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Dietary isoflavone intake among breast cancer survivors and cancer-free women

Sihan Song [1,2], **Hyeong-Gon Moon** [3], **Dong-Young Noh** [3], **So-Youn Jung** [4], **Eun Sook Lee** [4], **Zisun Kim** [5], **Hyun Jo Youn** [6], **Jihyoung Cho** [7], **Young Bum Yoo** [8], **Se Kyung Lee** [9], **Jeong Eon Lee** [9], **Seok Jin Nam** [9], **Yoo Seok Kim** [10], **Jun Won Min** [11], **Shinyoung Jun** [12], **Hyojee Joung** [13], and **Jung Eun Lee** [1,14§]

[1]Department of Food and Nutrition, Seoul National University, Seoul 08826, Korea
[2]Division of Population Health Research, Department of Precision Medicine, National Institute of Health, Cheongju 28159, Korea
[3]Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul 03080, Korea
[4]Research Institute and Hospital, National Cancer Center, Goyang 10408, Korea
[5]Department of Surgery, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon 14584, Korea
[6]Department of Surgery, Jeonbuk National University Medical School, Jeonju 54907, Korea
[7]Department of Surgery, Keimyung University School of Medicine, Daegu 42601, Korea
[8]Department of Surgery, Konkuk University Medical Center, Seoul 05030, Korea
[9]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Korea
[10]Department of Surgery, Chosun University Hospital, Chosun University College of Medicine, Gwangju 61453, Korea
[11]Department of Surgery, Dankook University Hospital, Dankook University College of Medicine, Cheonan 31116, Korea
[12]Department of Food Science and Nutrition, Soonchunhyang University, Asan 31538, Korea
[13]Department of Public Health, Graduate School of Public Health, Seoul National University, Seoul 08826, Korea
[14]Research Institute of Human Ecology, Seoul National University, Seoul 08826, Korea

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§Corresponding Author:
Jung Eun Lee
Department of Food and Nutrition, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Korea.
Tel. +82-2-880-6834
Fax. +82-2-884-0305
Email. jungelee@snu.ac.kr

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ORCID iDs
Sihan Song
https://orcid.org/0000-0003-1634-8004
Hyeong-Gon Moon
https://orcid.org/0000-0002-9981-0286
Dong-Young Noh
https://orcid.org/0000-0001-9418-7256
So-Youn Jung
https://orcid.org/0000-0002-4508-4522
Eun Sook Lee
https://orcid.org/0000-0003-1122-8230
Zisun Kim
https://orcid.org/0000-0002-1413-2800
Hyun Jo Youn
https://orcid.org/0000-0002-2407-8537

ABSTRACT

BACKGROUND/OBJECTIVES: Isoflavones are estrogen-like compounds found in plants and their health effects remain equivocal. We investigated dietary isoflavone intake and its associated factors in Korean breast cancer survivors, with a comparison to cancer-free women.

SUBJECTS/METHODS: The usual dietary intake of breast cancer survivors (n = 981, mean age 52 yrs) in 9 hospitals between 2012 and 2019 was assessed using 3-day food records or food frequency questionnaires (FFQs). They were age-matched to 2,943 cancer-free women who completed FFQs as part of a nationwide study conducted between 2012 and 2016. We used the flavonoid database of common Korean foods and the Phenol-Explorer database to estimate isoflavone intake. The contribution of each food or food group to the total isoflavone intake was calculated. The adjusted least-squares means of dietary isoflavone intake according to lifestyle and clinical factors were calculated using generalized linear models.

RESULTS: Breast cancer survivors had a higher mean dietary isoflavone intake (23.59 mg/day) than cancer-free women (17.81 mg/day). Major food sources, including tofu, soybeans, and doenjang, contributed to over 70% of the isoflavone intake in both groups. When we

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estimated dietary isoflavone intake according to lifestyle characteristics, isoflavone intake increased with higher scores of adherence to the American Cancer Society dietary guidelines but decreased with increasing body mass index in both groups. Among cancer-free women, dietary isoflavone intake was higher among those who had never smoked and among dietary supplement users. Among breast cancer survivors, dietary isoflavone intakes did not vary with clinical characteristics, including time since surgery and estrogen receptor status.
CONCLUSION: Breast cancer survivors were more likely to consume isoflavones than age-matched cancer-free women. Dietary isoflavone intake was associated with healthy lifestyle characteristics in women both with and without breast cancer. Further research is needed to understand the role of the higher isoflavone intake among breast cancer survivors compared to cancer-free women on their prognosis.

Keywords: Isoflavones; soy foods; breast cancer

Jihyoung Cho
https://orcid.org/0000-0002-1680-2919
Young Bum Yoo
https://orcid.org/0000-0002-6910-5076
Se Kyung Lee
https://orcid.org/0000-0003-1630-1783
Jeong Eon Lee
https://orcid.org/0000-0003-0037-2456
Seok Jin Nam
https://orcid.org/0000-0003-1072-8954
Yoo Seok Kim
https://orcid.org/0000-0002-5853-4748
Jun Won Min
https://orcid.org/0000-0001-7440-2561
Shinyoung Jun
https://orcid.org/0000-0003-2452-4709
Hyojee Joung
https://orcid.org/0000-0003-1182-7786
Jung Eun Lee
https://orcid.org/0000-0003-1141-878X

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Conflict of Interest
The authors declare no potential conflicts of interests.

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Lee JE[1], Jung Eun Lee; Lee JE[2], Jeong Eon Lee.

INTRODUCTION

Isoflavones are phytoestrogens primarily found in soy and have a structure similar to that of 17-β-estradiol [1]. Isoflavones possess properties of selective estrogen receptor modulators (SERMs), exhibiting both estrogenic and antiestrogenic activities depending on the target tissue, and may serve as preventive and therapeutic agents for breast cancer [2,3]. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among women globally [4], with approximately two-thirds of cases being hormone-dependent [5]. Findings from epidemiological studies suggest that high isoflavone intake may be associated with reduced breast cancer incidence [6], recurrence, and all-cause mortality [7]. However, conflicting results from *in vitro* and *in vivo* studies raise potential concerns regarding the interactions between genistein and tamoxifen, a widely used SERM, in hormone-dependent breast cancer [8-10].

There is limited evidence on dietary isoflavone intake after breast cancer diagnosis. According to the results from the After Breast Cancer Pooling Project (ABCPP), breast cancer survivors with higher postdiagnostic isoflavone intake were more likely to engage in physical activity and consume cruciferous vegetables than those with low intake, among both Chinese and US women [11]. In Korea, breast cancer is the most commonly diagnosed cancer among women [12], and the consumption of food sources of isoflavones is relatively higher than in Western countries [13-15]. However, to our knowledge, few data exist on postdiagnostic intake and the consumption of food sources of isoflavones among breast cancer survivors in Korea.

Our study aimed to estimate dietary isoflavone intake and identify demographic, lifestyle, and clinical factors associated with breast cancer survivors in Korea. To provide context for isoflavone intake levels and their associated factors, we also examined data from cancer-free women participating in a nationwide survey. When examining dietary isoflavone intake levels in relation to clinical characteristics among breast cancer survivors, we included factors such as hormone receptor status and hormone therapy.

SUBJECTS AND METHODS

Study population

Women diagnosed with breast cancer were recruited from 9 hospitals in Korea between September 2012 and June 2019. Eligible participants were women who had undergone breast cancer surgery at least 6 mon prior to study entry and had histologically confirmed in situ or invasive breast cancer. Dietary intake was assessed using either 3-day food records (3-DFRs) or food frequency questionnaires (FFQs). Among the 1,152 eligible women, those without dietary data (n = 157) or with implausible dietary intakes (n = 4) were excluded. Additionally, women with energy intake values outside 3 SDs from the mean log-transformed energy intake (n = 10) were excluded. A total of 981 breast cancer survivors aged 21–81 yrs (mean age: 52 yrs) were included (**Fig. 1**). The median (interquartile range) time since surgery was 2.5 yrs (1.5–4.8 yrs).

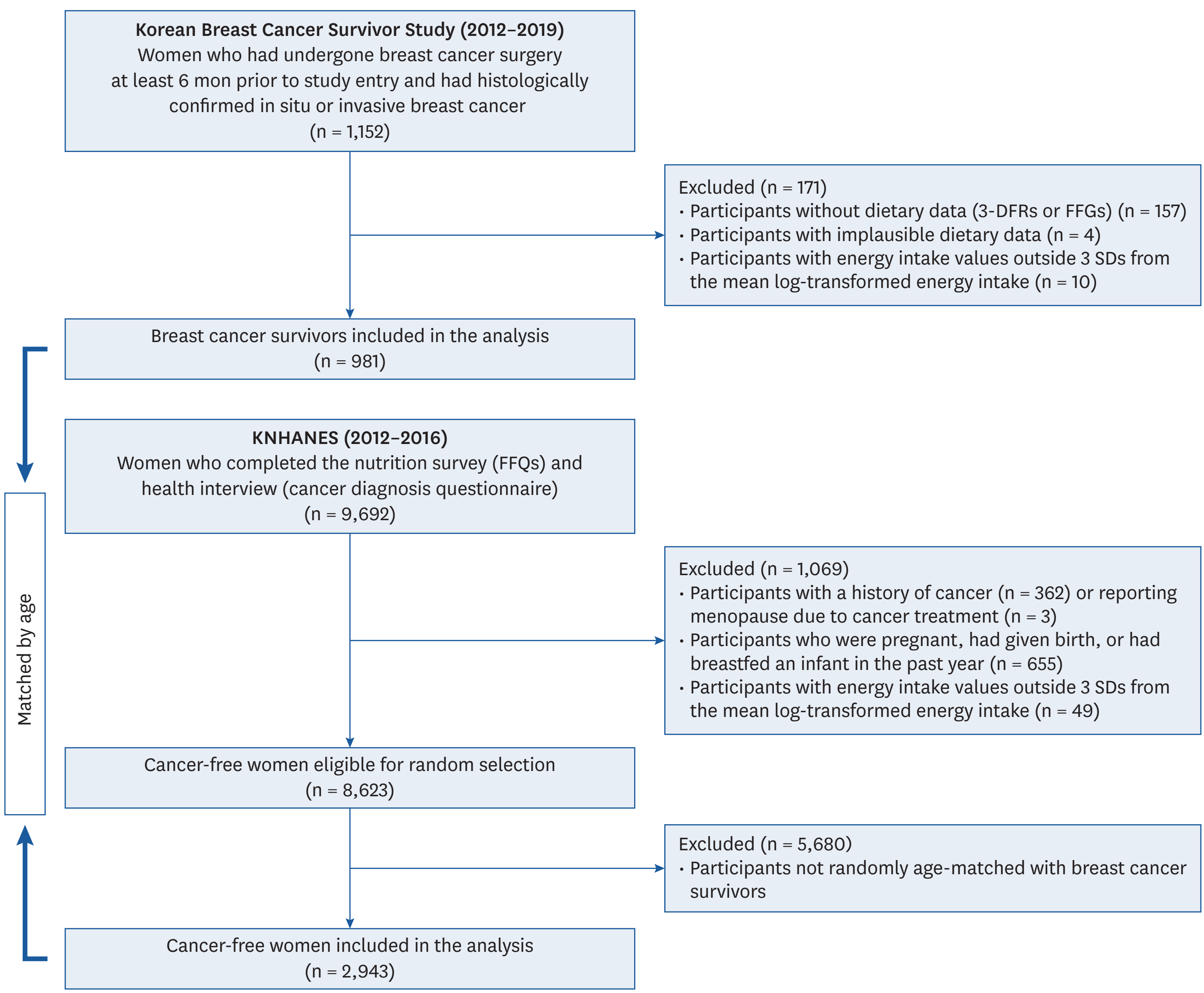

Fig. 1. Flowchart of the study population. For each breast cancer survivor, 3 cancer-free women were randomly age-matched.
3-DFRs, 3-day food records; FFQs, food frequency questionnaires; KNHANES, Korea National Health and Nutrition Examination Survey.

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This study was approved by the Institutional Review Board (IRB) of each of the following 9 hospitals: Seoul National University Hospital (H-1111-080-387), The National Cancer Center, Korea (NCC2014-0101), Soonchunhyang University Hospital (SCHBC2014-12-004-001), Jeonbuk National University Hospital (CUH2014-05-002-005 and CUH2018-02-004-004), Keimyung University Dongsan Medical Center (DSMC2015-03-026), Konkuk University Medical Center (KUH1020068), Samsung Medical Center (SMC2016-07-073-004), Chosun University Hospital (CHOSUN 2016-06 and CHOSUN 2018-06), and Dankook University Hospital (DKUH 2016-07-001-002). All participants provided written informed consent.

Cancer-free women were selected from the Korea National Health and Nutrition Examination Survey (KNHANES) 2012–2016. The KNHANES is a nationally representative annual survey conducted by the Korea Disease Control and Prevention Agency (KDCA) to assess the health and nutritional status of the Korean population [16]. Usual dietary intake was assessed using an FFQ among adults aged 19–64 yrs in the KNHANES 2012–2016. Among the 9,692 women who completed the FFQs and responded to the question of whether they had ever been diagnosed with cancer by a physician, we excluded women who had a history of cancer (n = 362); who reported menopause due to cancer treatment (n = 3); who were pregnant, had given birth, or had breastfed an infant in the past year (n = 655); or who had energy intake values outside 3 SDs from the mean log-transformed energy intake (n = 49). Consequently, 8,623 cancer-free women were eligible for this analysis. We randomly selected 3 age-matched cancer-free women for each breast cancer survivor using the PROC SURVEYSELECT procedure in SAS (SAS Institute Inc., Cary, NC, USA). Because the FFQs were administered to adults aged 19–64 yrs in the KNHANES 2012–2016, exact age matching was not possible for breast cancer survivors aged > 64 yrs (n = 68; median age 69 yrs), and they were matched to cancer-free women aged 60–64 yrs. As a result, a total of 2,943 cancer-free women aged 21–64 yrs (mean age: 52 yrs) were included in our study.

The KNHANES 2012–2014 was approved by the KDCA IRB. In the KNHANES 2015 and 2016, IRB approval was waived by the Bioethics and Safety Act. All participants provided written informed consent.

Dietary assessment

The dietary intake of breast cancer survivors was assessed using 3-DFRs from 2012 to 2017. Based on the dietary data obtained, FFQs were developed and used between 2016 and 2019. Among the 981 breast cancer survivors, 644 completed the 3-DFRs, including 2 weekdays and one weekend day. Participants recorded all foods and beverages consumed over a 3-day period and were given a booklet with images of common food items to help estimate portion sizes. Dietary data from the 3-DFRs were analyzed using the Computer-Aided Nutritional Analysis Program version 4.0 [17]. The program's nutrient database is derived from publications by the Korean Nutrition Society [18] and the Rural Development Administration (RDA) of Korea [19]. A total of 337 women completed FFQs specifically designed for breast cancer survivors in Korea [20]. The 123-item FFQ developed for breast cancer survivors demonstrated acceptable validity and reproducibility when compared to 9-DFRs collected over a 1-yr period [21]. Participants reported their average frequency of consumption of each item over the past year using a 9-category frequency scale, ranging from 'never or almost never' to '3 times per day.' Participants also reported their usual portion size as small, medium, or large. The portion sizes and nutrient content of food items in the FFQ were determined based on 3-DFRs from breast cancer survivors recruited in our study between 2012 and 2014 and 24-h recall data from the KNHANES 2013 and 2014, which were primarily based on the RDA publications. The frequency data were converted to daily values, and then multiplied by the portion size to calculate the daily intake.

The KNHANES semi-quantitative FFQ was developed for Korean adults in the fourth KNHANES 2007–2009 [22]. The KNHANES FFQ included 112 food items and was administered to adults aged 19–64 yrs through personal interviews. Participants were asked to report their average frequency of consumption for each food item over the past year, using a 9-category frequency scale ranging from 'none' to '3 times per day.' Participants were also asked to report their usual portion size as small, medium, or large, based on the portion sizes commonly consumed by Korean adults. Daily intake was calculated using the selected portion size and consumption frequency. The nutrient database for the KNHANES FFQ was primarily based on the food composition table of the RDA and provided by the KDCA [23].

Estimation of isoflavone intake

To ensure the robustness of the estimates, we used 2 databases to estimate isoflavone intake separately: the flavonoid database of common Korean foods (KFDB) and the Phenol-Explorer database. The KFDB food list was based on the fourth and fifth KNHANES (2007–2012), and the flavonoid values were derived from the database of RDA of Korea, the United States Department of Agriculture, the French National Institute for Agricultural Research (INRA), and published articles [13]. The KFDB for isoflavones was developed for 3 aglycones (daidzein, genistein, and glycitein)–the more bioavailable forms of isoflavones. Total isoflavones were calculated as the sum of these 3 components. A detailed description of database construction and expansion is available in Jun *et al.*'s study [13]. Food items from the 3-DFRs or FFQs were matched to those in the KFDB. Commercial products were assigned isoflavone values from similar types of foods. For similar food items with different processing or preparation methods, isoflavone content was estimated by applying the moisture conversion factors developed by the KDCA. A value of zero was assigned to food items with logical zeros or missing values. The Phenol-Explorer database, developed by the INRA, provides data from scientific peer-reviewed articles on the content of 500 polyphenols in over 400 foods (www.phenol-explorer.eu) [24]. The isoflavone database in Phenol-Explorer was developed for aglycones (daidzein, genistein, glycitein, formononetin, and biochanin A), glycosides, acetylglucosides, and malonylglucosides. We calculated the isoflavone content as aglycone equivalents using molecular weight ratios. Food items in our study were matched to those in the Phenol-Explorer database. Isoflavone contents in processed foods were estimated from raw foods using the retention factor, yield factor, or moisture conversion factor. If none of these factors were available, isoflavone values were assigned from raw foods, and a value of zero was given to food items without data.

Dietary isoflavone intake (mg/day) was calculated by multiplying the food intake (g/day) reported in the 3-DFRs or FFQ by the isoflavone content (mg/g) of each food item. Pearson's correlation coefficient between isoflavones calculated using the KFDB and Phenol-Explorer database was 0.88 for both breast cancer survivors and cancer-free women. Additionally, the dietary intakes of soy foods (g/day) and soy protein (g/day) were calculated.

Assessment of demographic, lifestyle, and clinical factors

We asked breast cancer survivors about their age, educational level, marital status, reproductive factors, and lifestyle factors, including smoking status, dietary supplement use, and physical activity level, using a structured questionnaire. Information on dietary supplement use over the past year was collected, including the type of supplement and product name. The type of physical activity performed and the time spent (per week) engaging in physical activity were obtained. The amount of time spent in vigorous-intensity activities requiring ≥ 6 metabolic equivalent tasks was calculated (h/week). Body weight and height at baseline were self-reported. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2). The BMI at diagnosis was used when the BMI at baseline (study entry) was not available (4% of participants). Clinical information, including time since surgery, breast cancer stage, menopausal status at diagnosis, and hormone receptor status, was collected from the medical records at each hospital.

In the KNHANES, data on age, education level, marital status, reproductive factors, medical conditions, and lifestyle factors, including smoking status, dietary supplement use, and physical activity level, were collected through self- or interviewer-administered questionnaires [16]. Information on dietary supplement use for at least 2 weeks during the past year (yes, no) was collected. In the KNHANES 2015–2016, information on dietary supplement use on the preceding day, including the type of supplement and product name, was collected in the nutrition survey. For physical activity level, the time spent (h/week) in vigorous physical activity was calculated. Body weight and height were measured by trained personnel.

We evaluated adherence to the American Cancer Society (ACS) dietary guidelines for cancer prevention [25], as these guidelines are also recommended for cancer survivors. In our previous studies of breast cancer survivors, higher adherence scores to ACS guidelines were associated with favorable levels of health-related quality of life [26] and inflammatory markers [27]. The score included the intake (g/day) of vegetables and fruits, whole grains, and red and processed meat. For each food group, participants received a score of 1–4 for the quartiles of intake. The highest quartile was assigned 4 points for vegetable and fruit intake and whole grain intake and 1 point for red and processed meat intake. Consequently, the overall score ranged from 3 to 12 for both breast cancer survivors and cancer-free women, with higher scores indicating greater adherence to the guidelines.

Statistical analysis

We compared characteristics between breast cancer survivors and cancer-free women within matched sets using conditional logistic regression. To account for energy intake, we calculated the density intakes of soy and isoflavones by dividing the daily intake by the total energy intake and multiplying by 1,000. We reported the crude and density intakes of soy and isoflavones as means and SDs among breast cancer survivors and cancer-free women and compared them using conditional logistic regression. The contribution of each food or food group to the total isoflavone intake was calculated as a percentage based on the KFDB and the Phenol-Explorer database among breast cancer survivors and cancer-free women separately. We estimated age-adjusted least-squares means (LSmeans) and SEs of the density intakes of soy and isoflavones according to the demographic and lifestyle factors among the 2 groups, and according to clinical factors among breast cancer survivors using a generalized linear model. Adjusted means were compared using an F test. For ordinal variables, the *P* for trend was calculated by assigning the median value to each category and treating it as a continuous variable in the model. To improve the normality of the data, dietary intake values were log-transformed.

We conducted several sensitivity analyses: 1) we analyzed the data by including only breast cancer survivors under 65 yrs of age (n = 913) and cancer-free women matched by exact age, as the KNHANES FFQ was administered to adults aged 19–64 yrs; 2) we compared isoflavone intake between breast cancer survivors who completed the FFQ (n = 337) and matched cancer-free women; and 3) we restricted the analysis to breast cancer survivors enrolled between 2012 and 2016 (n = 537) and matched cancer-free women to compare individuals from the same time period. Additionally, we compared age-adjusted LSmeans of isoflavone density intake between breast cancer survivors and cancer-free women across subgroups of education level, dietary supplement use, marital status, menopausal status, and age.

Complex sampling design analysis was not applied to the KNHANES data because we used a matched subset of participants (n = 2,943) for comparison with breast cancer survivors, rather than the entire survey population.

A 2-sided *P*-value of < 0.05 was considered statistically significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.).

RESULTS

Characteristics of breast cancer survivors and cancer-free women

The characteristics of cancer survivors and cancer-free women are presented in **Table 1**. The mean age was 52.05 ± 8.31 yrs for breast cancer survivors and 51.53 ± 7.32 yrs for cancer-free women. Breast cancer survivors were more likely to have a lower BMI, use dietary supplements, have a higher level of education, be unmarried, and experience medically induced menopause than cancer-free women. There was no significant difference between

Table 1. Characteristics of breast cancer survivors and cancer-free women

Characteristics	Breast cancer survivors (n = 981)	Cancer-free women (n = 2,943)	*P*-value[1)]
Age (yrs)	52.05 ± 8.31	51.53 ± 7.32	0.961
Energy intake (kcal/day)	1,760.37 ± 526.97	1,722.71 ± 578.69	0.071
BMI (kg/m^2)	23.16 ± 2.92	23.80 ± 3.33	< 0.001
Smoking status			0.340
Never	860 (93.17)	2,701 (92.12)	
Ever	63 (6.83)	231 (7.88)	
Dietary supplement use			0.001
No	361 (37.18)	1,271 (43.19)	
Yes	610 (62.82)	1,672 (56.81)	
Education level			< 0.001
Elementary school or below	89 (9.14)	556 (18.92)	
Middle school	88 (9.03)	454 (15.45)	
High school	469 (48.15)	1,193 (40.59)	
College or above	328 (33.68)	736 (25.04)	
Marital status			< 0.001
Unmarried	59 (6.05)	76 (2.59)	
Married/cohabiting	787 (80.72)	2,477 (84.28)	
Divorced/widowed/separated	129 (13.23)	386 (13.13)	
Menopausal status			< 0.001
Premenopause	140 (14.31)	1,276 (43.45)	
Induced menopause	485 (49.59)	262 (8.92)	
Natural menopause	353 (36.09)	1,399 (47.63)	

Values are presented as mean ± SD or number (%).
Missing data for cases: BMI (n = 2), smoking status (n = 58), dietary supplement use (n = 10), education level (n = 7), marital status (n = 6), and menopausal status (n = 3); for controls: BMI (n = 2), smoking status (n = 11), education levels (n = 4), marital status (n = 4), and menopausal status (n = 6).
BMI, body mass index.
[1)] *P*-values obtained from the conditional logistic regression models.

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the groups in terms of energy intake or smoking status. When we restricted the analyses to women who were matched by exact age, the results were similar (**Supplementary Table 1**).

Estimated intakes of soy and isoflavones

The mean daily intakes of soy and isoflavones are shown in **Table 2**. Breast cancer survivors had higher mean intakes of soy and isoflavones than cancer-free women. The mean dietary isoflavone intake values calculated using the KFDB were 23.59 mg/day for breast cancer survivors and 17.81 mg/day for cancer-free women. The mean dietary isoflavone intake values per 1,000 kcal were 13.28 mg/day for cancer survivors and 10.28 mg/day for cancer-free women. Isoflavones presented as aglycones using the Phenol-Explorer database were similar to those calculated using the KFDB (*P*-value from the paired *t*-test > 0.10 for both groups). The mean dietary intake values of soy foods and soy protein were 78.96 g/day and 8.37 g/day for breast cancer survivors and 60.46 g/day and 5.62 g/day for cancer-free women, respectively.

Similarly, breast cancer survivors had higher mean intakes of soy and isoflavones than cancer-free women in the sensitivity analyses restricted to women matched by exact age (< 65 yrs) (**Supplementary Table 2**), those with FFQ data (**Supplementary Table 3**), or those enrolled between 2012 and 2016 (**Supplementary Table 4**). Consistently, stratified analyses showed higher dietary isoflavone intake among breast cancer survivors compared to cancer-free women across subgroups defined by education level, dietary supplement use, and marital status (**Supplementary Table 5**). Regarding menopausal status at enrollment, breast cancer survivors tended to have higher dietary isoflavone intake than cancer-free women among those with natural or induced menopause, but not among premenopausal women. However, when participants were stratified by age (< 50 and ≥ 50 yrs), using the median age of menopause among cancer-free women as the cut-off, dietary isoflavone intake remained significantly higher among breast cancer survivors in both age groups.

Major food sources of isoflavones

The major sources of isoflavones were similar in both breast cancer survivors and cancer-free women (**Table 3**). For isoflavones estimated using the KFDB, the major food sources among

Table 2. Soy and isoflavone intakes among breast cancer survivors and cancer-free women

Dietary intake	Crude			Density		
	Breast cancer survivors (n = 981)	Cancer-free women (n = 2,943)	*P*-value[1)]	Breast cancer survivors (n = 981)	Cancer-free women (n = 2,943)	*P*-value[1)]
KFDB	(mg/day)			(mg/1,000 kcal/day)		
Daidzein	10.83 ± 8.94	7.75 ± 5.12	< 0.001	6.11 ± 4.70	4.48 ± 2.52	< 0.001
Genistein	10.81 ± 9.33	8.51 ± 5.93	< 0.001	6.08 ± 4.89	4.91 ± 2.95	< 0.001
Glycitein	1.95 ± 1.76	1.55 ± 1.13	< 0.001	1.10 ± 0.94	0.89 ± 0.57	< 0.001
Isoflavones	23.59 ± 19.82	17.81 ± 12.14	< 0.001	13.28 ± 10.41	10.28 ± 6.01	< 0.001
Phenol-Explorer	(mg/day)			(mg/1,000 kcal/day)		
Daidzein	10.61 ± 9.74	6.73 ± 4.10	< 0.001	6.01 ± 5.24	3.92 ± 2.00	< 0.001
Genistein	13.67 ± 12.35	8.66 ± 5.24	< 0.001	7.74 ± 6.58	5.04 ± 2.54	< 0.001
Glycitein	2.58 ± 2.40	1.62 ± 0.98	< 0.001	1.46 ± 1.29	0.94 ± 0.48	< 0.001
Formononetin	0.59 ± 0.67	0.32 ± 0.20	< 0.001	0.34 ± 0.36	0.19 ± 0.11	< 0.001
Isoflavones[2)]	27.45 ± 24.96	17.34 ± 10.43	< 0.001	15.54 ± 13.33	10.09 ± 5.07	< 0.001
Soy and its products	(g/day)			(g/1,000 kcal/day)		
Soy foods	78.96 ± 68.35	60.46 ± 55.04	< 0.001	44.15 ± 34.38	34.61 ± 28.15	< 0.001
Soy protein	8.37 ± 6.24	5.62 ± 3.57	< 0.001	4.72 ± 3.14	3.26 ± 1.71	< 0.001

Values are presented as mean ± SD.
KFDB, flavonoid database of common Korean foods.
[1)] *P*-values obtained from the conditional logistic regression models.
[2)] Total isoflavone intake included biochanin A, with an average intake of less than 0.01 mg/day in both groups.

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Table 3. Major food sources of dietary isoflavones among breast cancer survivors and cancer-free women

Isoflavones	Rank	Breast cancer survivors (n = 981)				Cancer-free women (n = 2,943)			
		Food item	Mean intake (mg/day)	% Contribution	Cumulative % Contribution	Food item	Mean intake (mg/day)	% Contribution	Cumulative % Contribution
KFDB	1	Tofu	8.17	34.63	34.63	Tofu	7.49	42.05	42.05
	2	Soybeans	6.17	26.16	60.79	Soybeans	3.79	21.29	63.34
	3	Doenjang	2.72	11.52	72.31	Doenjang	1.96	11.03	74.37
	4	Cheonggukjang	2.16	9.14	81.44	Soymilk	1.44	8.07	82.43
	5	Soybean sprouts	2.10	8.89	90.34	Cheonggukjang	1.28	7.19	89.62
Phenol-Explorer	1	Soybeans	15.93	58.01	58.01	Soybeans	8.24	47.54	47.54
	2	Tofu	6.48	23.60	81.61	Tofu	5.78	33.35	80.89
	3	Cheonggukjang	2.33	8.50	90.11	Soymilk	1.31	7.58	88.47
	4	Soymilk	1.50	5.48	95.59	Cheonggukjang	1.28	7.39	95.86
	5	Soybean sprouts	0.75	2.73	98.32	Soybean sprouts	0.39	2.24	98.10

The percent contribution of each food or food group to total isoflavone intake was calculated as the ratio of isoflavone intake from each food to the total isoflavone intake.
KFDB, flavonoid database of common Korean foods.

breast cancer survivors were tofu (34.63%), soybeans (26.16%), doenjang (soybean paste) (11.52%), cheonggukjang (fast-fermented soybean paste) (9.14%), and soybean sprouts (8.89%), totalling a contribution of 90.34%. Similarly, the major food sources of isoflavones among cancer-free women were tofu (42.05%), soybeans (21.29%), doenjang (11.03%), soymilk (8.07%), and cheonggukjang (7.19%). For isoflavones estimated using the Phenol-Explorer database, soybeans were the main contributor to the total isoflavone intake (58.01% for breast cancer survivors and 47.54% for cancer-free women), followed by tofu, cheonggukjang or soymilk, and soybean sprouts.

Isoflavone supplement use was not reported among breast cancer survivors. Among the 1,104 cancer-free women from the KNHANES 2015–2016, 387 (35%) used dietary supplements on the day preceding the nutrition survey, and 2 women reported isoflavone supplement use.

Dietary soy and isoflavone intake according to demographic, lifestyle, and clinical factors

Both breast cancer survivors and cancer-free women who were older tended to consume more soy and isoflavone than younger women (**Table 4**). Women with a lower BMI, higher physical activity level, or a higher score for adherence to the ACS dietary guidelines were more likely to consume soy and/or isoflavones among women both with and without breast cancer. Among cancer-free women, those who had never smoked, dietary supplement users, those with higher education levels, and those who were married/cohabiting were more likely to consume soy and/or isoflavones. Among breast cancer survivors, dietary soy and isoflavone intakes did not vary significantly by smoking status, education level, marital status, or menopausal status. When we examined dietary intakes of soy and isoflavones based on clinical characteristics, no significant differences were observed in relation to time since surgery, cancer stage, menopausal status at diagnosis, hormone receptor status, or hormone therapy use (**Table 5**).

DISCUSSION

In this study, estimated isoflavone intakes were higher among breast cancer survivors than among age-matched cancer-free women. The major food sources of isoflavone intake were soy foods, including tofu and soybeans, in both groups. Healthy lifestyle factors, including

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Table 4. Age-adjusted LSmeans of soy and isoflavone intakes among breast cancer survivors and cancer-free women according to their characteristics

Characteristics	Breast cancer survivors (n = 981)					Cancer-free women (n = 2,943)				
	No. (%)	Soy intake (g/1,000 kcal/day)		Isoflavone intake (mg/1,000 kcal/day)		No. (%)	Soy intake (g/1,000 kcal/day)		Isoflavone intake (mg/1,000 kcal/day)	
		Soy foods	Soy protein	KFDB	Phenol-Explorer		Soy foods	Soy protein	KFDB	Phenol-Explorer
Age (yrs)										
21–39	53 (5.4)	25.34 ± 1.11	2.92 ± 1.08	7.28 ± 1.10	6.72 ± 1.13	159 (5.4)	23.06 ± 1.05	2.30 ± 1.03	7.29 ± 1.04	6.66 ± 1.04
40–49	321 (32.7)	33.00 ± 1.04	3.65 ± 1.03	9.81 ± 1.04	9.41 ± 1.05	963 (32.7)	26.39 ± 1.02	2.75 ± 1.01	8.50 ± 1.02	8.17 ± 1.02
50–59	444 (45.3)	33.95 ± 1.04	4.05 ± 1.03	10.54 ± 1.03	11.21 ± 1.04	1,332 (45.3)	29.75 ± 1.02	3.17 ± 1.01	9.60 ± 1.01	9.58 ± 1.01
60–64	95 (9.7)	39.95 ± 1.08	4.81 ± 1.06	12.40 ± 1.07	14.32 ± 1.10	489 (16.6)	27.21 ± 1.03	3.17 ± 1.02	8.99 ± 1.02	10.05 ± 1.02
≥ 65	68 (6.9)	40.07 ± 1.09	4.75 ± 1.07	12.22 ± 1.09	14.38 ± 1.12	-[1)]	-	-	-	-
P for trend		< 0.001	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	< 0.001
BMI (kg/m²)										
< 23	515 (52.6)	35.68 ± 1.03	4.14 ± 1.02	10.89 ± 1.03	11.30 ± 1.04	1,315 (44.7)	28.53 ± 1.02	3.02 ± 1.01	9.15 ± 1.01	9.11 ± 1.01
23–24.9	241 (24.6)	34.71 ± 1.05	3.96 ± 1.04	10.36 ± 1.05	10.77 ± 1.06	701 (23.8)	28.57 ± 1.02	3.02 ± 1.01	9.23 ± 1.02	9.20 ± 1.02
≥ 25	223 (22.8)	29.64 ± 1.05	3.56 ± 1.04	9.20 ± 1.05	9.47 ± 1.06	925 (31.5)	26.25 ± 1.02	2.88 ± 1.01	8.60 ± 1.02	8.67 ± 1.02
P for trend		0.004	0.008	0.008	0.033		0.003	0.026	0.009	0.034
Vigorous physical activity (h/week)										
None	515 (52.5)	32.68 ± 1.03	3.83 ± 1.02	10.06 ± 1.03	10.37 ± 1.04	2,416 (82.2)	27.23 ± 1.01	2.93 ± 1.01	8.87 ± 1.01	8.88 ± 1.01
< Median	235 (24.0)	34.12 ± 1.05	3.89 ± 1.04	10.25 ± 1.05	10.61 ± 1.06	261 (8.9)	30.58 ± 1.04	3.14 ± 1.02	9.51 ± 1.03	9.51 ± 1.03
≥ Median	231 (23.6)	37.13 ± 1.05	4.34 ± 1.04	11.20 ± 1.05	11.78 ± 1.06	262 (8.9)	30.60 ± 1.04	3.19 ± 1.02	9.72 ± 1.03	9.57 ± 1.03
P for trend		0.035	0.021	0.077	0.104		0.002	0.003	0.004	0.014
ACS dietary guidelines (adherence scores)										
Quartile1	184 (18.8)	24.65 ± 1.06	2.57 ± 1.04	7.14 ± 1.05	5.88 ± 1.07	965 (32.8)	27.28 ± 1.02	2.62 ± 1.01	8.74 ± 1.02	7.26 ± 1.01
Quartile2	303 (30.9)	33.61 ± 1.04	3.73 ± 1.03	9.93 ± 1.04	9.84 ± 1.05	584 (19.8)	29.00 ± 1.03	3.06 ± 1.01	9.28 ± 1.02	9.15 ± 1.02
Quartile3	306 (31.2)	36.94 ± 1.04	4.59 ± 1.03	11.58 ± 1.04	13.59 ± 1.05	603 (20.5)	28.72 ± 1.03	3.17 ± 1.01	9.30 ± 1.02	9.96 ± 1.02
Quartile4	188 (19.2)	41.55 ± 1.05	5.08 ± 1.04	13.21 ± 1.05	14.84 ± 1.07	791 (26.9)	26.90 ± 1.02	3.23 ± 1.01	8.88 ± 1.02	10.6 ± 1.02
P for trend		< 0.001	< 0.001	< 0.001	< 0.001		0.734	< 0.001	0.473	< 0.001
Smoking status										
Never	860 (93.2)	34.32 ± 1.03	4.00 ± 1.02	10.43 ± 1.02	10.95 ± 1.03	2,701 (92.1)	27.97 ± 1.01	2.99 ± 1.01	9.04 ± 1.01	9.07 ± 1.01
Ever	63 (6.8)	33.79 ± 1.10	3.91 ± 1.07	10.33 ± 1.09	10.79 ± 1.12	231 (7.9)	26.38 ± 1.04	2.79 ± 1.02	8.57 ± 1.03	8.20 ± 1.03
P-value		0.877	0.776	0.924	0.904		0.188	0.035	0.145	0.005
Dietary supplement use										
No	361 (37.2)	34.05 ± 1.04	3.96 ± 1.03	10.60 ± 1.04	10.62 ± 1.05	1,271 (43.2)	25.93 ± 1.02	2.84 ± 1.01	8.56 ± 1.01	8.60 ± 1.01
Yes	610 (62.8)	34.14 ± 1.03	3.97 ± 1.02	10.26 ± 1.03	10.86 ± 1.04	1,672 (56.8)	29.31 ± 1.02	3.08 ± 1.01	9.34 ± 1.01	9.29 ± 1.01
P-value		0.960	0.956	0.526	0.729		< 0.001	< 0.001	< 0.001	< 0.001
Education level										
Elementary school or below	89 (9.1)	33.54 ± 1.09	3.93 ± 1.06	10.08 ± 1.08	10.07 ± 1.11	556 (18.9)	26.32 ± 1.03	2.96 ± 1.02	8.81 ± 1.02	9.00 ± 1.02
Middle school	88 (9.0)	41.15 ± 1.08	4.72 ± 1.06	12.31 ± 1.08	13.89 ± 1.10	454 (15.5)	26.20 ± 1.03	2.89 ± 1.02	8.63 ± 1.02	8.75 ± 1.02
High school	469 (48.2)	33.48 ± 1.03	3.87 ± 1.03	10.11 ± 1.03	10.45 ± 1.04	1,193 (40.6)	28.73 ± 1.02	3.03 ± 1.01	9.23 ± 1.01	9.15 ± 1.01
College or above	328 (33.7)	33.35 ± 1.04	3.93 ± 1.03	10.37 ± 1.04	10.69 ± 1.05	736 (25.0)	28.50 ± 1.02	2.94 ± 1.01	8.98 ± 1.02	8.87 ± 1.02
P for trend		0.376	0.431	0.676	0.682		0.016	0.821	0.290	0.946
Marital status										
Unmarried	59 (6.1)	37.50 ± 1.10	4.57 ± 1.07	12.09 ± 1.10	12.59 ± 1.13	76 (2.6)	26.18 ± 1.08	2.92 ± 1.04	8.45 ± 1.06	8.84 ± 1.06
Married/ cohabiting	787 (80.7)	33.74 ± 1.03	3.90 ± 1.02	10.25 ± 1.03	10.59 ± 1.03	2,477 (84.3)	27.82 ± 1.01	2.99 ± 1.01	9.05 ± 1.01	9.09 ± 1.01
Divorced/ widowed/ separated	129 (13.2)	34.40 ± 1.07	4.07 ± 1.05	10.40 ± 1.06	10.98 ± 1.08	386 (13.1)	28.05 ± 1.03	2.88 ± 1.02	8.77 ± 1.03	8.44 ± 1.02
P-value		0.586	0.199	0.283	0.423		0.714	0.336	0.331	0.032
Menopausal status at enrollment										
Premenopause	140 (14.3)	30.90 ± 1.07	3.80 ± 1.05	9.93 ± 1.07	10.31 ± 1.09	1,276 (43.5)	26.89 ± 1.02	2.90 ± 1.01	8.77 ± 1.02	8.87 ± 1.02
Induced menopause	485 (49.6)	34.45 ± 1.04	3.98 ± 1.03	10.34 ± 1.03	10.70 ± 1.04	262 (8.9)	29.66 ± 1.04	3.07 ± 1.02	9.37 ± 1.03	9.20 ± 1.03
Natural menopause	353 (36.1)	34.56 ± 1.05	3.98 ± 1.03	10.51 ± 1.04	10.93 ± 1.06	1,399 (47.6)	28.29 ± 1.02	3.02 ± 1.01	9.12 ± 1.02	9.06 ± 1.02
P-value		0.378	0.803	0.843	0.900		0.131	0.233	0.239	0.622

Values are presented as LSmeans ± SE. Model adjusted for age (yrs), except for the associations between age group and soy and isoflavone intakes.
LSmeans, least-squares means; KFDB, flavonoid database of common Korean foods; BMI, body mass index; ACS, American Cancer Society.
[1)]Food frequency questionnaires were not administered for adults aged 65 or more in the Korea National Health and Nutrition Examination Survey.

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Table 5. Age-adjusted LSmeans of soy and isoflavone intakes among breast cancer survivors according to clinical characteristics

Characteristics	No. (%)	Soy intake (g/1,000 kcal/day)		Isoflavone intake (mg/1,000 kcal/day)	
		Soy foods	Soy protein	KFDB	Phenol-Explorer
Time since surgery (yrs)					
0.5 to < 1	44 (4.5)	36.70 ± 1.12	4.30 ± 1.09	10.66 ± 1.11	10.82 ± 1.15
1 to < 2	338 (34.9)	34.89 ± 1.04	4.08 ± 1.03	10.71 ± 1.04	11.31 ± 1.05
2 to < 5	369 (38.0)	33.81 ± 1.04	3.92 ± 1.03	10.25 ± 1.04	10.71 ± 1.05
≥ 5	219 (22.6)	32.15 ± 1.05	3.77 ± 1.04	9.87 ± 1.05	9.93 ± 1.06
P for trend		0.176	0.135	0.227	0.153
AJCC stage					
0	28 (2.9)	40.34 ± 1.15	4.77 ± 1.11	12.16 ± 1.14	14.04 ± 1.19
I	451 (46.8)	33.98 ± 1.04	3.93 ± 1.03	10.38 ± 1.03	10.47 ± 1.04
II	373 (38.7)	34.09 ± 1.04	3.98 ± 1.03	10.40 ± 1.04	11.12 ± 1.05
III–IV	112 (11.6)	34.36 ± 1.07	4.07 ± 1.05	10.34 ± 1.07	10.64 ± 1.09
P for trend		0.749	0.915	0.671	0.942
Menopausal status at diagnosis					
Premenopause	618 (63.1)	34.54 ± 1.03	3.97 ± 1.03	10.36 ± 1.03	10.71 ± 1.04
Postmenopause	361 (36.9)	32.9 ± 1.05	3.92 ± 1.04	10.29 ± 1.05	10.72 ± 1.06
P-value		0.469	0.818	0.927	0.989
PR status					
Negative	348 (36.0)	33.67 ± 1.04	3.92 ± 1.03	10.19 ± 1.04	10.66 ± 1.05
Positive	618 (64.0)	34.24 ± 1.03	3.99 ± 1.02	10.45 ± 1.03	10.81 ± 1.04
P-value		0.744	0.723	0.629	0.840
ER status					
Negative	244 (25.2)	33.30 ± 1.05	3.81 ± 1.04	10.02 ± 1.05	10.16 ± 1.06
Positive	723 (74.8)	34.27 ± 1.03	4.02 ± 1.02	10.47 ± 1.03	10.97 ± 1.03
P-value		0.609	0.280	0.437	0.302
Among ER-positive					
Current hormone therapy use					
No	120 (16.8)	31.84 ± 1.07	3.89 ± 1.05	10.44 ± 1.07	10.56 ± 1.09
Yes	596 (83.2)	34.45 ± 1.03	4.01 ± 1.02	10.37 ± 1.03	10.90 ± 1.04
P-value		0.320	0.680	0.931	0.755
Type of hormone therapy					
SERMs only	355 (59.6)	36.25 ± 1.04	4.13 ± 1.03	10.84 ± 1.04	11.22 ± 1.05
AIs only	219 (36.7)	31.56 ± 1.06	3.80 ± 1.04	9.62 ± 1.06	10.29 ± 1.07
Others	22 (3.7)	30.97 ± 1.18	3.47 ± 1.13	8.90 ± 1.17	9.09 ± 1.22
P-value		0.148	0.263	0.179	0.464
Radiation therapy					
No	385 (39.6)	32.35 ± 1.04	3.75 ± 1.03	9.92 ± 1.04	10.17 ± 1.05
Yes	588 (60.4)	35.11 ± 1.03	4.11 ± 1.02	10.64 ± 1.03	11.15 ± 1.04
P-value		0.102	0.042	0.162	0.156
Chemotherapy					
No	247 (25.4)	33.00 ± 1.05	3.90 ± 1.04	10.20 ± 1.05	10.45 ± 1.06
Yes	726 (74.6)	34.34 ± 1.03	3.98 ± 1.02	10.41 ± 1.03	10.86 ± 1.03
P-value		0.479	0.675	0.719	0.607

Values are presented as LSmeans ± SE.
LSmeans, least-squares means; KFDB, flavonoid database of common Korean foods; AJCC, American Joint Committee on Cancer; PR, progesterone receptor; ER, estrogen receptor; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors.

a normal BMI, higher physical activity levels, and higher adherence to the ACS dietary guidelines, were associated with higher intakes of soy and/or isoflavones in both breast cancer survivors and cancer-free women. Isoflavone intake did not differ based on hormone receptor status or the type of adjuvant hormonal therapy.

According to a previous review article, the mean daily isoflavone intake among Asian women, including Korean women, ranged from 6.3 mg/day to 54.3 mg/day [28]. Isoflavone intake was found to be lower in the Western populations than in the Asian populations; the mean isoflavone intake was 0.9 mg/day in US women [15] and 1.4 mg/day in women from 10 European countries [29]. We estimated dietary isoflavone intakes using the KFDB and the

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Phenol-Explorer database and found the values from these 2 sources to be highly correlated and similar in both breast cancer survivors and cancer-free women. The mean isoflavone intake based on the KFDB (daidzein, genistein, and glycitein) among cancer-free women (17.81 mg/day) in our study was similar to that reported in a previous study that used the same database to estimate isoflavone intake (daidzein and genistein) among 5,259 Korean women aged ≥ 40 yrs without chronic diseases (15.3 mg/day) [30]. Although isoflavone intake was higher among breast cancer survivors than among cancer-free women, the estimated value was within the range reported in previous studies conducted in Korea (15–47 mg/day) [30-35].

Only a few Korean studies that assessed isoflavone intake among breast cancer patients [36-38] showed relatively lower isoflavone intake than that reported in our study. In a previous study that found no significant association between isoflavone intake and the risk of breast cancer recurrence among 339 newly diagnosed Korean breast cancer patients, the mean isoflavone intake ranged from 12.4 mg/day to 14.3 mg/day according to the breast cancer subtype [37]. A Korean case-control study found a significant inverse association between isoflavone intake and the risk of breast cancer among postmenopausal women; the mean dietary isoflavone intake was 13.7 mg/day among 358 breast cancer patients and 16.2 mg/day among 360 controls [36].

Asian breast cancer survivors generally had higher isoflavone intakes than non-Asian breast cancer survivors in Western countries. In a study that assessed prediagnostic (n = 4,769) or postdiagnostic (n = 1,466) isoflavone intake among breast cancer survivors from the Breast Cancer Family Registry (BCFR) in the US and Canada, the mean isoflavone intake was higher among the Asian American group (6.1 mg/day; n = 690) than among the other racial/ethnic groups (1.3 mg/day; n = 5,545) [39]. In a US cross-sectional study of 192 Chinese-American and 173 non-Hispanic white breast cancer survivors, the proportions of women who did not consume isoflavone (soy foods) were 16% for Chinese-American women and 42% for non-Hispanic white women [40]. In previous studies that assessed postdiagnostic isoflavone intake among Chinese breast cancer survivors, isoflavone intakes were higher than those in Western populations and remained stable over time [41-43]. For example, in the Hong Kong NTEC-KWC Breast Cancer Survival Study, the mean isoflavone intakes at 18, 36, and 60 mon after breast cancer diagnosis were 7.1 mg/day (n = 1,307), 7.2 mg/day (n = 1,157), and 7.2 mg/day (n = 1,171), respectively [41]. In that study, the proportion of isoflavone supplement users was only 0.1% at both 18 and 60 mon after diagnosis. In studies of US breast cancer survivors, predominantly non-Hispanic white, the mean isoflavone intakes after breast cancer diagnosis were 2.6 mg/day in the Women's Healthy Eating and Living (WHEL) Study (n = 2,729) and 4.1 mg/day in the Life After Cancer Epidemiology (LACE) Study (n = 1,929) [11]. The proportions of isoflavone supplement users were 2.1% in the WHEL study [44] and 2.7% in the LACE study [45].

There is a possible explanation for the higher isoflavone intake among breast cancer survivors compared to cancer-free women. Cancer survivors are often highly motivated to change their lifestyle, including an increased consumption of fruits and vegetables [46,47]. Soy consumption may coincide with a healthy diet and lifestyle among breast cancer survivors, as observed in our study.

Our study results suggested that healthy lifestyle factors may be associated with dietary soy and isoflavone intake. Consistent with our study, in age- and energy-adjusted models, middle-aged Korean women with higher isoflavone intake were more likely to engage in exercise, have higher Diet Quality Index scores, and were less likely to smoke [30]. In the KNHANES 2008–2011, isoflavone density intake was inversely associated with BMI and waist circumference among 13,847 Korean women [48]. Few studies have presented the characteristics of breast cancer survivors according to their dietary isoflavone intake. In the ABCPP, US and Chinese breast cancer survivors with higher isoflavone intakes tended to engage in physical activity and consume more cruciferous vegetables [11]. In that study, US breast cancer survivors with higher isoflavone intakes tended to have a lower BMI and higher levels of education and be less likely to smoke, whereas Chinese breast cancer survivors with higher isoflavone intakes tended to have a higher BMI. Among breast cancer survivors enrolled in the BCFR, women with higher isoflavone intake were more likely to have a lower BMI, engage in higher levels of physical activity, attain higher education, have higher Healthy Eating Index scores, and were less likely to smoke [39]. In our study, older women tended to consume more isoflavones. A similar trend was observed in previous studies in Korea [34] and Japan [28].

We assessed dietary isoflavone intake among breast cancer survivors at a median of 2.6 yrs after diagnosis. Evidence on the effects of postdiagnostic isoflavone exposure on breast cancer prognosis remains limited and controversial [11,43]. Specifically, *in vitro* and *in vivo* studies have suggested both the anticancer and cancer-promoting potential of isoflavones [8-10]. Thus, the interaction between isoflavone intake and tamoxifen therapy may be of interest. Although our study did not observe a difference in isoflavone intake by hormone therapy use or by type, including tamoxifen, further large studies are warranted in populations with high isoflavone intake.

To our knowledge, this is the first study to assess postdiagnostic isoflavone intake among Korean breast cancer survivors from multiple hospitals, with a comparison with age-matched cancer-free women. This study provides robust findings using 2 databases of isoflavones. Consistent results were also found for soy foods, the major sources identified in both databases, and the protein intake derived from them. Additionally, we investigated whether isoflavone intake differs according to various clinical information, including menopausal status at diagnosis and the use of hormone therapy.

There are some limitations in our study. Our study participants were not from a nested population in a single cohort. However, food sources of isoflavone intake and factors associated with isoflavone intake were similar between breast cancer survivors and cancer-free women, suggesting no substantial heterogeneity. Food intakes were assessed using 3-DFRs or FFQs, both of which may provide estimates of usual intake. Although the dietary assessment tools differ in their time frames and the range of food items assessed, the FFQ items were based on the previously collected 3-DFRs, and soy foods—the main sources of isoflavones—were adequately captured, with estimated isoflavones values within the range of previous Korean studies. Furthermore, when we restricted our analyses to breast cancer survivors with FFQ data and their matched cancer-free women, the results were similar to those of the main analysis. However, we cannot rule out the possibility of non-systematic measurement error in the dietary assessment.

In conclusion, breast cancer survivors were more likely to consume isoflavones than cancer-free women, with an estimated mean intake of 23.59 mg/day among breast cancer survivors. Dietary isoflavone intake was associated with a healthy diet, physical activity, and a lower BMI in both breast cancer survivors and cancer-free women. The relatively higher intake of soy and isoflavones among breast cancer survivors, compared to cancer-free women, may be attributed to lifestyle changes following diagnosis. Further research is warranted to elucidate the long-term effects of this relatively higher isoflavone intake along with healthy behaviors on breast cancer prognosis.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Characteristics of breast cancer survivors and cancer-free women who were matched by exact age (< 65 yrs)

Supplementary Table 2

Soy and isoflavone intakes among breast cancer survivors and cancer-free women who were matched by exact age (< 65 yrs)

Supplementary Table 3

Soy and isoflavone intakes among breast cancer survivors who completed the food frequency questionnaires and matched cancer-free women

Supplementary Table 4

Soy and isoflavone intakes among breast cancer survivors who enrolled between 2012 and 2016 and matched cancer-free women

Supplementary Table 5

Age-adjusted LSmeans of isoflavone intake among breast cancer survivors and cancer-free women, stratified by other factors

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