone or soy intake: Korean breast cancer survivor study.

Energy-adjusted intake	Tertile 1	Tertile 2	Tertile 3	*P* for trend	Continuous
Isoflavone					
Median intake, mg/day	7.5	17.3	35.9		per 10 mg/d increment
No. of event/at risk	12/197	16/198	19/197		47/592
Person-years	916.2	873.6	951.6		2741.4
Age-adjusted HRs (95% CIs)	Reference	1.41 (0.66–2.99)	1.57 (0.76–3.25)	0.26	1.00 (0.86–1.16)
Multivariate HRs (95% CIs)[a]	Reference	1.33 (0.61–2.89)	1.33 (0.63–2.80)	0.53	0.98 (0.83–1.15)
Multivariate HRs (95% CIs)[b]	Reference	1.44 (0.65–3.16)	1.29 (0.60–2.78)	0.65	0.97 (0.82–1.15)
Soy protein					
Median intake, g/day	2.9	6.6	12.5		per 5 g/d increment
No. of event/at risk	14/197	17/198	16/197		47/592
Person-years	897.5	890.1	953.8		2741.4
Age-adjusted HRs (95% CIs)	Reference	1.23 (0.60–2.53)	1.10 (0.53–2.29)	0.86	0.99 (0.78–1.27)
Multivariate HRs (95% CIs)[a]	Reference	1.09 (0.52–2.29)	0.94 (0.45–1.98)	0.81	0.92 (0.71–1.20)
Multivariate HRs (95% CIs)[b]	Reference	1.03 (0.48–2.17)	0.87 (0.40–1.89)	0.67	0.89 (0.67–1.17)
Soy food					
Median intake, g/day	26.4	57.4	111.9		per 10 g/d increment
No. of event/at risk	14/197	16/198	17/197		47/592
Person-years	902.6	890.3	948.5		2741.4
Age-adjusted HRs (95% CIs)	Reference	1.17 (0.57–2.41)	1.18 (0.58–2.41)	0.68	1.00 (0.96–1.05)
Multivariate HRs (95% CIs)[a]	Reference	1.27 (0.61–2.66)	1.11 (0.54–2.30)	0.87	1.00 (0.95–1.05)
Multivariate HRs (95% CIs)[b]	Reference	1.20 (0.57–2.54)	1.03 (0.48–2.19)	0.98	0.99 (0.94–1.05)

CIs; confidence intervals, HRs; hazard ratios.

[a]Models were adjusted for age at baseline (years, continuous), energy intake (kcal/day, continuous), center (A or others), breast cancer stage (0–I, II, or III), estrogen receptor status (positive or negative), time since surgery (<2, ≥2 years), menopausal status at diagnosis (pre- and postmenopausal), and history of chronic diseases (no, yes).

[b]Models were additionally adjusted for body mass index (<23, 23–<25, and ≥25 kg/m^2), physical activity (tertiles of metabolic equivalents-hours/week), American Cancer Society diet guidelines scores (tertiles), alcohol drinking (never, ever), dietary supplement use (no, yes), and educational levels (high school or below, college or above).

of the studies included in this meta-analysis is presented in Supplementary Table 2. Of the 15 included studies, 12 (or 14 if individual studies from the ABCPP were counted) investigated the association between dietary isoflavone intake and breast cancer prognosis: five (7) studies, including ours, were on breast cancer recurrence (9,10,43,46); six (8) were on breast cancer-specific mortality (9,24,31,43,47,48), and nine (11) on all-cause mortality (9,24,31,43,46,48–51). Three Chinese studies examined the association between soy protein intake and all-cause mortality (44,49,50). Three Korean studies, including ours, examined the association between soy food intake and breast cancer recurrence (10,52). Two studies examined the association between soy food intake and all-cause mortality (31,52). All studies, except for that by Boyapati et al. (47) were included in the dose-response meta-analysis.

A previous study of 339 Korean breast cancer survivors observed no significant association between pre-diagnostic isoflavone intake and breast cancer recurrence (10). In a Chinese study, an inverse association was observed between soy isoflavone intake and breast cancer recurrence among post-menopausal women, but not among pre-menopausal women (46). In the Hong Kong Breast Cancer Survival Study (HKBCSS), women in the second quartile of post-diagnostic isoflavone intake had a significantly lower risk of recurrence than those in the lowest quartile (9). In the ABCPP study, a pooled analysis of US and Chinese women revealed a significant inverse association between dietary isoflavone intake and breast cancer recurrence (43). Dietary isoflavone intake has not been clearly shown to be associated with breast cancer-specific mortality in previous studies. However, in three cohort studies, a significant risk reduction was observed in the moderate category of isoflavone intake (9,24,43). A significant inverse association (48–51) or no association (31,43,46) has been reported between isoflavone intake and all-cause mortality. Consistent with breast cancer-specific mortality, two cohort studies showed a significant risk reduction in all-cause mortality in the moderate isoflavone intake category (9,24).

Overall, a higher isoflavone intake was associated with a lower risk of recurrence and all-cause mortality (Figure 2 and Table 3). In the random-effects models, the combined HRs (95% CIs) comparing extreme categories of isoflavone intake were 0.81 (0.67–0.98, I^2 = 36%) for recurrence (Figure 2A) and 0.85 (0.76–0.96, I^2 = 52%) for all-cause mortality (Figure 2C). In the fixed-effects models, each 10 mg/day increment in isoflavone intake was associated with a 7% reduction in the risk of recurrence (combined HR: 0.93, 95% CI 0.90–0.97) and all-cause mortality (HR: 0.93, 95% CI 0.89–0.98) (Table 3). When we fitted a

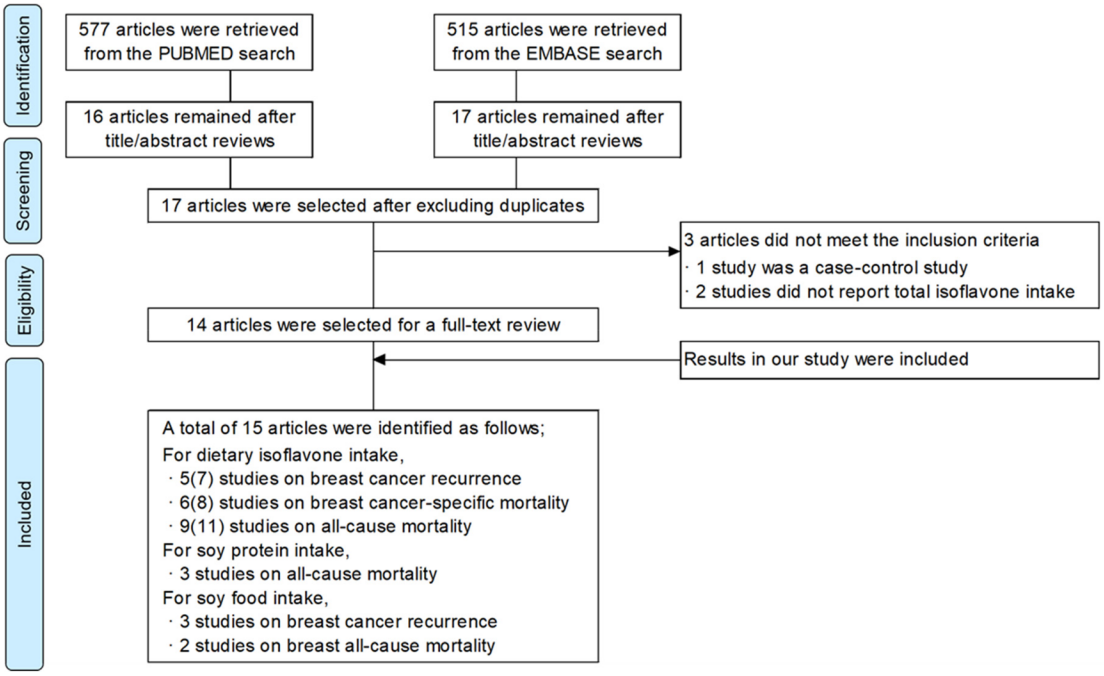

Figure 1. Flow diagram of study selection for meta-analysis.
Number in brackets refers to individual studies in the pooled study (43).

restricted cubic spline curve by including studies on recurrence or all-cause mortality, we observed evidence of a nonlinear relationship in the fixed effects models (P for nonlinearity < 0.001) (Figure 3). The greatest risk reduction was observed when the intake increased from very low levels to approximately 20 mg/day. A similar nonlinear relationship was observed when the analysis was restricted to studies in which the isoflavone intake was aglycone. There were no significant associations between isoflavone intake and the risk of breast cancer-specific mortality in either the categorical or dose-response meta-analysis (Figure 2B and Table 3). Three studies were eligible for the meta-analysis of the association between soy protein intake and all-cause mortality. The combined HRs (95% CIs) for the risk of all-cause mortality were 0.68 (0.56–0.83) comparing extreme categories (Figure 4A) and 0.89 (0.84–0.95) per 5 g/day increment of soy protein intake (Table 3). For soy food intake, no significant association was observed with breast cancer recurrence (Figure 4B) or all-cause mortality (Figure 4C).

There were no significant differences in subgroups of the timing of dietary assessment, menopausal status, ER status, geographic location, or sources of isoflavones (Supplementary Table 3). Although the test for difference did not reach statistical significance level, the inverse association between isoflavone intake and recurrence was more pronounced in post-menopausal (combined HR: 0.71, 95% CI 0.60–0.85) than in premenopausal women (P value for subgroup differences = 0.08).

There was no evidence of possible publication bias for the association between isoflavone intake and recurrence, breast cancer-specific mortality, or all-cause mortality based on the funnel plot and Egger's test (Egger test P-value > 0.10, each).

Discussion

In this meta-analysis of our current and six prospective studies, we found an inverse association between isoflavone intake and recurrence among breast cancer survivors. A significantly lower risk of all-cause mortality was observed with high isoflavone intake. A meta-analysis of three studies also reported an inverse association of soy protein with mortality. Furthermore, we observed an inverse association between isoflavone intake and risk of recurrence and all-cause mortality combined in a nonlinear manner. When the meta-analysis was limited to women with ER-positive breast cancer or post-menopausal women, no adverse associations were observed. Although our study of 592 breast cancer survivors did not show significant associations of post-diagnostic isoflavone or soy intake with breast cancer recurrence, the small number of endpoints partly due to the large proportion of early-stage patients, a shorter follow-up, and a small

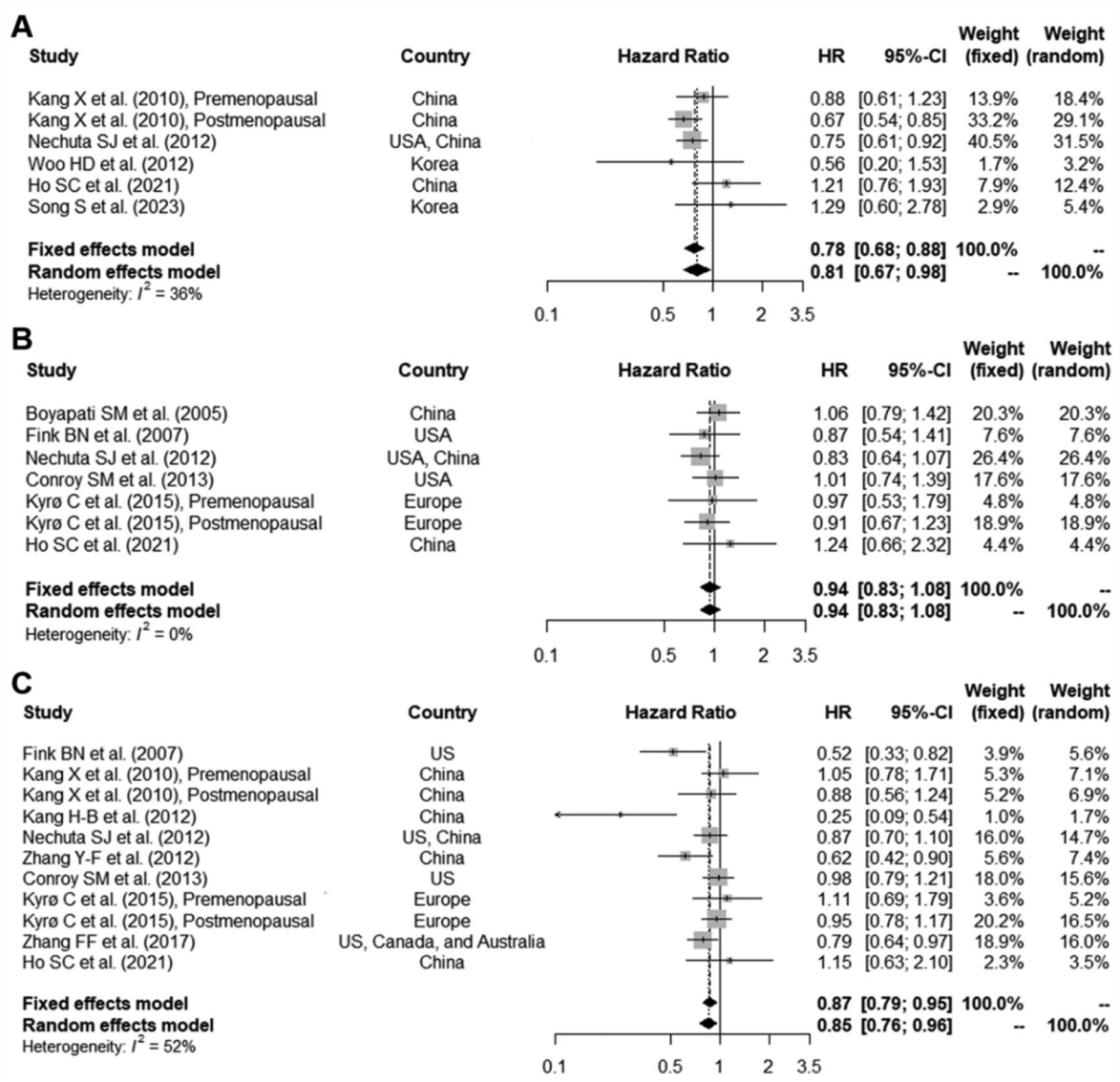

Figure 2. Forest plots of prospective associations comparing the highest versus the lowest intakes. (A) Isoflavone intake and risk of recurrence (defined as a local or regional recurrence, distant recurrence or metastasis, or a new primary cancer); (B) Isoflavone intake and risk of breast cancer-specific mortality; and (C) Isoflavone intake and risk of all-cause mortality. The diamond represents the combined point estimate, while horizontal lines represent the 95% confidence interval.

sample size, may have limited our potential to detect an association.

Evidence from experimental studies suggests a therapeutic role for isoflavones in various cancers, mainly by altering apoptosis, the cell cycle, and angiogenesis, and inhibiting metastasis (11,53). In *in vitro* studies on breast cancer cell lines, genistein, a major isoflavone, inhibited cell growth, induced apoptosis (54), and sensitized cells to the effects of therapeutic agents (55,56). An experimental animal study reported that genistein injections in rats during the prepubertal period showed a protective effect against chemically induced mammary cancer (57). However, adverse effects have been reported both *in vitro* (58,59) and *in vivo* (58,60,61). These results suggest that genistein may stimulate cell proliferation and abrogate the effects of therapeutic agents. However, the current study and meta-analysis did not show any adverse associations. In this meta-analysis, a higher isoflavone intake was associated with a lower risk of recurrence and all-cause mortality. Our meta-analysis suggests a nonlinear inverse association between isoflavone intake and breast cancer prognosis. In addition, we found no significant adverse association between dietary isoflavone intake and breast cancer prognosis among women with ER-positive breast cancers and tamoxifen users.

Evidence from observational studies (62) and randomized clinical trials (63) have shown that soy

Table 3. Combined hazard ratios (HRs) and 95% confidence intervals (CIs) in the meta-analysis.

	No.	Case/total	HR (95% CI)		I^2, %
			Fixed effects	Random effects	
Isoflavone intake					
Breast cancer recurrence					
Highest vs. lowest category	5 (7)	1,742/12,429	0.78 (0.68–0.88)	0.81 (0.67–0.98)	36
Per 10 mg/d increment	5 (7)	1,742/12,429	0.93 (0.90–0.97)	0.95 (0.85-1.06)	57
Breast cancer-specific mortality					
Highest vs. lowest category	6 (8)	2,483/29,201	0.94 (0.83–1.08)	0.94 (0.83–1.08)	0
Per 10 mg/d increment	5 (7)	2,187/27,746	0.99 (0.92–1.07)	1.00 (0.90–1.12)	0
All-cause mortality					
Highest vs. lowest category	9 (11)	5,283/35,471	0.87 (0.79–0.95)	0.85 (0.76–0.96)	52
Per 10 mg/d increment	9 (11)	5,283/35,471	0.93 (0.89–0.98)	0.89 (0.79–1.00)	67
Soy protein intake					
All-cause mortality					
Highest vs. lowest category	3	647/5,886	0.68 (0.56–0.83)	0.68 (0.56–0.83)	7
Per 5 g/d increment	3	647/5,886	0.89 (0.84–0.95)	0.89 (0.84–0.95)	39
Soy food intake					
Breast cancer recurrence					
Highest vs. lowest category	3	133/1,537	0.65 (0.40–1.06)	0.64 (0.33–1.24)	46
Per 10 g/d increment	3	133/1,537	0.95 (0.88–1.02)	0.90 (0.75–1.08)	72
All-cause mortality					
Highest vs. lowest category	2	839/4,448	0.99 (0.77–1.26)	0.51 (0.09–2.81)	78
Per 10 g/d increment	2	839/4,448	0.89 (0.72–1.10)	0.82 (0.50–1.35)	78

Number in brackets refers to individual studies in the pooled study (43).

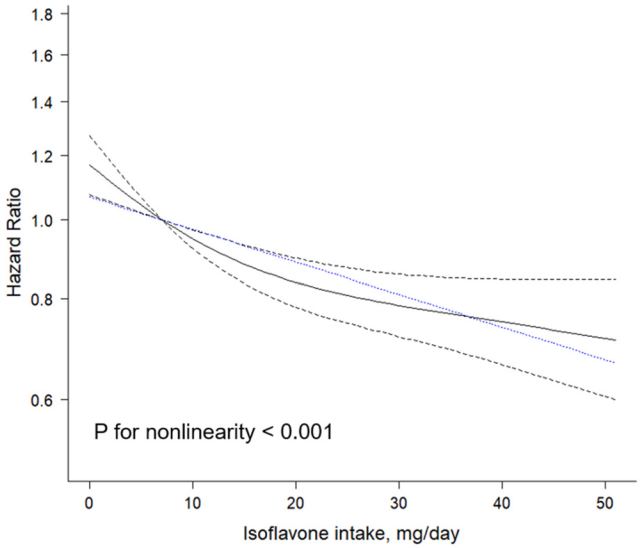

Figure 3. Pooled dose-response relation between isoflavone intake and risk of recurrence and all-cause mortality. Data were modeled using restricted cubic spline models with three knots in a multivariate fixed-effects dose-response model (I^2 = 56%). Dash lines represent the 95% confidence intervals for the fitted nonlinear trend (solid line). The dotted line represents the linear trend. The estimates for recurrence were included if the studies reported the recurrence results, and if otherwise, the estimates for all-cause mortality were reported. The value of 7 mg/day (50th percentile) served as the referent value.

protein intake lowers circulating cholesterol levels, which may result in CVD prevention. Also, a potential anti-inflammatory activity of soy protein was observed in experimental studies (64, 65). Because CVD is one of the major causes of death in breast cancer patients and CVD and breast cancer share risk factors (66), it is possible that favorable lipid or inflammatory profile provides protection from mortality among breast cancer patients.

In our subgroup meta-analysis, no significant difference was observed between pre- and post-diagnostic isoflavone intakes in terms of breast cancer prognosis. In two cohort studies that assessed both pre- and post-diagnostic isoflavone intakes, the association of post-diagnostic intake with all-cause mortality was similar to that of pre-diagnostic intake (9, 51), which aligns with our observation. In our study, the inverse association between isoflavone intake and recurrence

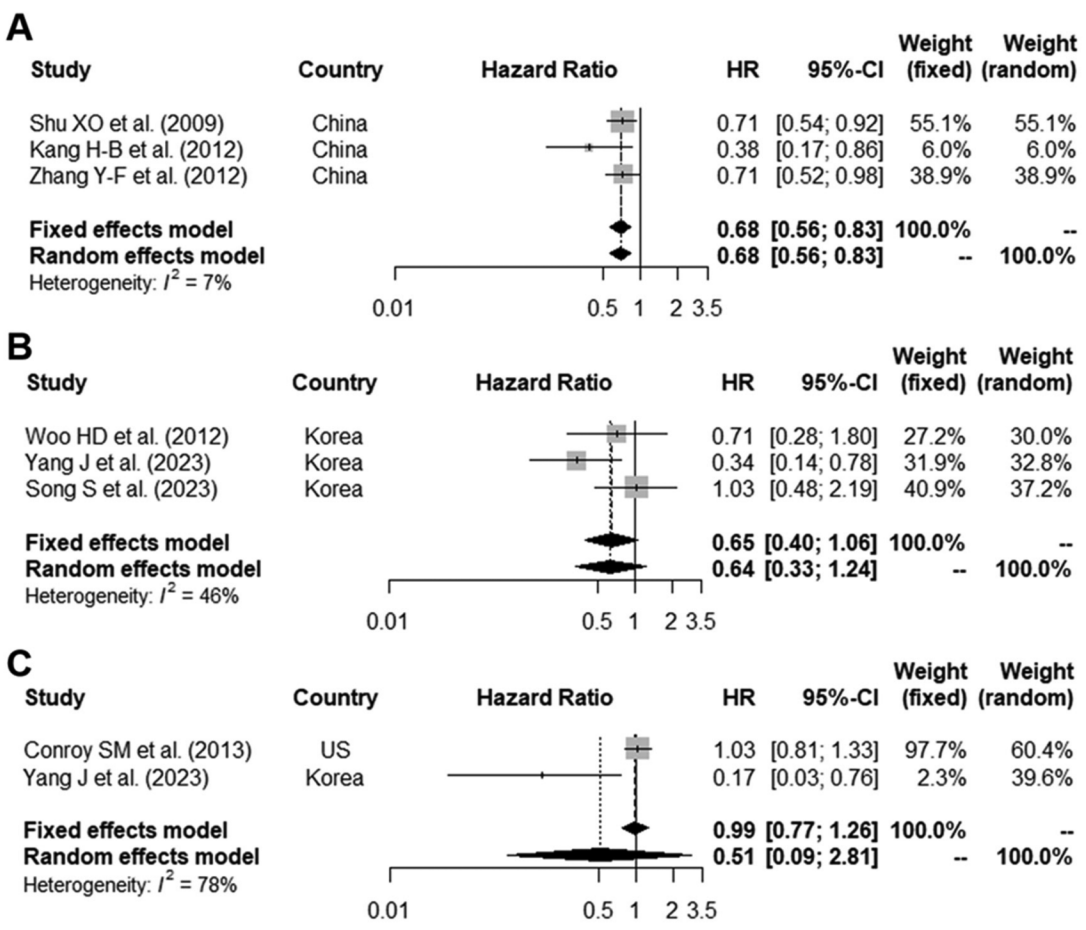

Figure 4. Forest plots of prospective associations comparing the highest versus the lowest intakes. (A) Soy protein intake and risk of all-cause mortality; (B) Soy food intake and risk of recurrence (defined as a local or regional recurrence, distant recurrence or metastasis, or a new primary cancer); and (C) Soy food intake and risk of all-cause mortality; The diamond represents the combined point estimate, while horizontal lines represent the 95% confidence interval.

tended to be stronger in post-menopausal women than in pre-menopausal women. Disease progression differs between patients with breast cancer diagnosed before and after menopause (67, 68) and the effects of dietary factors on breast cancer risk and prognosis may differ according to the menopausal status (4).

In this prospective analysis, we had a low rate of loss to follow-up and a relatively decent sample size compared to previous Asian studies that examined the association between dietary isoflavone intake and the risk of recurrence. However, we had a small number of recurrences and deaths because approximately 50% of breast cancers were diagnosed at stage I. Second, measurement errors in dietary assessments may be present. Third, there is a possibility of reverse causality. Although the results of sensitivity analysis by excluding women who experienced recurrence within the first year were similar to those of the main analysis, further confirmation is warranted due to the limited number of events. Finally, residual and unmeasured confounding factors could not be ruled out.

To our knowledge, this is the most updated and comprehensive meta-analysis summarizing the findings of cohort studies on the role of dietary isoflavone intake in the prognosis of breast cancer survivors. This meta-analysis included a limited number of studies on soy protein and soy intakes, for the subgroup analyses. Moreover, reverse causality between post-diagnostic isoflavone intake and breast cancer prognosis is possible, even though most studies did not include women with advanced breast cancer. Breast cancer is a heterogeneous disease and levels of isoflavone intake vary across countries. Although potential sources of heterogeneity were explored in subgroup analyses, results should be interpreted with caution due to the limited number of studies available. Nonetheless, our results suggest potential benefits of soy and isoflavones in breast cancer survivors and

warrant further studies from different populations to draw general conclusions.

This meta-analysis that included our current study and previously published studies supports the hypothesis that dietary isoflavone intake is associated with favorable prognosis in breast cancer survivors. Further prospective and interventional studies are warranted to confirm the role of dietary soy and isoflavone intakes in breast cancer survival.

Acknowledgments

The authors thank Dr. Cecilie Kyrø (Danish Cancer Society Research Center) for providing additional data for this meta-analysis.

Authors' Contributions

JEL contributed to the conception and design of the study, the acquisition of funding, data interpretation, and manuscript revision. SS contributed to literature search, data extraction, analysis, interpretation, and writing of the manuscript. J-HC, H-GM, D-YN, S-YJ, ESL, ZK, HJY, JC, and YBY contributed to the study design, data collection, and manuscript review. SJ and HJ contributed to the estimation of dietary exposure and review of the manuscript. All the authors have read and approved the final version of the manuscript.

Disclosure Statement

The authors report there are no competing interests to declare.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (Nos. 2014R1A2A2A01007794, 2019 R1F1A1061017, and 2021R1F1A1062476).

Data Availability Statement

The data that support the findings of this prospective study are available from the corresponding author upon reasonable request. The data supporting the findings of this meta-analysis are incorporated into the article and its online supplementary material.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. doi:10.3322/caac.21660.
2. Kang MJ, Won Y-J, Lee JJ, Jung K-W, Kim H-J, Kong H-J, Im J-S, Seo HG, Community of Population-Based Regional Cancer Registries. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2019. Cancer Res Treat. 2022;54(2):330–44. doi:10.4143/crt.2022.128.
3. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, Bandera EV, Hamilton KK, Grant B, McCullough M, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243–74. doi:10.3322/caac.21142.
4. World Cancer Research Fund/American Institute for Cancer Research. Diet, nutrition, physical activity and breast cancer. Continuous Update Project expert report. 2018.
5. Murkies AL, Wilcox G, Davis SR. Phytoestrogens. J Clin Endocrinol Metab. 1998;83(2):297–303. 10.1210/jcem.83.2.4577
6. Setchell KDR. The history and basic science development of soy isoflavones. Menopause. 2017;24(12):1338–50. doi:10.1097/gme.0000000000001018.
7. Palacios S. Selective Estrogen Receptor Modulators (SERMs): state of the Art. In: Postmenopausal diseases and disorders. Cham: Springer International Publishing; 2019. p. 349–66
8. Micek A, Godos J, Brzostek T, Gniadek A, Favari C, Mena P, Libra M, Del Rio D, Galvano F, Grosso G. Dietary phytoestrogens and biomarkers of their intake in relation to cancer survival and recurrence: a comprehensive systematic review with meta-analysis. Nutr Rev. 2021;79(1):42–65. 10.1093/nutrit/nuaa043
9. Ho SC, Yeo W, Goggins W, Kwok C, Cheng A, Chong M, Lee R, Cheung KL. Pre-diagnosis and early post-diagnosis dietary soy isoflavone intake and survival outcomes: a prospective cohort study of early stage breast cancer survivors. Cancer Treat Res Commun. 2021;27:100350. doi:10.1016/j.ctarc.2021.100350.
10. Woo HD, Park KS, Ro J, Kim J. Differential influence of dietary soy intake on the risk of breast cancer recurrence related to HER2 status. Nutr Cancer. 2012;64(2):198–205. doi:10.1080/01635581.2012.635261.
11. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, Nabavi SF, Devi KP, Loizzo MR, Tundis R, et al. Genistein and cancer: current status, challenges, and future directions. Adv Nutr. 2015;6(4):408–19. doi:10.3945/an.114.008052.
12. Korean Nutrition Society. Computer aided nutritional analysis program for professionals. Seoul (Republic of Korea): Korean Nutrition Society; 2011.
13. Shin WK, Song S, Hwang E, Moon HG, Noh DY, Lee JE. Development of a FFQ for breast cancer survivors in Korea. Br J Nutr. 2016;116(10):1781–6. doi:10.1017/s000711451600372x.
14. Moon S-E, Shin W-k, Song S, Koh D, Ahn JS, Yoo Y, Kang M, Lee JE. Validity and reproducibility of a food frequency questionnaire for breast cancer survivors in Korea. Nutr Res Pract. 2022;16(6):789–800. 10.4162/nrp.2022.16.6.789
15. Jun S, Shin S, Joung H. Estimation of dietary flavonoid intake and major food sources of Korean adults. Br J Nutr. 2016;115(3):480–9. 10.1017/S0007114515004006

16. Korean Nutrition Society. Food composition databases. Seoul (Republic of Korea): Korean Nutrition Society, 2009.
17. Rural Development Administration. Food composition table. 7th ed. Suwon (Republic of Korea): Rural Development Administration; 2007.
18. Rural Development Administration. Food composition table. 8th ed. Suwon (Republic of Korea): Rural Development Administration, 2011.
19. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Montoye HJ, Sallis JF, Paffenbarger RS. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993; 25(1):71–80. 10.1249/00005768-199301000-00011
20. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, JrTudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575–81. 10.1249/MSS.0b013e31821ece12
21. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T, American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2012;62(1):30–67. 10.3322/caac.20140
22. Willett W. Nutritional epidemiology. Oxford (UK): Oxford University Press, 2012.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
24. Kyrø C, Zamora-Ros R, Scalbert A, Tjonneland A, Dossus L, Johansen C, Bidstrup PE, Weiderpass E, Christensen J, Ward H, et al. Pre-diagnostic polyphenol intake and breast cancer survival: the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Breast Cancer Res Treat. 2015;154(2):389–401. doi:10.1007/s10549-015-3595-9.
25. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985;41(1):55–68.
26. Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. Biometrics. 1986; 42(2):311–23.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88. 10.1016/0197-2456(86)90046-2
28. Marín-Martínez F, Sánchez-Meca J. Weighting by inverse variance or by sample size in random-effects meta-analysis. Educ Psychol Meas. 2010;70(1):56–73. 10.1177/0013164409344534
29. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301–9. doi:10.1093/oxfordjournals.aje.a116237.
30. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. Stata J. 2006;6(1):40–57. doi:10.1177/1536867x0600600103.
31. Conroy SM, Maskarinec G, Park SY, Wilkens LR, Henderson BE, Kolonel LN. The effects of soy consumption before diagnosis on breast cancer survival: the multiethnic cohort study. Nutr Cancer. 2013;65(4): 527–37. doi:10.1080/01635581.2013.776694.
32. Crippa A, Orsini N. Multivariate dose-response meta-analysis: the dosresmeta R package. J Stat Soft. 2016;72(Code Snippet 1):1–15. 10.18637/jss.v072.c01
33. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012;175(1):66–73. doi:10.1093/aje/kwr265.
34. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing meta-analysis with R: a hands-on guide. Boca Raton (FL): CRC Press, 2021.
35. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: q statistic or I^2 index? Psychol Methods. 2006;11(2):193–206. 10.1037/1082-989X.11.2.193
36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. 10.1136/bmj.327.7414.557
37. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54(10):1046–55. 10.1016/s0895-4356(01)00377-8
38. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34. 10.1136/bmj.315.7109.629
39. Schwarzer G : meta: an R package for meta-analysis. R News. 2007;7:40–5.
40. Ho SY, Schooling M, Hui LL, McGhee SM, Mak KH, Lam TH. Soy consumption and mortality in Hong Kong: proxy-reported case-control study of all older adult deaths in 1998. Prev Med. 2006;43(1):20–6. doi:10.1016/j.ypmed.2006.03.007.
41. Guha N, Kwan ML, Quesenberry CP, Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat. 2009;118(2):395–405. 10.1007/s10549-009-0321-5
42. Jaskulski S, Jung AY, Huebner M, Poschet G, Hell R, Husing A, Gonzalez-Maldonado S, Behrens S, Obi N, Becher H, et al. Prognostic associations of circulating phytoestrogens and biomarker changes in long-term survivors of postmenopausal breast cancer. Nutr Cancer. 2020;72(7):1155–69. doi:10.1080/01635581.2019.1672762.
43. Nechuta SJ, Caan BJ, Chen WY, Lu W, Chen Z, Kwan ML, Flatt SW, Zheng Y, Zheng W, Pierce JP, et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr. 2012;96(1):123–32. 10.3945/ajcn.112.035972
44. Shu XO, Zheng Y, Cai H, Gu K, Chen Z, Zheng W, Lu W. Soy food intake and breast cancer survival. JAMA. 2009;302(22):2437–43. 10.1001/jama.2009.1783

45. Caan BJ, Natarajan L, Parker BA, Thomson CA, Newman VA, Rock CL, Pu M, Al-Delaimy WK, Pierce JP. Soy food consumption and breast cancer prognosis. Cancer Epidem Biomar. 2011;20(5):854–8.
46. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ. 2010;182(17):1857–62. 10.1503/cmaj.091298
47. Boyapati SM, Shu XO, Ruan ZX, Dai Q, Cai Q, Gao YT, Zheng W. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. Breast Cancer Res Treat. 2005;92(1):11–7. doi:10.1007/s10549-004-6019-9.
48. Fink BN, Steck SE, Wolff MS, Britton JA, Kabat GC, Gaudet MM, Abrahamson PE, Bell P, Schroeder JC, Teitelbaum SL, et al. Dietary flavonoid intake and breast cancer survival among women on Long Island. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2285–92. doi:10.1158/1055-9965.Epi-07-0245.
49. Kang H-B, Zhang Y-F, Yang J-D, Lu K-L. Study on soy isoflavone consumption and risk of breast cancer and survival. Asian Pac J Cancer Prev. 2012;13(3):995–8. 10.7314/apjcp.2012.13.3.995
50. Zhang Y-F, Kang H-B, Li B-L, Zhang R-M. Positive effects of soy isoflavone food on survival of breast cancer patients in China. Asian Pac J Cancer Prev. 2012;13(2):479–82. doi:10.7314/apjcp.2012.13.2.479.
51. Zhang FF, Haslam DE, Terry MB, Knight JA, Andrulis IL, Daly MB, Buys SS, John EM. Dietary isoflavone intake and all-cause mortality in breast cancer survivors: the Breast Cancer Family Registry. Cancer. 2017;123(11):2070–9. doi:10.1002/cncr.30615.
52. Yang J, Chung M, Park Y. Association of fermented products with risk of cancer recurrence and mortality among breast cancer survivors: a Prospective Cohort Study. Nutr Cancer. 2023;75(4):1189–99. doi:10.1080/01635581.2023.2186259.
53. Birt DF, Hendrich S, Wang W. Dietary agents in cancer prevention: flavonoids and isoflavonoids. Pharmacol Ther. 2001;90(2–3):157–77. doi:10.1016/s0163-7258(01)00137-1
54. Liu Y, Zhang Y-M, Song D-F, Cui H-B. Effect of apoptosis in human breast cancer cells and its probable mechanisms by genistein. Wei Sheng Yan Jiu. 2005;34(1):67–9.
55. Satoh H, Nishikawa K, Suzuki K, Asano R, Virgona N, Ichikawa T, Hagiwara K, Yano T. Genistein, a soy isoflavone, enhances necrotic-like cell death in a breast cancer cell treated with a chemotherapeutic agent. Res Commun Mol Pathol Pharmacol. 2003;113:149–58.
56. Mai Z, Blackburn GL, Zhou JR. Genistein sensitizes inhibitory effect of tamoxifen on the growth of estrogen receptor-positive and HER2-overexpressing human breast cancer cells. Mol Carcinog. 2007;46(7):534–42. 10.1002/mc.20300
57. Lamartiniere CA, Zhang JX, Cotroneo MS. Genistein studies in rats: potential for breast cancer prevention and reproductive and developmental toxicity. Am J Clin Nutr. 1998;68(6 Suppl):1400S–5S. doi:10.1093/ajcn/68.6.1400S.
58. Liu B, Edgerton S, Yang X, Kim A, Ordonez-Ercan D, Mason T, Alvarez K, McKimmey C, Liu N, Thor A. Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. Cancer Res. 2005;65(3):879–86.
59. Seo H-S, DeNardo DG, Jacquot Y, Laïos I, Vidal DS, Zambrana CR, Leclercq G, Brown PH. Stimulatory effect of genistein and apigenin on the growth of breast cancer cells correlates with their ability to activate ER alpha. Breast Cancer Res Treat. 2006;99(2):121–34. 10.1007/s10549-006-9191-2
60. Hsieh C-Y, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res. 1998;58(17):3833–8.
61. Ju YH, Allred KF, Allred CD, Helferich WG. Genistein stimulates growth of human breast cancer cells in a novel, postmenopausal animal model, with low plasma estradiol concentrations. Carcinogenesis. 2006;27(6):1292–9. 10.1093/carcin/bgi370
62. Nagata C, Takatsuka N, Kurisu Y, Shimizu H. Decreased serum total cholesterol concentration is associated with high intake of soy products in japanese men and women. J Nutr. 1998;128(2):209–13. doi:10.1093/jn/128.2.209.
63. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr. 2005;81(2):397–408. doi:10.1093/ajcn.81.2.397.
64. Young D, Ibuki M, Nakamori T, Fan M, Mine Y. Soy-derived di- and tripeptides alleviate colon and ileum inflammation in pigs with dextran sodium sulfate-induced colitis. J Nutr. 2012;142(2):363–8. doi:10.3945/jn.111.149104.
65. Kovacs-Nolan J, Zhang H, Ibuki M, Nakamori T, Yoshiura K, Turner PV, Matsui T, Mine Y. The PepT1-transportable soy tripeptide VPY reduces intestinal inflammation. Biochim Biophys Acta. 2012;1820(11):1753–63. doi:10.1016/j.bbagen.2012.07.007.
66. Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, Dent S, Kondapalli L, Ky B, Okwuosa T, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation. 2018;137(8):e30–e66. doi:10.1161/CIR.0000000000000556.
67. Alexander FE, Roberts MM. The menopause and breast cancer. J Epidemiol Community Health. 1987;41(2):94–100. doi:10.1136/jech.41.2.94.
68. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev. 1993;15(1):36–47. doi:10.1093/oxfordjournals.epirev.a036115.