Dietary intake and breast cancer among carriers and noncarriers of *BRCA* mutations in the Korean Hereditary Breast Cancer Study[1–3]

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ABSTRACT

Background: Soy intake is associated with a lower risk of breast cancer. However, it is unclear whether the same reduction in risk associated with high soy intake is also applicable to familial or genetic breast cancer.

Objective: The aim of this study was to assess the dietary factors among carriers and noncarriers of *BRCA* mutations in the Korean Hereditary Breast Cancer Study (KOHBRA).

Design: The KOHBRA Study is an ongoing project composed of affected breast cancer patients and familial members of breast cancer cases with *BRCA* mutations. To assess the association between dietary diversity and breast cancer risk, an HR was estimated by comparing affected subjects with their familial nonaffected members. To assess the interaction between the combination of *BRCA* mutation and diet diversity, the case-only OR (COR) was estimated by comparing *BRCA* mutation carriers and noncarriers only in affected subjects.

Results: Soy product intake was associated with a lower risk of breast cancer in carriers (HR: 0.39; 95% CI: 0.19, 0.79 for the highest quartile). The highest quartile of meat intake was associated with a higher risk of breast cancer regardless of *BRCA* mutation in carriers (HR: 1.97; 95% CI: 1.13, 3.44) and noncarriers (95% CI: 1.41; 1.12, 1.78). The associations of meat intake and soybean intake for breast cancer were more prominent in *BRCA2* mutation carriers. In the analysis with only cases, the highest quartile of soy intake, but not meat intake, was associated with *BRCA*-related breast cancer (COR: 0.57; 95% CI: 0.36, 0.91).

Conclusion: Our study suggests that soy product consumption is associated with lower breast cancer risk and it had an interaction with *BRCA* mutation. This trial was registered at clinicaltrials.gov as NCT00595348. *Am J Clin Nutr* 2013;98:1493–501.

INTRODUCTION

Breast cancer is the most commonly diagnosed female cancer in many parts of the world, including Korea. Approximately 5–10% of breast cancer cases are hereditary and are caused by germline mutations in a gene or genes showing dominant inheritance and moderate to high penetrance; 25–40% of these hereditary breast cancer cases are the result of mutations in 1 of the 2 breast cancer susceptibility genes: *BRCA1* and *BRCA2* (1). For women who carry *BRCA1* mutations, the RR of developing breast cancer can range from 3 to 200 (2). The prevalence of *BRCA* mutations was 24.8% among familial breast cancers in Korea, which was similar to the prevalence of non-Ashkenazi whites (3, 4). However, the *BRCA* mutation rate was 9.4% among nonfamilial breast cancers with high risk in Korea, which was higher than that in other countries, which ranged from 0.8% to 4.4% (3, 5, 6).

Accumulating evidence from epidemiology studies has suggested that several environmental factors are associated with hereditary breast cancer in *BRCA* mutation carriers. Specifically, BMI was associated with *BRCA*-related breast cancer risk, and high diet quality was associated with a low risk of *BRCA*-related breast cancer (7–9). In addition, some studies reported that vegetable and fruit intakes were modifiers in developing breast cancer in *BRCA* mutation carriers (10). However, these findings are limited to Western populations. Data on the associations between lifestyle factors, such as diet and high-risk breast cancer development, in Asian populations are lacking.

The annual incidence rate of breast cancer in Eastern Asia is 25.3 per 100,000, which is lower than that in Western Europe (89.9 per 100,000) and North America (76.7 per 100,000) (11). This difference may be caused by differences in genetics, reproductive factors, lifestyles, and dietary habits. One plausible

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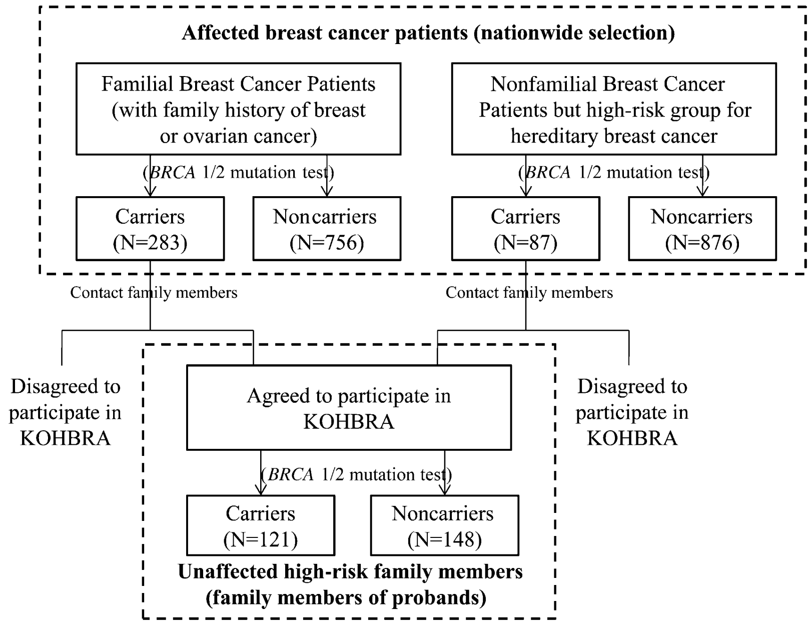

FIGURE 1. Scheme and study population of the KOHBRA Study. KOHBRA, Korean Hereditary Breast Cancer.

explanation for the discrepancies in incidence rates has been linked to high soy intake in Asian populations (12). Experimental and observational studies have suggested that soy intake is associated with a lower risk of developing breast cancer. It is, however, unclear whether the same reduction in risk associated with high soy intake is also applicable to familial or genetic breast cancer. The aim of this study was to assess the risk or preventive effects of dietary factors and modifiers on the development of *BRCA*-related breast cancers in the Korean Hereditary Breast Cancer (KOHBRA)[4] Study.

SUBJECTS AND METHODS

Study population and study design

The study population was obtained from the KOHBRA Study, which is an ongoing large prospective nationwide study in Korea aiming to evaluate the prevalence of *BRCA* mutations and establish a cohort with *BRCA* mutation carriers (**Figure 1**). The KOHBRA Study is described in detail elsewhere (3). Briefly, 40 medical centers have participated in the KOHBRA Study. Subjects aged ≥20 y since 2007 were enrolled in the study based on the following criteria: eligible subjects were familial breast cancer patients (breast cancer patients with a family history of breast cancer in first- and/or second-degree relatives) and nonfamilial breast cancer patients at high risk of hereditary breast cancer such as male breast cancer or early-onset breast cancer patients (diagnosed made at age ≤40 y), breast cancer patients with current or history of bilateral breast cancer, ovarian cancer, or other primary cancer. Genetic testing for a *BRCA* mutation was conducted. When a *BRCA* mutation was identified in a proband, genetic testing was offered to family members who agreed to participate in the KOHBRA Study.

To assess the association between dietary factors and *BRCA*-related breast cancer risk, we used a cohort study design to compare affected breast cancer subjects and their nonaffected familial subjects. Because genetic mutation is a nonmodifiable innate factor and we can follow up a disease onset since birth according to genetic or environmental factors, we analyzed differences in breast cancer risk according to dietary factors through a retrospective analysis based on Cox's regression model, as in previous studies related to breast cancer risk in *BRCA* mutation carriers (13, 14).

To assess the modifiers in the association between dietary diversity and *BRCA*-related breast cancer, we applied a case-only study to compare *BRCA* mutation carriers with non-*BRCA* mutation carriers among affected breast cancer subjects. If it is assumed that the exposure is independent of genotype in the population and that the disease is rare, case-only studies are the simplest and most efficient for estimating gene-environment interactions by evaluating differences in exposure between genotype groups in case subjects only (15). The case-only OR (COR) is a synergy index on a multiplicative scale.

The KOHBRA Study has enrolled 2500 subjects between October 2007 and January 2011. In this study, we excluded men and persons with ovarian cancer, yielding a total of 2271 subjects in our analysis. The study protocol was approved by the institutional review board of each participating center.

Data collection and dietary diversity measurement

Information on the family history of malignancies, general lifestyle, physical activity, reproductive factors, and diet were obtained by using structured questionnaire interviews. Anthropometric measurements and *BRCA* mutation testing were carried out at baseline. Clinical information about diagnosis, treatment, and recurrence were collected through medical record reviews. Blood samples were collected at the baseline, and whole blood, DNA, plasma, and serum samples were stored at −70°C.

[4]Abbreviations used: COR, case-only OR; FFQ, food-frequency questionnaire; KOHBRA, Korean Hereditary Breast Cancer.

Information on diet was collected by using a food-frequency questionnaire (FFQ) developed by the Korean National Institutes of Health. The validation test for FFQ was conducted (16). The FFQ included 103 food items for the assessment of usual dietary intake consumed during the preceding 12 mo. We further classified the food items into 5 groups: vegetables (25 items), fruit (12 items), meats (10 items), seafood (17 items), and soy products (5 items). Within each of the specific food groups, the total intake was calculated by summing up all foods consumed at least once per week.

Statistical analysis

The baseline characteristics and potential risk factors for breast cancer were compared between case subjects and their familial nonaffected subjects by using a chi-square test for categorical variables and a Student's *t* test for continuous variables. The baseline characteristics were compared between breast cancer cases that were either carriers or noncarriers of *BRCA* mutations.

Cox's proportional hazards model was used to assess the association between dietary intake and breast cancer risk in *BRCA* mutation carriers and noncarriers. Also, a stratified analysis was conducted according to *BRCA1* or *BRCA2* mutation, and heterogeneities of dietary effect for breast cancer between *BRCA1* and *BRCA2* mutation were tested by using Cochran's *Q* test. In Cox's proportional hazards model, we assumed that follow-up started at birth and ended at age of diagnosis of first breast cancer. The remaining individuals were censored at the age at interview or last follow-up. To assess the gene-environment interaction for the combination of *BRCA* mutation and dietary diversity in the cases, CORs and 95% CIs were estimated by using multiple logistic regressions for affected subjects. Because the dietary habit could be altered after a breast cancer diagnosis, the analyses were conducted with restricted subjects by excluding cases that participated to the KOHBRA Study >6 mo after a breast cancer diagnosis. All statistical analyses were conducted by using SAS 9.2 software (SAS Institute).

RESULTS

In the KOHBRA Study, the overall prevalence of the *BRCA* mutation was 21.6% (**Table 1**). The prevalence among familial breast cancer patients was 24.7%, and the prevalence among nonfamilial breast cancer patients with high risk was 9.0%. The breast cancer case subjects were older than the unaffected familial members among *BRCA* mutation carriers. Physical activity and history of pregnancy was different between affected breast cancer patients and unaffected subjects. In contrast, the age at menarche, BMI, total energy intake, educational level, smoking status, and alcohol drinking status were not significantly different between the 2 groups. In noncarriers, alcohol drinking history and history of pregnancy were different between affected breast cancer patients and unaffected subjects. Comparison of *BRCA* mutation carriers and noncarriers among affected cases showed that the age at study entry was greater in *BRCA* mutation carriers than in noncarriers ($P = 0.014$).

The association between dietary intake and breast cancer risk is shown in **Table 2**. In *BRCA* mutation carriers, meat consumption was positively associated with breast cancer risk (HR: 1.97; 95% CI: 1.13, 3.44), whereas soy consumption was inversely associated with breast cancer risk (HR: 0.39; 95% CI: 0.19, 0.79). In *BRCA*

TABLE 1
Baseline characteristics of the study subjects in the Korean Hereditary Breast Cancer Study (2007–2011)

Variables	*BRCA1* or *BRCA2* carriers (n = 491)				Noncarriers (n = 1780)				
	Total carriers (n = 491)	Affected breast cancer patients (n = 370)	Unaffected subjects (n = 121)	*P* value[1] (affected vs unaffected)	Total noncarriers (n = 1780)	Breast cancer cases (n = 1632)	Unaffected subjects (n = 148)	*P* value[1] (affected vs unaffected)	*P* value[1] (carriers vs noncarriers)
Age at study entry (y)	42.5 ± 11.5[2]	43.4 ± 10.7	39.7 ± 13.3	0.006	41.9 ± 10.2	41.9 ± 9.8	41.8 ± 14.1	0.891	0.301
Age at diagnosis (y)	—	40.9 ± 9.8	—	—	—	40.4 ± 9.5	—	—	0.871
Age at menarche (y)	14.7 ± 1.8	14.7 ± 1.8	14.8 ± 1.7	0.474	14.5 ± 1.7	14.4 ± 1.6	14.6 ± 2.0	0.299	0.005
BMI (kg/m^2)	22.2 ± 3.3	22.2 ± 3.3	22.0 ± 3.2	0.514	22.4 ± 3.4	22.4 ± 3.4	22.3 ± 3.1	0.658	0.285
Total energy intake (kcal)	1719 ± 870	1726 ± 854	1700 ± 923	0.780	1631 ± 589	1636 ± 583	1592 ± 662	0.439	0.037
Education >12 y [n (%)]	224 (45.8)	164 (44.6)	60 (49.6)	0.336	935 (52.7)	858 (52.7)	77 (52.0)	0.869	0.007
Ever smokers [n (%)]	50 (10.2)	42 (11.4)	8 (6.6)	0.135	150 (8.4)	141 (8.7)	9 (6.1)	0.282	0.225
Ever alcohol drinkers [n (%)]	196 (39.9)	143 (38.6)	53 (43.8)	0.315	680 (38.3)	605 (37.2)	75 (50.7)	0.001	0.517
Regular exercise [n (%)]	186 (37.9)	150 (40.5)	36 (29.8)	0.034	718 (40.4)	662 (40.6)	56 (37.8)	0.514	0.321
History of pregnancy [n (%)]	402 (81.9)	319 (86.2)	83 (69.7)	< 0.001	1443 (80.6)	1327 (81.5)	106 (71.6)	0.003	0.461

[1] *P* values were estimated by using a chi-square test for categorical variables and Student's *t* test for continuous variables.
[2] Mean ± SD (all such values).

TABLE 2
The association between diet diversity and breast cancer risk in the Korean Hereditary Breast Cancer Study (2007–2011)[1]

	Total population			Restricted population[3]		
Dietary diversity (no. of food items[2])	No. of participants	No. of breast cancer cases	HR (95% CI)[4]	No. of participants	No. of breast cancer cases	HR (95% CI)[4]
Carriers						
Total	491	370		273	152	
Vegetables						
Q1 (0–4)	115	83	1.00	75	43	1.00
Q2 (5–8)	148	104	1.01 (0.75, 1.36)	89	45	0.87 (0.55, 1.35)
Q3 (9–12)	100	80	0.88 (0.64, 1.23)	50	30	0.73 (0.44, 1.24)
Q4 (13–25)	128	103	1.02 (0.73, 1.43)	59	34	0.75 (0.43, 1.30)
P-trend			0.899			0.245
Fruit						
Q1 (0–3)	138	91	1.00	82	35	1.00
Q2 (4–6)	101	82	1.19 (0.87, 1.63)	48	29	1.03 (0.61, 1.73)
Q3 (7–9)	134	103	1.17 (0.87, 1.58)	82	51	1.28 (0.80, 2.04)
Q4 (10–12)	118	94	1.27 (0.91, 1.76)	61	37	0.98 (0.56, 1.71)
P-trend			0.184			0.751
Meat						
Q1 (0)	308	239	1.00	153	84	1.00
Q2 (1)	85	58	1.03 (0.76, 1.38)	52	25	1.03 (0.64, 1.68)
Q3 (2)	45	33	1.10 (0.75, 1.61)	32	20	1.29 (0.77, 2.17)
Q4 (3–10)	53	40	1.36 (0.92, 1.99)	36	23	1.97 (1.13, 3.44)
P-trend			0.156			0.026
Seafood						
Q1 (0–1)	149	106	1.00	83	40	1.00
Q2 (2)	85	61	1.11 (0.80, 1.54)	50	26	1.20 (0.70, 2.03)
Q3 (3–4)	119	98	1.04 (0.78, 1.39)	59	38	1.14 (0.71, 1.82)
Q4 (5–17)	138	105	0.81 (0.59, 1.11)	81	48	0.84 (0.51, 1.40)
P-trend			0.204			0.537
Soybean products						
Q1 (0–1)	101	68	1.00	68	35	1.00
Q2 (2)	142	112	1.22 (0.89, 1.67)	70	40	1.09 (0.68, 1.76)
Q3 (3)	195	153	0.98 (0.72, 1.34)	107	65	0.72 (0.45, 1.14)
Q4 (4–5)	53	37	0.69 (0.45, 1.06)	28	12	0.39 (0.19, 0.79)
P-trend			0.07			0.005
Noncarriers						
Total	1780	1632		994	846	
Vegetables						
Q1 (0–4)	395	348	1.00	243	196	1.00
Q2 (5–8)	517	474	1.11 (0.96, 1.27)	319	276	1.17 (0.97, 1.41)
Q3 (9–12)	426	390	0.96 (0.83, 1.12)	227	191	0.97 (0.79, 1.19)
Q4 (13–25)	442	420	0.89 (0.76, 1.04)	205	183	0.83 (0.67, 1.04)
P-trend			0.033			0.036
Fruit						
Q1 (0–3)	443	395	1.00	282	234	1.00
Q2 (4–6)	384	347	0.99 (0.86, 1.15)	229	192	0.97 (0.80, 1.18)
Q3 (7–9)	513	475	1.09 (0.95, 1.25)	270	232	0.97 (0.80, 1.17)
Q4 (10–12)	440	415	0.98 (0.85, 1.13)	213	188	0.95 (0.78, 1.16)
P-trend			0.961			0.635
Meat						
Q1 (0)	1148	1,061	1.00	558	471	1.00
Q2 (1)	337	304	1.09 (0.96, 1.24)	221	188	1.16 (0.98, 1.38)
Q3 (2)	125	115	1.19 (0.98, 1.45)	92	82	1.32 (1.03, 1.68)
Q4 (3–10)	170	152	1.28 (1.07, 1.54)	123	105	1.41 (1.12, 1.78)
P-trend			0.003			0.001
Seafood						
Q1 (0–1)	477	427	1.00	295	245	1.00
Q2 (2)	299	274	0.89 (0.76, 1.03)	157	132	0.86 (0.69, 1.06)
Q3 (3–4)	499	455	1.02 (0.89, 1.16)	273	229	1.00 (0.83, 1.20)
Q4 (5–17)	505	476	0.88 (0.76, 1.01)	269	240	0.88 (0.72, 1.07)
P-trend			0.221			0.391

(Continued)

TABLE 2 (*Continued*)

Dietary diversity (no. of food items[2])	Total population: No. of participants	Total population: No. of breast cancer cases	Total population: HR (95% CI)[4]	Restricted population[3]: No. of participants	Restricted population[3]: No. of breast cancer cases	Restricted population[3]: HR (95% CI)[4]
Soybean products						
Q1 (0–1)	278	239	1.00	178	139	1.00
Q2 (2)	459	428	1.05 (0.89, 1.23)	247	216	1.02 (0.82, 1.27)
Q3 (3)	836	772	0.96 (0.83, 1.12)	464	400	0.95 (0.78, 1.16)
Q4 (4–5)	207	193	0.89 (0.74, 1.09)	105	91	0.77 (0.59, 1.02)
P-trend			0.124			0.068

[1] Q, quartile.

[2] Total number of food items consumed more than once a week in recent 1 y.

[3] The restricted population comprised the affected breast cancer patients having the diet questionnaire surveyed at the time of breast cancer diagnosis or surgery (patients who participated in the Korean Hereditary Breast Cancer Study >6 mo after a breast cancer diagnosis were excluded) and all unaffected subjects.

[4] HR was estimated by using Cox's proportional hazard model adjusted for age at menarche, calorie intake, years of education, smoking history, alcohol drinking history, parity, and regular exercise.

noncarriers, high meat consumption was associated with the risk of breast cancer (HR: 1.41; 95% CI: 1.12, 1.78). There was a dose-response trend for an association between low risk of breast cancer and high intake of vegetables (*P*-trend = 0.036). An inverse association with borderline significance was observed between soy intake and breast cancer risk among noncarriers (*P*-trend = 0.068).

The association between dietary intake and breast cancer risk according to *BRCA1* or *BRCA2* mutation status is shown in **Table 3**. In *BRCA2* mutation carriers, when compared with restricted breast cancer subjects and unaffected familial members, higher meat consumption was associated with a risk of breast cancer (HR: 2.48; 95% CI: 1.26, 4.89), and a higher consumption of soy products was associated with a lower risk of breast cancer (HR: 0.38; 95% CI: 0.16, 0.93). In *BRCA1* mutation carriers, however, an association between dietary intake and breast cancer risk was not observed. There was no heterogeneity by Cochran's *Q* test between the HR (95% CI) of the higher quartile intake of soybean products or meat in *BRCA1* mutation carriers and that in *BRCA2* mutation carriers.

In the analysis of all affected cases, soy product consumption was associated with the risk of *BRCA*-associated breast cancer after adjustment for age, age at menarche, calorie intake, educated years, smoking history, and history of pregnancy (COR: 0.57; 95% CI: 0.36, 0.90), as shown in **Table 4**. This significant association did not change when only the restricted cases were included in the analysis (subjects who participated in the KOHBRA Study for >6 mo after a breast cancer diagnosis were excluded).

DISCUSSION

Findings from the KOHBRA Study show that soy product consumption is associated with a lower breast cancer risk in *BRCA* mutation carriers than in unaffected familial members. In breast cancer cases only, the intake of soybean products was associated with *BRCA* mutation risk, which suggests that soybean product consumption had a joint effect with *BRCA* mutation on breast cancer risk. This joint effect means that the combination of the intake of soybean products and *BRCA* mutation decreased breast cancer risk 47% more than the expected combined risk, which was the independent effect of *BRCA* mutation multiplied by the independent effect of soybean products.

Because isoflavones in soybeans have a chemical structure similar to that of estrogen, the anticarcinogenic effect of soybean in the context of breast cancer has attracted attention. Several epidemiologic studies have suggested that soybean consumption inhibited the development of breast cancer (17–19). However, a recent meta-analysis showed the protective effects of soybean consumption on breast cancer in Asian populations but not in Western populations (12). This geographic difference may be caused by the different amount of soy consumption between the 2 populations, because isoflavone blood concentrations in Asian populations were >10 times those in Western populations (20). Because of different lifestyles, including soybean intake, the age-standardized incidence of breast cancer is 97.0 per 100,000 in Western Europe but is 35.1 in Southeastern Asia (21).

However, little epidemiologic evidence shows a relation between soybean intake and *BRCA* gene–related breast cancer because hereditary breast cancer is a rare disease and soybean intake is not common in Western populations. It has been suggested that the risk of hereditary breast cancer in *BRCA* mutation carriers can be biologically modified by hormonal factors (22). *BRCA* genes are implicated in DNA repair, the maintenance of genomic stability, cell-cycle checkpoints, and the coactivation of p53 responsive genes (23). Genistein, which is a component of soybean, upregulates *BRCA1* and *BRCA2* gene expression in human breast cancer cell lines by activating endoplasmic reticulum stress response signaling (24). Results from our KOHBRA Study, that there was an interaction between soybean intake and the *BRCA* genes in breast cancer development, were consistent for biological plausibility.

Although soybean products intake had statistical significance in *BRCA2* carriers but not in *BRCA1* carriers, the beneficial association of soybean products intake with breast cancer might not be different between *BRCA1* and *BRCA2* carriers because of the relatively small sample size in *BRCA1* carriers and similar point estimation between *BRCA1* and *BRCA2* carriers.

In our study, the intake of meat and vegetables was also associated with *BRCA*-related breast cancer. Although there was

TABLE 3
The association between the dietary intake of meat and soy products and breast cancer risk according to *BRCA1* and *BRCA2* mutations in the Korean Hereditary Breast Cancer Study (2007–2011)[1]

Dietary diversity (no. of food items[2])	Total population: No. of participants	Total population: No. of breast cancer cases	Total population: HR (95% CI)[4]	Restricted population[3]: No. of participants	Restricted population[3]: No. of breast cancer cases	Restricted population[3]: HR (95% CI)[4]
BRCA1 mutation carriers						
Total	184	150		95	61	
Meat						
Q1 (0)	114	94	1.00	54	34	1.00
Q2 (1)	29	26	1.42 (0.89, 2.25)	15	12	1.24 (0.58, 2.65)
Q3 (2)	18	13	1.21 (0.65, 2.24)	14	9	1.18 (0.52, 2.65)
Q4 (3–10)	23	17	1.13 (0.58, 2.23)	12	6	1.04 (0.28, 3.81)[5]
P-trend			0.435			0.715
Soybean products						
Q1 (0–1)	35	29	1.00	21	15	1.00
Q2 (2)	52	39	1.25 (0.75, 2.09)	28	15	0.66 (0.29, 1.48)
Q3 (3)	74	63	1.08 (0.67, 1.74)	38	27	0.77 (0.37, 1.61)
Q4 (4–5)	23	19	1.45 (0.75, 2.79)	8	4	0.49 (0.14, 1.75)[6]
P-trend			0.541			0.409
BRCA2 mutation carriers						
Total	311	224		178	91	
Meat						
Q1 (0)	197	148	1.00	99	50	1.00
Q2 (1)	57	33	0.85 (0.57, 1.27)	37	13	0.83 (0.42, 1.64)
Q3 (2)	27	20	0.96 (0.58, 1.58)	18	11	1.16 (0.57, 2.37)
Q4 (3–10)	30	23	1.41 (0.85, 2.33)	24	17	2.48 (1.26, 4.89)[5]
P-trend			0.428			0.027
Soybean products						
Q1 (0-1)	68	41	1.00	47	20	1.00
Q2 (2)	91	74	1.36 (0.89, 2.07)	42	25	1.41 (0.75, 2.65)
Q3 (3)	122	91	1.10 (0.72, 1.67)	69	38	0.76 (0.40, 1.44)
Q4 (4–5)	30	18	0.53 (0.29, 0.98)	20	8	0.38 (0.16, 0.93)[6]
P-trend			0.060			0.022

[1] Q, quartile.
[2] Total number of food items consumed more than once a week in recent 1 y.
[3] The restricted population comprised the affected breast cancer patients having the diet questionnaire surveyed at the time of breast cancer diagnosis or surgery (patients who participated in the Korean Hereditary Breast Cancer Study >6 mo after a breast cancer diagnosis were excluded) and all unaffected subjects.
[4] HR was estimated by using Cox's proportional hazard model adjusted for age at menarche, calorie intake, years of education, smoking history, alcohol drinking history, parity, and regular exercise.
[5] There was no heterogeneity (Cochran's *Q* test) between the HR (95% CI) of the higher quartile intake of meat in *BRCA1* mutation carriers and that in *BRCA2* mutation carriers.
[6] There was no heterogeneity (Cochran's *Q* test) between the HR (95% CI) of the higher quartile intake of soybean products in *BRCA1* mutation carriers and that in *BRCA2* mutation carriers.

no relation between meat intake and breast cancer risk in the meta-analysis (25, 26), there is possible biological evidence supporting a relation between meat intake and breast cancer risk. After being cooked at high temperatures, meat contains carcinogens such as heterocyclic amines, *N*-nitroso compounds, and polycyclic aromatic hydrocarbons (27–29). Red meat contains heme iron, which enhances tumor formation by inducing estrogen (30). In addition, fat, which is a suggestive risk factor for breast cancer, is a major component of meat (31). However, we could not clarify the independent association of meat intake with breast cancer because of the lack of information on confounding effects such as cooking method, fat intake, or other potential confounder. In our results, the association between the meat intake and breast cancer risk was observed in *BRCA2* but not in *BRCA1* mutation carriers, although heterogeneity was not significant. Exposure to polycyclic aromatic hydrocarbons from burned meat may be a predisposing factor of breast cancer by disrupting the expression of *BRCA1* (32). Thus, the risk effect for breast cancer might be prominent in *BRCA2* mutation carriers. However, the biological plausibility of a prominent effect in *BRCA2* mutation carriers has not yet been clarified, and we could not exclude the possibility of results of a chance event attributable to small sample size.

Although the World Cancer Research Fund and the American Institute for Cancer Research reported in 2007 that the evidence of an association between vegetable intake and breast cancer risk was limited, vegetables have been recognized as healthy foods that prevent many types of chronic diseases. Recently, 2 meta-analyses released results regarding vegetable intake and breast cancer risk. Aune et al (33) reported that the high intake of fruit and vegetables combined, but not vegetables alone, was associated with a lower risk of breast cancer. However, Liu and Lv (34) reported

TABLE 4
Gene-environment interaction for the combination of *BRCA* mutation and diet diversity among affected cases in the Korean Hereditary Breast Cancer Study (2007–2011)[1]

	Total affected cases (n = 2002)			Restricted affected cases[3] (n = 998)		
Dietary diversity (no. of food items[2])	*BRCA* carriers (n = 370)	*BRCA* noncarriers (n = 1632)	COR[4] (95% CI)	*BRCA* carriers (n = 152)	*BRCA* noncarriers (n = 846)	COR[4] (95% CI)
	n (%)	*n (%)*		*n (%)*	*n (%)*	
Vegetables						
Q1 (0–4)	83 (22.4)	348 (21.3)	1.00	43 (28.3)	196 (23.2)	1.00
Q2 (5–8)	104 (28.1)	474 (29.0)	0.87 (0.63, 1.20)	45 (29.6)	276 (32.6)	0.73 (0.46, 1.16)
Q3 (9–12)	80 (21.6)	390 (23.9)	0.78 (0.55, 1.11)	30 (19.7)	191 (22.6)	0.68 (0.40, 1.15)
Q4 (13–25)	103 (27.8)	420 (25.7)	0.86 (0.61, 1.22)	34 (22.4)	183 (21.6)	0.75 (0.44, 1.29)
P-trend			0.366			0.283
Fruit						
Q1 (0–3)	91 (24.6)	395 (24.2)	1.00	35 (23.0)	234 (27.7)	1.00
Q2 (4–6)	82 (22.2)	347 (21.3)	1.02 (0.73, 1.43)	29 (19.1)	192 (22.7)	0.98 (0.57, 1.68)
Q3 (7–9)	103 (27.8)	475 (29.1)	0.94 (0.68, 1.30)	51 (33.6)	232 (27.4)	1.46 (0.90, 2.37)
Q4 (10–12)	94 (25.4)	415 (25.4)	0.91 (0.65, 1.28)	37 (24.3)	188 (22.2)	1.30 (0.77, 2.20)
P-trend			0.507			0.155
Meat						
Q1 (0)	239 (64.6)	1061 (65.0)	1.00	84 (55.3)	471 (55.7)	1.00
Q2 (1)	58 (15.7)	304 (18.6)	0.83 (0.61, 1.15)	25 (16.5)	188 (22.2)	0.71 (0.44, 1.16)
Q3 (2)	33 (8.9)	115 (7.1)	1.25 (0.82, 1.92)	20 (13.2)	82 (9.7)	1.31 (0.75, 2.29)
Q4 (3–10)	40 (10.8)	152 (9.3)	1.05 (0.69, 1.60)	23 (15.1)	105 (12.4)	1.13 (0.64, 1.98)
P-trend			0.677			0.559
Seafood						
Q1 (0–1)	106 (28.7)	427 (26.2)	1.00	40 (26.3)	245 (29.0)	1.00
Q2 (2)	61 (16.5)	274 (16.8)	0.88 (0.61, 1.25)	26 (17.1)	132 (15.6)	1.25 (0.72, 2.15)
Q3 (3–4)	98 (26.5)	455 (27.9)	0.82 (0.60, 1.12)	38 (25.0)	229 (27.1)	1.00 (0.61, 1.63)
Q4 (5–17)	105 (28.4)	476 (29.2)	0.76 (0.55, 1.06)	48 (31.6)	240 (28.4)	1.15 (0.70, 1.89)
P-trend			0.094			0.744
Soybean products						
Q1 (0-1)	68 (18.4)	239 (14.6)	1.00	35 (23.0)	139 (16.4)	1.00
Q2 (2)	112 (30.3)	428 (26.2)	0.90 (0.64, 1.27)	40 (26.3)	216 (25.5)	0.72 (0.43, 1.20)
Q3 (3)	153 (41.4)	772 (47.3)	0.63 (0.45, 0.88)	65 (42.8)	400 (47.3)	0.60 (0.37, 0.96)
Q4 (4–5)	37 (10.0)	193 (11.8)	0.57 (0.36, 0.91)	12 (7.9)	91 (10.8)	0.49 (0.24, 1.02)
P-trend			0.001			0.020

[1] COR, case-only OR; Q, quartile.

[2] Total number of food items consumed more than once a week in recent 1 y.

[3] The restricted population comprised the affected breast cancer patients having the diet questionnaire surveyed at the time of breast cancer diagnosis or surgery (patients who participated in the Korean Hereditary Breast Cancer Study >6 mo after a breast cancer diagnosis were excluded) and all unaffected subjects.

[4] CORs were used to estimate the risk of *BRCA* mutation = 1 by using a logistic regression model adjusted for age, age at menarche, calorie intake, years of education, smoking history, and history of pregnancy.

that cruciferous vegetable intake was inversely associated with breast cancer risk. Vegetables contain fiber that may be anticarcinogenic by binding estrogen (35). Indole-3-carbonyl and diindolylmethane from cruciferous vegetables may also prevent breast cancer by repressing estrogen receptor signaling and stimulating *BRCA1* signaling (36). Because we had no information on cooking method and we could not purify cruciferous vegetable intake from the vegetable diversity, the results from the diversity of vegetable intake might be diluted, and weak associations were observed between vegetable intake and breast cancer.

Our study was limited in its ability to assert the association between dietary intake and *BRCA*-related breast cancer. First, dietary diversity obtained from the FFQ may be limited. Dietary intake could limit the intake of other food constituents, and this limitation may lead to altered food choices that include more or less of certain foods. Second, the dietary information reflects dietary consumption in a year before study participation. Some cases could modify dietary habits after a breast cancer diagnosis, and this modification could lead to temporal bias. In addition to temporal bias, there might be healthy survival bias because prevalent affected cases were included. However, to minimize the temporal bias and healthy survival bias, we reported the results from both all affected cases and restricted cases separately, and we observed that the strength of the associations was larger in the analysis with restricted cases. Third, the case-only study design was limited. To assess the gene-environment interaction with the use of a case-only study design, it is essential to assume that genetic variables and environmental variables are independent. Although a case-only study is more efficient for assessing a gene-environment interaction than is a case-control study, we could not estimate the joint effect of *BRCA* mutation and dietary diversity with a case-only design. In our study, however, we compared *BRCA*-related breast cancer cases and their familial noncases to assess the point estimation in *BRCA* carriers and noncarriers. We observed that the beneficial association of soybean products with breast cancer was a 73% risk reduction in *BRCA* gene carriers and a 27% risk reduction in noncarriers in a comparison of the highest with the lowest quartile.

We also assessed the risk or preventive dietary factors in the development of *BRCA*-related breast cancer. Generally, it is difficult to conduct a case-control study in cases of rare exposure rates. We included the family members of affected cases to overcome this limitation. In addition, we improved the variability of exposure and the statistical power because our study population comprised Asians who consumed large amounts of soybeans.

In conclusion, our study suggests that the intake of vegetables, soy products, and meat were associated with breast cancer, specifically for *BRCA*-related breast cancer. The identification of a positive association of soybean product consumption with *BRCA*-related breast cancer suggests a possible role for lifestyle modification in *BRCA* mutation carriers. It is necessary to verify the modifier effect of soybean consumption in *BRCA* mutation carriers through intervention studies.

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