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EPIDEMIOLOGY

Isoflavone intake on the risk of overall breast cancer and molecular subtypes in women at high risk for hereditary breast cancer

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Abstract

Purpose We investigated the association between isoflavone (ISF) intake and hereditary breast cancer (BC) risk, particularly by molecular subtype, in East-Asian *BRCA1/2* mutation carriers and non-carriers at a high risk of hereditary breast cancer (i.e., family history of BC (FHBC) and early-onset BC [EOBC, age < 40 years]).

Methods The association between ISF intake and BC risk by molecular subtypes was assessed in 1709 participants (407 *BRCA1/2* carriers, 585 FHBC non-carriers, 586 EOBC non-carriers, and 131 unaffected non-carriers) from the Korean Hereditary Breast Cancer Study using hazard ratios (HRs) and 95% confidence intervals (CIs) in weighted Cox regression models. Daily ISF intake was assessed using a validated food frequency questionnaire. We evaluated gene-environment interactions between *BRCA1/2* mutation and ISF intake in 1604 BC cases by calculating the case-only odds ratios (CORs) and 95% CIs in logistic regression models.

Results ISF intake was inversely associated with luminal A BC risk in *BRCA2* mutation carriers and FHBC non-carriers (HR = 0.14, 95% CI = 0.04–0.50 for high intake [ISF intake ≥ 15.50 mg/day]; HR = 0.27, 95% CI = 0.11–0.69 for high intake, respectively). We observed a reduced risk of triple negative BC (TNBC) in *BRCA1* carriers and FHBC non-carriers (HR = 0.09, 95% CI = 0.02–0.40 for high intake; HR = 0.19, 95% CI = 0.05–0.69 for high intake, respectively). In the case-only design, an interaction between *BRCA1* mutation carrier status and ISF intake emerged in TNBC patients (COR = 0.39, 95% CI = 0.16–0.95).

Conclusions This study suggests that ISF intake is inversely associated with BC risk in women at high risk of hereditary BC and that the effect could differ by molecular subtypes.

Keywords Hereditary breast cancer syndrome · Familial breast cancer · *BRCA* mutation · Isoflavones · Soy · Molecular subtypes

Abbreviations

BC	Breast cancer
COR	Case-only odds ratio
EOBC	Early-onset breast cancer
ER	Estrogen receptor
FFQ	Food frequency questionnaire
FHBC	Family history of breast cancer
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
IKK	IkB kinase
ISF	Isoflavone
KOHBRA	Korean Hereditary Breast Cancer Study
NF-kB	Nuclear factor kappa B
PR	Progesterone receptor

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Introduction

Breast cancer (BC) is a heterogeneous disease with a varying risk of disease progression and therapeutic resistance. Approximately 5%–10% of BC cases are hereditary and are classified into high risk BC groups. Furthermore, 25%–40% of these hereditary BC cases can be attributed to the BC

susceptibility genes, *BRCA1* and *BRCA2* [1]. Non-*BRCA* mutated BC accounting for the majority of hereditary BC cases, exhibits distinct differences from sporadic BC in the general population in terms of clinical features, molecular biology, and outcomes [2]. Such genes and prevention targets of associated mutations will likely play a critical role in preventing hereditary BC in the future. Previous studies have found a higher incidence of *BRCA1/2*-associated BC in carriers in more recent birth cohorts [3, 4], suggesting that non-genetic factors may modify the inherited risk of *BRCA* -mutated BC. Further studies of probable non-surgical factors associated with BC risk will help in developing preventive strategies for high-risk women who would consider a prophylactic mastectomy as a preventive intervention.

Many studies have substantiated the protective effect of soy-derived isoflavones (ISFs) on BC risk in the general population—particularly in the Asian population because soy foods are common in traditional Asian foods [5–10]. Soy-based foods contain high ISF concentrations, including mainly genistein and daidzein, and these have a similar structure to estradiol. Previous experimental studies have reported the potential biological mechanisms of the anti-carcinogenic effects of ISFs in the context of BC, including the regulation of estrogenic effects, apoptosis, cell proliferation and survival, inhibition of angiogenesis, and antioxidant effects [11]. However, whether ISF intake has a similar effect on BC patients with a high familial risk remains unclear. Our preliminary study suggested an inverse association between soy product consumption and the risk of hereditary BC in the Korean Hereditary BC (KOHBRA) study [12]. However, this study assessed the protective effect of soy intake only by counting the number of soy products consumed more than once a week (0–1, 2, 3, and 4–5 soy products), which has limited utility in demonstrating the effect of ISFs as a putative chemopreventive agent on BC risk. Furthermore, it did not consider this association by BC molecular subtype.

Thus, we aimed to investigate the association between ISF intake and BC risk in women at high risk of hereditary BC, such as *BRCA1/2* mutation carriers and non-carriers meeting the high risk criteria of *BRCA* mutations, including non-carriers with a BC family history (FHBC non-carriers) and non-carriers with early-onset BC (EOBC non-carriers, diagnosed with BC before age 40), particularly by BC molecular subtypes.

Participants and methods

Study population and design

The KOHBRA study is a nationwide, multicenter cohort study that was conducted from 2007 to 2014 to estimate the prevalence of *BRCA1/2* mutations among women at high risk of hereditary BC, and to identify clinical characteristics and prognostic factors of *BRCA1/2*-related BC. The eligibility criteria for participation were the following: familial BC patients with first- or second-degree relatives and non-familial BC patients at a high risk of hereditary BC, such as male BC, early-onset BC, bilateral BC patients, or BC patients with another primary malignancy. Patients underwent genetic testing for *BRCA* mutations—those who were positive were advised to recruit family members who were at least 20 years old and who agreed to participate in the study. The details of the KOHBRA study are described elsewhere [13].

Of the 2962 KOHBRA participants at baseline, our study only included females ($n=2810$) (Fig. 1). We excluded subjects with no information on the date of genetic testing or interview ($n=157$). We also excluded participants with ovarian cancer or first- or second-degree relatives with ovarian cancer for the analysis in *BRCA* non-carriers ($n=213$), those with insufficient dietary information collected using a food frequency questionnaire (FFQ) during the interview ($n=96$), 484 affected participants who participated in the study more than six months after BC diagnosis, and 151 affected non-carriers older than 40 years who did not have a family history of BC. Finally, we included 1709 cohort participants: 407 *BRCA1/2* mutation carriers (153 *BRCA1* mutation carriers and 254 *BRCA2* mutation carriers) and 1302 non-carriers (585 FHBC non-carriers, 586 EOBC non-carriers, and 131 unaffected non-carriers).

Data collection and definition

Data on general lifestyle, reproductive factors, family history of malignancies, and diet were collected using a structured questionnaire. Dietary information was collected using a semi-quantitative FFQ that was developed and validated for the Korean Genome Epidemiology Study [14, 15]. The FFQ included 103 food items to assess the usual dietary intake during the 12 months prior to enrollment in the KOHBRA study. The frequency of intake of each food item was classified into nine levels: “never or little”, “once a month”, “two to three times a month”, “one to two times a week”, “three to four times a week”, “five to six times a week”, “once a day”, “twice a day”, and “three times or more a day”. The portion size of each food was classified as “less than standard”, “standard”, and “more than standard”. The daily ISF intake was estimated by multiplying the frequency of consumption of each food, the portion size, and the ISF content obtained from the standardized food and nutrient composition database published by the Korean Nutrition Society [16]; the intake was summed across all food items. We grouped the participants into three groups, with the optimal ISF intake cut-points determined using a restricted spline survival analysis [17]: low intake, 0–7.99 mg/day; intermediate intake,

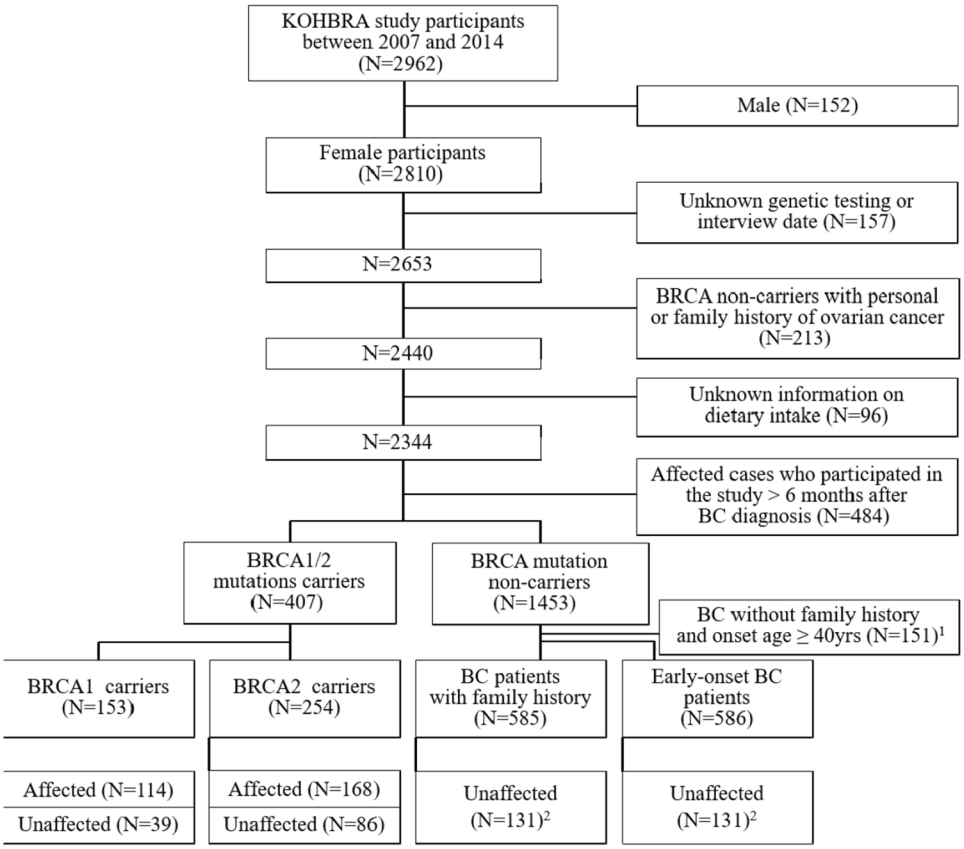

Fig. 1 Flow chart of study subjects selection in the Korean Hereditary BC Study, 2007–2014. [1]These patients were used in the case-only gene-environment interaction study. [2]Same unaffected non-carriers were used in comparing with both of BC patients with family history and early-onset BC patients. *BC* Breast cancer

8.00–15.49 mg/day; and high intake, ≥ 15.50 mg/day. Clinical information regarding patient characteristics, diagnosis, and treatment was collected from a medical record review. Molecular subtypes of BC were defined by the 2011 St. Gallen Consensus based on immunohistochemistry results for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 and the FISH results for HER2: luminal A (ER+ and/or PR+, and HER2− and low Ki-67), luminal B (ER+ and/or PR+, HER2− and/or high Ki-67), HER2−enriched (ER− and PR− and HER2 +) and triple negative BC (TNBC) (ER− and PR− and HER2−) [18]. According to a population-based case–control study in Korea, the distribution of molecular subtypes of BC in the general population are different from that of women in high risk of hereditary BC, including luminal A (30.8%), luminal B (22.0%), HER2-enriched (11.5%), TNBC (15.9%), and unclassified BC (19.8%) [19].

We collected blood samples at baseline and used them for *BRCA1/2* mutation testing within 24 h of sampling. *BRCA* genetic testing was performed using genomic DNA from peripheral blood via Sanger's sequencing. The *BRCA1/2* mutation carriers were defined as those who had the protein-truncating mutations or the missense mutation on the *BRCA1/2* genes [13]. A review of 14 studies on non-*BRCA* familial BC suggests well-defined criteria, including the following for mutation-negative "*BRCA X*" cases: early-onset diagnosis of BC or having one or more first- or second-degree relatives with BC [20]. According to a recent study addressing tumor heterogeneity between these two traits in non-carriers [21], we defined two separate groups in the same way: non-carriers having one or more first- or second-degree relatives with BC at any age and non-carriers diagnosed with BC before 40 years of age. We confined this study to women with no personal or family history of ovarian cancer because ovarian cancer may have other traits distinct from those two groups.

Retrospective cohort analysis

We conducted a retrospective cohort analysis as an optimal study design to investigate the association between ISF intake and *BRCA1/2*-related BC risk, as shown in previous studies [22, 23]. Because the *BRCA1/2* gene testing guidelines in Korea had not been fully established when the study began, we could not find the number of affected *BRCA1/2* mutation carriers and were unable to collect data on the unaffected carriers for the prospective cohort. Additionally, women determined to contain a *BRCA1/2* mutation may consider preventive measures or lifestyle changes to lower the risk of developing BC, which also complicates a prospective cohort study. In this study, we modeled time to first BC diagnosis from birth, censoring at the age at baseline interview

or genetic testing or at the last follow-up at the end of 2014, whichever occurred first. All participants were unaware that they carried the *BRCA1/2* mutation during the retrospective follow-up. *BRCA1/2* mutation carriers were not randomly selected with respect to BC status. To correct for this potential testing bias, all analyses of the retrospective cohort were conducted using the weighted cohort approach developed by Antoniou et al. because a standard Cox proportional hazard model can lead to a biased estimate of the HR in this study design [24]. This method involves assigning relative weights reflecting their sampling probabilities to all person-years of each study participant. We computed the weights by obtaining the age-specific penetrance of *BRCA1* and *BRCA2* mutations estimated by the meta-analysis of Antoniou et al. for carriers [3] and the age-specific incidence of BC in the Korean population from the Korean Central Cancer Registry in 2010 for non-carriers (Supplemental Table 1).

Statistical analysis

We compared the baseline characteristics for hereditary BC between affected and unaffected participants, using the chi-square test or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. The association between ISF intake and BC risk in women at high risk of hereditary BC across the four groups (*BRCA1/2* mutation carriers, FHBC non-carriers, and EOBC non-carriers) was assessed using a weighted Cox proportional hazards model with age as the timescale by estimating the HRs and 95% CIs. No major violation of the proportional hazard assumption was identified, suggesting that the HRs did not vary with the exposure (ISF intake) over time in a Cox proportional regression model, in which one-year dietary information can be extrapolated to lifetime dietary information. A robust variance–covariance estimation method was used to correct for potential correlations of related individuals from the same family [25]. A dose–response relationship for ISF intake was estimated by entering intake amount as a continuous variable in the model. The weighted Cox proportional regression models were intrinsically stratified for birth cohort groups (< 1963, 1964–1971, 1972–1976, and 1977+), clustered to 154 families to correct for potential within-family correlations in risk factors, and adjusted for marriage, parity, family history of ovarian cancer, alcohol consumption, regular physical activity, and total energy intake.

We assessed the effect of ISF intake on the risk of BC by three major molecular subtypes of BC: luminal A BC, luminal B BC, and TNBC. We have assessed the association with luminal BC by combining luminal A BC and luminal B BC, but could not investigate this association with HER2-overexpressed BC due to the small sample size. We employed a case-only study design to assess potential gene-environment interactions between ISF intake and *BRCA1/2* gene mutations in the affected participants by estimating the case-only odds ratios (CORs) and 95% CIs from multiple logistic regression models, assuming that genetic and environmental factors are independent [26]. Statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Results

We evaluated the effect of ISF consumption on the risk of BC in a cohort of 1709 East-Asian females at high risk of hereditary BC (153/254 *BRCA1/2* carriers, 585 affected FHBC non-carriers, 586 EOBC non-carriers, and 131 unaffected non-carriers). The affected *BRCA2* carriers and FHBC non-carriers were older than the unaffected participants, whereas the EOBC non-carriers were younger than the unaffected non-carriers, as shown in Supplemental Table 2. The proportion of patients with a history of marriage and pregnancy was higher among the affected *BRCA1/2* mutation carriers and affected non-carriers compared to the unaffected non-carriers. A higher proportion of postmenopausal women comprised affected *BRCA2* carriers, whereas a relatively lower proportion of EOBC non-carriers had gone through menopause than unaffected non-carriers.

Among all participants, the ISF intake was significantly associated with a lower risk of BC in *BRCA2* mutation carriers and FHBC non-carriers (Tables 1 and 2) (p-trend < 0.01, HR = 0.23, 95% CI = 0.08–0.68 for high intake [ISF intake ≥ 15.50 mg/day]; p-trend = 0.02, HR = 0.42, 95% CI = 0.19–0.97 for high intake, respectively).

In terms of BC molecular subtypes, ISF intake was inversely associated with the risk of TNBC among *BRCA1* mutation carriers and FHBC non-carriers (p-trend = 0.01, HR = 0.09, 95% CI = 0.02–0.40 for high intake; p-trend = 0.01, HR = 0.19, 95% CI = 0.05–0.69 for high intake, respectively), as shown in Tables 1 and 2 and Fig. 2a. A significant luminal A BC risk reduction according to ISF intake was found in *BRCA2* mutation carriers and FHBC non-carriers (p-trend < 0.01, HR = 0.14, 95% CI = 0.04–0.50 for high intake; p-trend < 0.01, HR = 0.27, 95% CI = 0.11–0.69 for high intake, respectively). Similar inverse trends were shown in both *BRCA1* and *BRCA2* mutation carriers for luminal BC risk in which luminal A BC and luminal B BC were combined. We additionally observed a similar inverse association on HR-negative BC in *BRCA1* carriers and HR-positive BC in *BRCA2* carriers in terms of the expression of HRs (HR = 0.14, 95% CI = 0.03–0.54 for high intake; HR = 0.18, 95% CI = 0.06–0.62 for high intake, respectively) (Fig. 2b; Supplemental Table 3). For the expression of HER2, high ISF intake was also correlated with a lower risk of HER2-negative BC in *BRCA1* carriers, *BRCA2* carriers, and FHBC non-carriers (HR = 0.24, 95%

Table 1 The association between ISF intake and BC risk according to BC molecular subtypes in each *BRCA1* and *BRCA2* mutation carrier group in the Korean Hereditary BC Study, 2007–2014

ISF intake (mg/day)	Total cohorts[a]		*BRCA1* mutation carriers		*BRCA2* mutation carriers	
	BC cases *N*	HR (95% CI)[b]	BC cases *N*	HR (95% CI)[b]	BC cases *N*	HR (95% CI)[b]
Total subjects						
≤7.99	834	1.00	60	1.00	92	1.00
8.00–15.49	478	0.67 (0.38–1.20)	34	0.93 (0.40–2.17)	49	0.58 (0.31–1.11)
15.50+	292	0.52 (0.26–1.03)	20	0.32 (0.09–1.17)	27	0.23 (0.08–0.68)
p-trend		0.04		0.20		< 0.01
Luminal type[c]						
≤7.99	498	1.00	6	1.00	59	1.00
8.00–15.49	274	0.76 (0.43–1.34)	6	1.34 (0.50–3.57)	36	0.79 (0.36–1.64)
15.50+	148	0.47 (0.23–0.95)	5	0.35 (0.01–26.25)	16	0.25 (0.11–0.62)
p-trend		0.02		0.24		0.02
Luminal A type						
≤7.99	351	1.00	4	1.00	40	1.00
8.00–15.49	189	0.61 (0.29–1.31)	5	1.18 (0.17–8.07)	21	0.74 (0.27–2.08)
15.50+	107	0.34 (0.13–0.88)	0	–	9	0.14 (0.04–0.50)
p-trend		0.02		0.90		< 0.01
Luminal B type						
≤7.99	147	1.00	2	1.00	19	1.00
8.00–15.49	85	1.01 (0.42–2.41)	1	2.71 (0.22–34.23)[d]	15	0.85 (0.30–2.44)
15.50+	41	0.69 (0.24–1.98)	5	1.37 (0.12–15.91)[d]	7	0.33 (0.06–1.85)
p-trend		0.56		0.71[d]		0.23
Triple negative						
≤7.99	133	1.00	38	1.00	9	1.00
8.00–15.49	71	0.57 (0.22–1.49)	16	0.73 (0.30–1.78)	6	0.39 (0.08–1.96)
15.50+	53	0.36 (0.12–1.11)	10	0.09 (0.02–0.40)	2	0.12 (0.01–1.76)
p-trend		0.06		0.01		0.13

BC Breast cancer, *ISF* Isoflavone

[a]Total cohort population including *BRCA1/2* carriers and high risk non-carrier group with higher likelihoods of having *BRCA* mutations (such as having family history of breast cancer, ovarian cancer, personal history of past and current ovarian cancer or *BRCA* mutation-related cancers, early-onset breast cancer, past history of stage 0 BC, TNBC, etc.)

[b]Weighted Cox proportional hazards model stratified for birth cohort, clustered on family (154 families), and adjusted for marriage, parity, family history of ovarian cancer, alcohol consumption, regular physical activity and total energy intake. The weights were computed using the equation and penetrance of *BRCA1* and *BRCA2* mutation carriers described by Antoniou et al. [3, 24]. A dose–response relationship for ISF intake was estimated by entering intake amount as a continuous variable in the model

[c]Combining luminal A and luminal B BC

[d]Unadjusted for potential confounders for *BRCA1* mutation carriers due to the small sample size

CI = 0.07–0.90; HR = 0.15, 95% CI = 0.04–0.52; HR = 0.27, 95% CI = 0.11–0.66, respectively).

In a case-only design using 1604 BC cases, high ISF intake was inversely associated with the risk of *BRCA*-related BC (COR = 0.66, 95% CI = 0.44–0.98), particularly with *BRCA*-related TNBC (COR = 0.42, 95% CI = 0.19–0.95), as shown in Table 3. The effect of the interaction between the gene (*BRCA*) and environment (ISF) was persistent in the *BRCA1*-associated TNBC risk (COR = 0.39, 95% CI = 0.16–0.95 for high intake). Because both an inverse association of ISF intake and an interactive effect of ISF intake on *BRCA1*-related BC were identified, we further investigated which sources of ISF could explain this association, as shown in Supplemental Table 4. We found that soy-derived ISF intake could significantly affect *BRCA1*-related TNBC risk compared with ISFs derived from vegetables (HR = 0.47 for soy product intake two to three times per week; HR = 0.17 for soy product intake more than four times per week).

Table 2 The association between ISF intake and BC risk according to BC molecular subtypes in each high- risk group of *BRCA* mutations, such as non-carrier high risk group with BC family history and non-carrier high risk group with early-onset BC in the Korean Hereditary BC Study, 2007–2014

ISF intake (mg/day)	Non-carriers with BC family history		Non-carriers with early-onset BC risk	
	BC cases *N*	HR (95% CI)[a]	BC cases *N*	HR (95% CI)[a]
Total subjects				
≤7.99	286	1.00	321	1.00
8.00–15.49	175	0.54 (0.28–1.05)	183	0.75 (0.28–1.99)
15.50+	124	0.42 (0.19–0.97)	82	0.42 (0.10–1.73)
p-trend		0.02		0.24
Luminal type[b]				
≤7.99	276	1.00	2684	1.00
8.00–15.49	160	0.42 (0.21–0.84)	124	0.70 (0.31–1.55)
15.50+	104	0.33 (0.16–0.67)	62	0.21 (0.06–0.72)
p-trend		< 0.01		< 0.01
Luminal A type				
≤7.99	138	1.00	134	1.00
8.00–15.49	80	0.42 (0.19–0.91)	62	0.61 (0.20–1.79)
15.50+	52	0.27 (0.11–0.69)	31	0.26 (0.05–1.46)
p-trend		< 0.01		0.11
Luminal B type				
≤7.99	44	1.00	64	1.00
8.00–15.49	28	0.43 (0.17–1.09)	35	0.81 (0.25–2.56)
15.50+	18	0.45 (0.15–1.34)	11	0.17 (0.03–1.02)
p-trend		0.13		0.09
Triple negative				
≤7.99	32	1.00	49	1.00
8.00–15.49	18	0.46 (0.16–1.31)	29	0.93 (0.26–3.30)
15.50+	15	0.19 (0.05–0.69)	22	1.66 (0.22–12.88)
p-trend		0.01		0.74

BC Breast cancer, *ISF* isoflavone

[a]Weighted Cox proportional hazards model stratified for birth cohort, clustered on family (154 families), and adjusted for marriage, parity, family history of ovarian cancer, alcohol consumption, regular physical activity and total energy intake. The weights were computed using the equation described by Antoniou et al. and the age-specific incidence of BC from the Korean Central Cancer Registry in 2010 for non-carriers [24]. A dose–response relationship for ISF intake was estimated by entering intake amount as a continuous variable in the model.

[b]Combining luminal A and luminal B BC

Discussion

In this study, a high ISF intake was found to be beneficial for BC risk in *BRCA2* mutation carriers and non-carriers with FHBC in the total population. Since BC is known to have different clinical prognoses depending on the molecular subtype, we wanted to observe whether the preventive effect of ISFs from BC was stronger in certain BC molecular subtypes. In the analysis of BC by molecular subtypes, a high ISF intake was significantly associated with a reduced risk of *BRCA1*-associated TNBC and *BRCA2*-associated luminal A BC. For FHBC non-carriers, a reduced risk of BC was observed with increased ISF intake in both luminal A BC and TNBC. In the case-only analysis, a high ISF intake was negatively associated with the *BRCA* mutation in the overall BC cases, and the presence of a negative interaction was identified with the *BRCA1* mutant gene with respect to TNBC.

The favorable associations between soy food or ISF intake and overall BC risk in Asian women were summarized in two recent meta-analyses [27, 28]. By contrast, ISF intake was not correlated with BC risk in studies conducted in Western women consuming relatively low levels of ISF (median highest ISF intake ≥ 0.8 mg/day). The results of our study for Korean women at high risk of hereditary BC are generally in accordance with epidemiological studies conducted in Asian women.

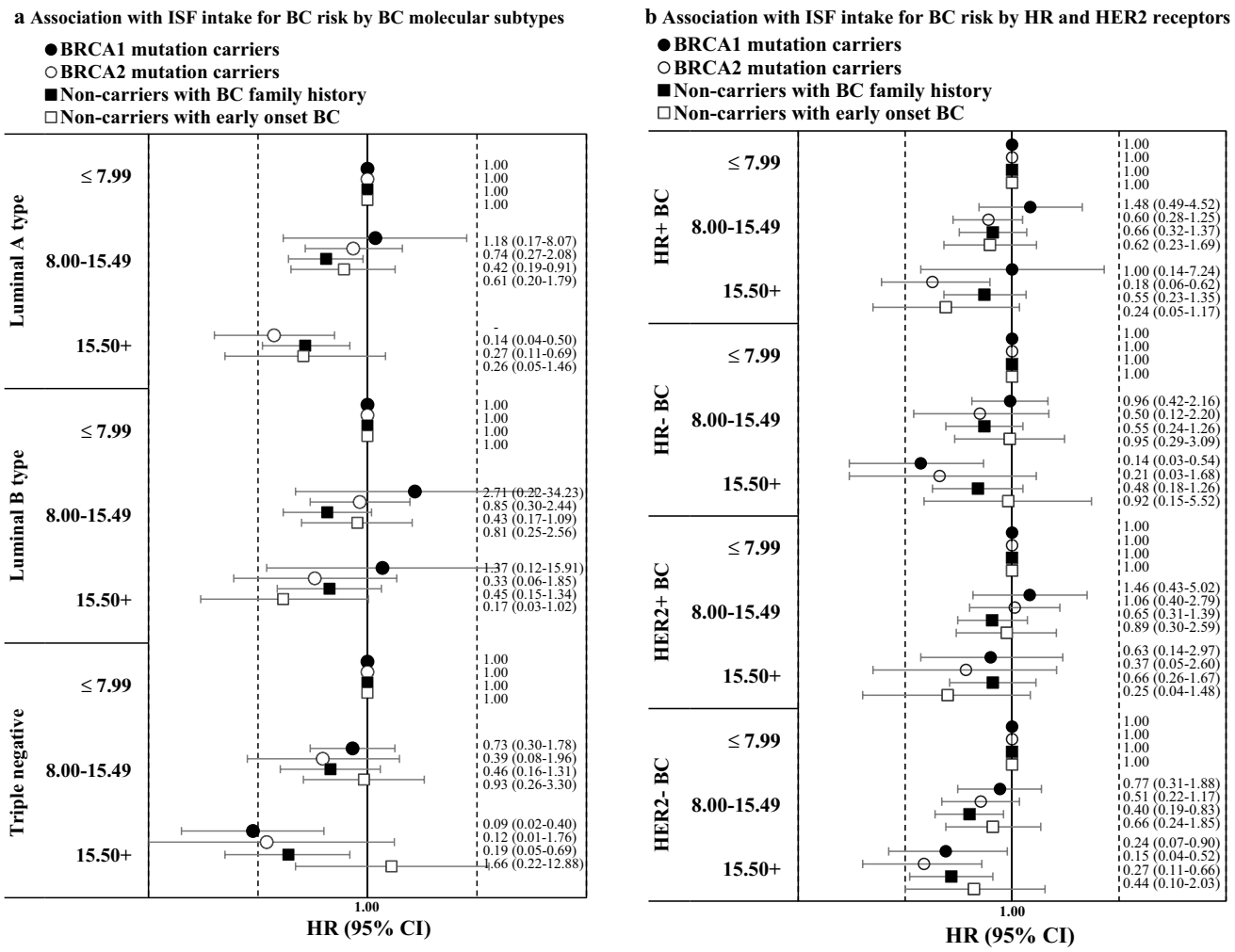

Fig. 2 The association between ISF intake and BC risk according to BC molecular subtypes, and HRs and HER2 status in each group classified by *BRCA1* and *BRCA*2 mutation carriers, and non-carriers with BC family history and early-onset BC in the Korean Hereditary BC Study, 2007–2014

Several epidemiological studies have assessed the association between soy or ISF intake and BC risk stratified by HR and HER2 status in the general population; however, these studies have yielded inconsistent findings. The Shanghai Breast Cancer Study found a greater reduction in risk of BC for ER+/PR+ status than those with other ER/PR status [5]. In other case–control studies, the protective effect of soy products against BC risk was similar across all subtypes of ER/PR status [9, 10, 29]. Two cohort studies also reported similar association across all subtypes of ER/PR status [8, 30]. Among these studies, Baglia et al. observed a significantly decreased risk of ER-/PR- BC only in premenopausal women and that of ER+/PR+ BC only in postmenopausal women [30]. However, another case–control study found no significant association according to HR status [31]. With respect to the HER2 status, in a case–control study in Japan, high levels of intake of soybean products significantly reduced the risk (21%) of HER2-negative BC [6]; however, the cohort study of Baglia et al. found no significant association according to HER2 status [30]. To date, only Suzuki et al. have investigated the impact of intake of soybean products on BC risk according to joint receptor status; they observed a beneficial effect in HER+/HER2− BC (top tertile OR = 0.73, 95% CI = 0.54–0.97). In our study, ISF intake was associated with decreased risk of HR-positive and HR-negative BC; however, the association differed by *BRCA1/2* mutation status and in subgroups of non-carriers who are at high risk of hereditary BC. Our results are, to some extent, inconsistent with the findings from other observational studies conducted in the general population; this may be attributable to the fact that the other studies did not account for the *BRCA1/2* status.

Several biologically plausible mechanisms may explain the protective effect of ISF intake against hereditary BC

Table 3 Gene-Environment interaction in case-only design: The association with ISF intake for the risk of *BRCA* mutations relative to *BRCA* wild-types according to BC molecular subtypes in the Korean Hereditary BC Study, 2007–2014

ISF intake[a] (mg/day)	*BRCA* wild-type	*BRCA* mutation	COR (95% CI)[a]	*BRCA1* mutation	COR (95% CI)[a]	*BRCA2* mutation	COR (95% CI)[a]
Total subjects							
≤7.99	682 (51.6)	152 (53.9)	1.00	60 (52.6)	1.00	92 (54.8)	1.00
8.00–15.49	395 (29.9)	83 (29.4)	0.86 (0.64–1.16)	34 (29.8)	0.84 (0.54–1.31)	49 (29.2)	0.90 (0.62–1.32)
15.50+	245 (18.5)	47 (16.7)	0.66 (0.44–0.98)	20 (17.5)	0.59 (0.32–1.06)	27 (16.1)	0.73 (0.45–1.20)
p-trend			0.04		0.08		0.22
Luminal type[b]							
≤7.99	433 (54.4)	65 (52.4)	1.00	6 (46.1)	1.00	59 (53.2)	1.00
8.00–15.49	232 (29.1)	42 (33.9)	1.08 (0.76–1.68)	6 (46.1)	2.02 (0.66–6.18)	36 (32.4)	1.03 (0.64–1.65)
15.50+	131 (16.5)	17 (13.7)	0.77 (0.31–1.91)	1 (0.8)	1.66 (0.15–18.30)	16 (14.4)	0.82 (0.34–2.00)
p-trend			0.74		0.53		0.98
Luminal A							
≤7.99	307 (54.1)	44 (55.7)	1.00	4 (44.4)	1.00	40 (57.1)	1.00
8.00–15.49	163 (28.7)	26 (32.9)	0.99 (0.58–1.70)	5 (55.6)	2.25 (0.57–8.92)	21 (30.0)	0.87 (0.48–1.55)
15.50+	98 (17.2)	9 (11.4)	0.50 (0.22–1.14)	0 (0.0)	–	9 (12.9)	0.55 (0.24–1.25)
p-trend			0.16		0.74		0.17
Luminal B							
≤7.99	126 (55.3)	21 (46.7)	1.00	2 (50.0)	1.00	19 (46.3)	1.00
8.00–15.49	69 (30.3)	16 (35.5)	1.29 (0.60–2.74)	1 (25.0)	1.64 (0.24–11.16)[c]	15 (36.6)	1.39 (0.63–3.06)
15.50+	33 (14.5)	8 (17.8)	1.28 (0.48–3.45)	1 (25.0)	2.83 (0.39–20.45)[c]	7 (17.1)	1.37 (0.49–3.83)
p-trend			0.53		0.67		0.44
Triple negative							
≤7.99	86 (48.9)	47 (58.0)	1.00	38 (59.4)	1.00	9 (52.9)	1.00
8.00–15.49	49 (27.8)	22 (27.2)	0.76 (0.40–1.45)	16 (25.0)	0.68 (0.33–1.38)	6 (35.3)	1.30 (0.42–3.98)[b]
15.50+	41 (23.3)	12 (14.8)	0.42 (0.19–0.95)	10 (15.6)	0.39 (0.16–0.95)	2 (11.8)	0.67 (0.14–3.16)[b]
p-trend			0.04		0.03		0.25

BC Breast cancer, *COR* case-only odds ratio, *ISF* isoflavone

[a]Logistic regression model adjusted for marriage, parity, alcohol consumption, regular physical activity and total energy intake

[b]Combining luminal A and luminal B BC

[c]Logit estimate by Cochran–Mantel Haenszel test adjusted for marriage, parity, alcohol consumption and regular physical activity, but not for total energy intake due to continuous variable

observed in our study. Soy ISFs have structural similarities to estradiol; previous studies suggest that these may mediate biological phenomenon such as cell proliferation, differentiation, or apoptosis by competitively binding to ERs with endogenous estrogen through the modulation of estrogen-signaling pathways [11]. Other molecular mechanisms of action of ISFs may also explain the protective effect of ISF intake against hereditary BC, particularly HR-independent BC; these include apoptosis induction, anti-proliferative and anti-inflammatory effects, induction of cell cycle arrest via inhibition of the activity of tyrosine protein kinase, mitogen-activated kinase, or DNA topoisomerase II, and inhibition of angiogenesis [11, 32].

In terms of *BRCA1/2* mutation status, the effect of ISF intake on *BRCA1*-mutated TNBC observed in our study is consistent with the results of a previous experimental study in which genistein treatment was shown to inhibit the proliferation and growth of TNBC cells by targeting G

protein-coupled receptor 30 (GPR3), which led to down-regulation of Akt and Cyclin B1 expression in cell cycle progression in the G2/M phase naly the *BRCA1* mutated condition [33]. This particular study also observed similar gene expression in ER-positive *BRCA1* mutant cell lines, although *BRCA1* mutant TNBC cells were apparently more sensitive to genistein, which suggested that ISF intake also plays a role in *BRCA1*-mutated HR-positive BC. However, we could not demonstrate a significant association in our study due to the small sample size. The beneficial effect of ISF intake against *BRCA2*-mutated BC may also be explained by upregulating *BRCA1/2* genes and inducing apoptosis under *BRCA2* knockdown conditions, according to another previous experimental study [34]. Many studies have investigated the biologically plausible nalyzing of the protective effect of ISF against BC; however, the precise molecular mechanisms are yet to be fully elucidated, particularly for hereditary BC related *BRCA1/2* mutation status.

One of the limitations of this study is the relatively small sample size of subgroups according to the presence of *BRCA1/2* mutations and molecular subtypes of BC, which may limit the study power and hamper the generalizability to women at high risk of hereditary BC. We could not obtain significant results for HR-positive *BRCA1* mutant BC and HR-negative *BRCA2*-mutant BC owing to the small sample size due to BC heterogeneity, including the finding that *BRCA1* mutation carriers are closely linked to ER-negative BC and TNBC, whereas *BRCA2* mutated tumors are linked to ER-positive BC [35]. In our cohort, patients with HR-positive *BRCA1* mutated BC accounted for only 17% of all patients with *BRCA1*-mutated BC. Women in Korea have a higher prevalence of *BRCA2* rather than *BRCA1* mutations, which is similar result to that in most Asian countries [36]. Due to its heterogeneity, however, we could not perform combined analyses with *BRCA1/2* mutation carriers and molecular subtypes to increase the statistical power. Further large-scale investigations are required to understand the relation between ISF intake and BC in these groups. To the best of our knowledge, however, no prior epidemiological studies have assessed the potential benefits of ISF against the risk of *BRCA1/2*-mutated BC according to molecular subtypes. Second, the FFQ, used to collect dietary information, reflects only dietary intake in the year before study enrollment. Some of the affected individuals may have modified their dietary behavior after BC diagnosis, which may have caused a temporary bias. To avoid this bias, we excluded BC patients who participated in the study more than six months after their BC diagnosis. Finally, we could not consider equol-producing status in relation to BC risk. Equol, a metabolite of daidzein, is produced differently depending on human intestinal bacteria. Since equol has been reported to bind with greater affinity to the ERβ protein, which may lead to a lower BC risk for equol producers, assessing equol-producing status might contribute to better findings for this study [37]. Our study, however, is one of few observational studies supporting several experimental studies on the association between ISF intake and hereditary BC risk in *BRCA1/2* carriers and high-risk non-carriers. We also examined whether this association would be modified by different types of molecular BC in women at high risk of hereditary BC.

Based on our findings, we propose that high ISF intake in women at high risk of hereditary BC can act as a preventive factor against BC, particularly in *BRCA2*-mutated luminal A type BC and *BRCA1*-mutated TNBC. We also suggest that ISF intake may interact with *BRCA1* mutations to decrease the risk of TNBC for whom the chemotherapeutic regimen has not yet been established. However, our findings warrant further investigation, including large-scale perspective cohort studies and intervention studies, to evaluate the novel preventive or therapeutic approach of ISF intake on developing BC risk to women at high risk of hereditary BC and to clarify the mechanistic interaction by which ISF intake can alter the genetic risk of *BRCA1* mutated genes on TNBC.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedure performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was registered at clinicaltrials.gov as NCT00595348, and approved by the Institutional Review Boards of Seoul National University (IRB number: C-0709–050-219) and all ethics committees of each participating centers.

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