

RESEARCH ARTICLE

Glycemic Index and Glycemic Load Dietary Patterns and the Associated Risk of Breast Cancer: A Case-control Study

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Abstract

The glycemic index (GI) and glycemic load (GL) have been considered risk factors for breast cancer, but association studies of breast cancer risk using simple GI and GL might be affected by confounding effects of the overall diet. A total of 357 cases and 357 age-matched controls were enrolled, and dietary intake was assessed using a validated food frequency questionnaire (FFQ) with 103 food items. GI and GL dietary patterns were derived by reduced rank regression (RRR) method. The GI and GL pattern scores were positively associated with breast cancer risk among postmenopausal women [OR (95% CI): 3.31 (1.06-10.39), *p* for trend=0.031; 9.24 (2.93-29.14), *p* for trend<0.001, respectively], while the GI pattern showed no statistically significant effects on breast cancer risk, and the GL pattern was only marginally significant, among premenopausal women (*p* for trend=0.043). The GI and GL pattern scores were positively associated with the risk of breast cancer in subgroups defined by hormone receptor status in postmenopausal women. The GI and GL patterns based on all food items consumed were positively associated with breast cancer.

Keywords: Case-control study - glycemic index (GI) - glycemic load (GL) - breast cancer

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Introduction

Habitual consumption of a high glycemic index (GI) food causes postprandial increases in the blood glucose level, resulting in high insulin demand (Jenkins et al., 2002). The GI and GL, which considers both the quantity and quality of carbohydrate intake, have been shown to be related to chronic disease and increased risk of cancer (Patel et al., 2007; Jiao et al., 2009; Bao et al., 2010), including breast cancer (Lajous et al., 2005; Gnagnarella et al., 2008; Lajous et al., 2008; Larsson et al., 2009; Belle et al., 2011; Shikany et al., 2011). Because breast cancer risk is influenced by various kinds of foods (Pierce et al., 2007; Zhang et al., 2009; Butler et al., 2010; Zeng et al., 2013), association studies between breast cancer risk and simple GI and GL values might not explain the effects of overall diet. According to the Korea National Health and Nutrition Examination Survey (KNHANES) (Korea Health Statistics, 2009; <http://knhanes.cdc.go.kr/> 2011.05.09), the average carbohydrate intake of Korean women was 268g, which accounted for 68.3% of the total energy intake. However, Korean diets are rich in vegetables and fruits in addition to carbohydrates. Thus, the GI and GL patterns considering all of the foods consumed may provide a more precise association with breast cancer risk than simple GI and GL values.

Reduced rank regression (RRR) in dietary pattern analysis is useful method to combine the advantages of a posteriori and a priori approaches because the pattern is extracted considering all predictor variables

by maximizing the variation of the response variables (Hoffmann et al., 2004; Edefonti et al., 2009). Association studies between breast cancer risk and GI and GL patterns derived by RRR might remove the confounding effects. The effects of the GI and GL values on breast cancer were found to be inconsistent according to menopausal status and hormone receptor status (Sieri et al., 2007; Wen et al., 2009), and there has been only one study that used the GI or GL dietary pattern score with a population comprising individuals with considerably different food cultures (McCann et al., 2007). We investigated the association between breast cancer risk and the GI and GL dietary pattern stratified by hormone receptor status and menopausal status.

Materials and Methods

Study population

Cases were breast cancer patients admitted for surgery at the Center for Breast Cancer in the National Cancer Center Hospital in Korea between July 2007 and September 2008. Among the 415 women with breast cancer who agreed to participate in the study, patients with a previous history of cancer (*n*=14), the inability to complete an interview (*n*=2) and daily energy intakes of <600 or >3500kcal (*n*=1) were excluded. Controls were recruited among individuals who underwent health screening examinations at the Center for Cancer Prevention and Detection at the same hospital during same period. Among the 713 women who agreed to participate

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in the study, women with a history of cancer or missing information about dietary intake were excluded. The remaining 653 women were matched to the 398 cases based on 5-year age groups. In total, 357 cases and 357 controls were selected for analysis. All participants were provided an written informed consent form according to the procedures approved by the institutional review board of the National Cancer Center Hospital (IRB protocol number NCCNCS 07-083).

Data collection and dietary assessment

A trained dietitian conducted in-person interviews using a structured questionnaire covering demographics, lifestyle, and medical history. Physical activity (MET-min/wk) was evaluated using the short form of the International Physical Activity Questionnaire (IPAQ). The validated food frequency questionnaire (FFQ) covering of 103 types of food was used to assess typical dietary intake (Ahn et al., 2007). The de-attenuated and age-, sex-, and energy-adjusted correlation coefficients between the FFQ and the 12-day dietary records ranged between 0.23 (vitamin A) and 0.64 (carbohydrates), and the median for all nutrients was 0.39. Correlations between the two FFQs were 0.45 for all nutrient intake levels and 0.39 for nutrient densities. All participants were asked about the average frequency of intake and portion size of specific foods during the previous year. Three portion sizes (small, medium, and large) and 9 categories of frequency (never or rarely, once a month, 2 or 3 times a month, once or twice a week, 3 or 4 times a week, 5 or 6 times a week, once a day, twice a day, and 3 times a day) were specified on the FFQ. The GI values of each food were obtained from international tables (Foster-Powell et al., 2002). GI values for foods not found in the tables were estimated based on the most similar food according to physical and chemical factors. The GI values were matched to each of the individual foods, multiplied by the quantity of carbohydrates and divided by total amount of carbohydrate consumed per day; the overall GI was calculated by summing up all of these values. The GL represents both the quality and quantity of carbohydrate intake. The overall GL was calculated by summing up all GI values multiplied by the amount of carbohydrate of each food and dividing the values by 100. The estrogen receptor (ER) and progesterone receptor (PR) status evaluations were performed on tissue sections cut from formalin-fixed, paraffin-embedded breast tumors by immunohistochemistry (Ventana Medical Systems, Tucson, AZ). Any focal positivity, including weakly positive expression, was recorded (Regitnig et al., 2002).

Statistical analysis

Statistical analysis was performed using the SAS version 9.1 statistical package (SAS Institute Inc, Cary, NC). Thirty-nine food groups covering 410 kinds of food contained in 103 FFQ items were used to derive the dietary pattern by reduced rank regression (RRR) using PROC PLS with the RRR method option (Hoffmann et al., 2004). The GI and GL, which were adjusted for total energy intake using the nutrient residual model (Willett and Stampfer, 1986), were used as response variables separately, and the mass of the 39 food groups in grams was considered

as predictor variables. Each factor score for GI and GL was categorized into tertiles for further analysis. Trends in the characteristics of the study population with respect to tertile of the GI and GL pattern factor scores identified using a generalized linear model. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer were calculated across the tertiles of GI or GL using logistic regression after controlling for known risk factors such as total energy intake (continuous), dietary fiber intake (log-transformed), age (continuous), body mass index (continuous), age at menarche (≤ 13 , 14, 15, and ≥ 16), menopausal status (premenopausal, postmenopausal), alcohol consumption (never, ever), smoking (never, ever), parity (yes, no), family history of breast cancer (yes, no), education ($\leq$ high school, and $\geq$ college), physical activity (log-transformed) and postmenopausal hormone use for postmenopausal women. To test the tertile trend, a median value was assigned to each tertile of the GI or GL pattern scores as a continuous variable.

Results

Among the 39 food groups, the factor scores of the GI and GL patterns with absolute values ≥ 0.15 are shown in Table 1. One dietary pattern for each response variable, GI and GL, was identified because the number of extracted factors cannot be greater than the number of response variables in the RRR method. The GI and GL patterns explained 7.5% and 9.0% of the variation in the predictor variables, respectively, and 77.4% and 96.1% of the variation in the response variables, respectively. Grain intake explained most of the variance in the factor scores in both the GI and GL patterns, and green/yellow vegetables

Table 1. Factor Loadings of Glycemic Index and Glycemic Load Patterns Derived from Reduced Rank Regression

	Glycemic index pattern	Glycemic load pattern
Grain	0.45	0.41
Dairy products	-0.15	-0.15
Coffee, tea	-0.15	-
Bonefish	-0.15	-
Shellfish	-0.16	-0.17
Tofu, soymilk	-0.17	-0.16
Yogurt	-0.18	-
Tubers	-0.19	-
Fruit product	-0.2	-
Light-colored vegetables	-0.21	-0.22
Milk	-0.21	-0.2
Seaweeds	-0.21	-0.18
Mushrooms	-0.22	-0.21
Condiments	-0.24	-0.19
Fruits	-0.24	-
Green/yellow vegetables	-0.28	-0.22
Eggs	-	-0.15
Other seafood	-	-0.16
Lean fish	-	-0.17
Bread	-	-0.19
Fatty fish	-	-0.21
High-fat red meat	-	-0.22
Red meat	-	-0.26

*Factor loadings of either glycemic index or glycemic load pattern with absolute values ≥ 0.15 were listed in the table among 39 food groups

Table 2. Characteristics of Study Participants According to Tertile of Glycemic Index and Glycemic Load Pattern Scores

	Controls (n=357)			p for trend	Cases (n=357)			p for trend
	First tertile	Second tertile	Third tertile		First tertile	Second tertile	Third tertile	
Glycemic index pattern								
Glycemic Index	62.7 (5.5) ^a	72.2 (4.0)	78.2 (3.5)	<0.001	64.2 (5.7)	72.6 (3.5)	79.4 (3.7)	<0.001
Age (y)	48.8 (8.9)	48.7 (8.4)	46.8 (8.5)	0.065	47.5 (5.7)	47.5 (9.3)	48.8 (9.2)	0.305
BMI (kg/m2)	22.9 (2.4)	22.8 (2.5)	23.1 (3.1)	0.699	23.2 (2.7)	23.6 (3.3)	23.6 (3.2)	0.402
Physical activity (MET-min/wk)	2910 (2755)	2885 (3681)	2858 (3099)	0.918	2195 (2137)	2086 (2290)	2242 (3126)	0.909
Smoker, ever (%)	10.6	6.3	4.3	0.062	26.2	9.6	6.9	<0.001
Alcohol, ever (%)	50.4	53.5	46.9	0.595	55.7	41.5	46	0.362
Education, ≥college (%)	50	50	49.1	0.749	36.1	31.9	20.3	<0.001
Family history of cancer (%)	2.5	5.9	1.7	0.72	4.9	6.4	4.5	0.725
Parity, yes (%)	88.2	89.9	88.2	>0.999	95.1	88.3	91.1	0.566
Nutrient consumption								
Total energy intake (kcal)	1746 (640.8)	1531 (496.5)	1801 (444.2)	0.43	1876 (615.1)	1688 (476.0)	1844 (454.8)	0.655
Carbohydrate (g)	280.8 (104.1)	264.2 (8.5)	327.8 (80.6)	<0.001	314.2 (108.1)	297.1 (86.1)	343.0 (86.9)	0.031
Carbohydrate (% energy)	64.0 (7.4)	69.3 (6.0)	74.0 (5.7)	<0.001	66.5 (8.8)	70.6 (6.4)	75.6 (5.4)	<0.001
Protein (% energy)	15.8 (2.8)	14.4 (2.2)	12.8 (2.0)	<0.001	13.8 (3.0)	13.5 (2.2)	12.4 (1.7)	<0.001
Fat (% energy)	20.1 (5.5)	16.3 (4.3)	13.2 (4.1)	<0.001	19.7 (7.0)	15.9 (3.9)	12.0 (4.2)	<0.001
Dietary fiber (g)	25.0 (17.0)	17.2 (6.9)	16.4 (6.0)	<0.001	21.3 (8.9)	18.3 (6.9)	16.7 (5.9)	<0.001
Glycemic Load pattern								
Glycemic Load	172.1 (63.3)	197.0 (63.2)	253.1 (66.6)	<0.001	188.8 (64.8)	212.5 (54.8)	272.8 (68.3)	<0.001
Age (y)	49.3 (9.1)	47.8 (8.0)	47.3 (8.6)	0.071	45.0 (6.6)	48.0 (8.1)	49.2 (9.3)	0.002
BMI (kg/m2)	23.2 (2.6)	22.5 (2.4)	23.1 (3.0)	0.82	23.1 (2.8)	23.4 (3.2)	23.7 (3.2)	0.266
Physical activity (MET-min/wk)	3097 (2957)	2846 (3743)	2716 (2836)	0.438	1997 (1856)	2096 (2338)	2281 (3099)	0.513
Smoker, ever (%)	10.5	7	3.4	0.034	30.9	8.1	7	<0.001
Alcohol, ever (%)	53.5	50.5	46.9	0.323	69.1	50.6	39.1	<0.001
Education, ≥college (%)	50.9	50	48.3	0.689	41.8	35.6	18.1	<0.001
Family history of cancer (%)	4.2	4.2	1.7	0.281	7.3	3.5	5.1	0.729
Parity, yes (%)	88.2	89.1	89.1	0.837	92.7	89.7	91.2	0.87
Nutrient consumption								
Total energy intake (kcal)	1744 (623.1)	1589 (519.1)	1745 (470.9)	0.986	1857 (591.6)	1710 (445.3)	1835 (484.1)	0.768
Carbohydrate (g)	269.3 (96.4)	276.4 (88.9)	327.1 (90.4)	<0.001	287.8 (93.6)	296.9 (78.5)	347.5 (91.6)	<0.001
Carbohydrate (% energy)	61.5 (6.0)	69.9 (3.6)	76.0 (4.3)	<0.001	61.6 (6.7)	69.7 (4.4)	76.8 (4.0)	<0.001
Protein (% energy)	16.6 (2.6)	14.2 (1.5)	12.2 (1.7)	<0.001	15.0 (3.2)	13.7 (1.9)	12.1 (1.3)	<0.001
Fat (% energy)	21.9 (4.6)	15.9 (2.9)	11.8 (3.0)	<0.001	23.4 (5.3)	16.6 (3.3)	11.1 (3.2)	<0.001
Dietary fiber (g)	24.2 (17.3)	17.7 (6.4)	16.8 (6.7)	<0.001	18.8 (8.2)	18.3 (5.8)	17.5 (7.0)	0.246

*MET: metabolic equivalent; ^aMean (SD), all such values**Table 3. Odds Ratio and 95%CI of Breast Cancer Risk According to Glycemic Index, Glycemic Load, and Glycemic Index and Glycemic Load Pattern Scores with Menopausal Status**

		All		Premenopausal		Premenopausal	
		Controls/ Cases	Multivariate- adj. model ^b	Controls/ Cases	Multivariate- adj. model	Controls/ Cases	Multivariate- adj. model
Energy-Adjusted dietary GI	First tertile	119/52		68/31		51/21	
	Second tertile	119/104	1.67 (0.98-2.83)	80/63	1.96 (1.00-3.83)	39/41	1.36 (0.47-3.97)
	Third tertile	119/201	2.50 (1.46-4.31)	80/116	2.79 (1.40-5.56)	39/85	2.46 (0.85-7.15)
	p for trend ^a		<0.001		0.003		0.089
GI pattern score	First tertile	119/61		70/40		49/21	
	Second tertile	119/94	1.31 (0.78-2.22)	71/53	1.33 (0.68-2.59)	48/41	1.46 (0.51-4.14)
	Third tertile	119/202	1.97 (1.14-3.42)	87/117	1.71 (0.87-3.35)	32/85	3.31 (1.06-10.39)
	p for trend ^a		0.014		0.119		0.031
Energy-Adjusted dietary GL	First tertile	119/54		69/36		50/18	
	Second tertile	119/81	1.72 (1.00-2.94)	77/46	1.24 (0.64-2.42)	42/35	3.54 (1.21-10.42)
	Third tertile	119/222	3.27 (1.94-5.50)	82/128	2.62 (1.40-4.92)	37/94	7.68 (2.48-23.72)
	p for trend ^a		<0.001		0.002		<0.001
GL pattern score	First tertile	119/55		65/38		54/17	
	Second tertile	119/87	1.65 (0.97-2.80)	80/52	1.11 (0.58-2.14)	39/35	4.31 (1.43-12.99)
	Third tertile	119/215	2.66 (1.57-4.49)	83/120	1.87 (0.98-3.57)	36/95	9.24 (2.93-29.14)
	p for trend ^a		<0.001		0.043		<0.001

^aTests for trend were conducted by assigning the median value to each quartile of dietary pattern score as a continuous variable; ^badjusted for total energy intake (continuous), dietary fiber intake (log-transformed), age (continuous), body mass index (continuous), age at menarche (≤13, 14, 15, and ≥16), menopausal status (premenopausal, postmenopausal), alcohol (never, ever), smoking (never, ever), parity (yes, no), family history of breast cancer (yes, no), education (≤ middle school, ≥high school), physical activity (log-transformed) and postmenopausal hormone use for postmenopausal women

for GI and red meat for GL had negative loadings. The characteristics of the study participants according to the tertiles of GI and GL pattern scores are presented in Table 2. Among the breast cancer cases, smoking and higher education declined across the tertiles of both the GI and GL pattern scores (p for trend<0.001). Cases with higher

GL pattern scores were older and reported a lower alcohol intake.

The ORs and 95% CIs of breast cancer risk were analyzed across the tertiles of GI and GL pattern scores (Table 3). Women in the highest tertiles of GI and GL pattern scores compared to those in the lowest tertiles

Table 4. Odds Ratio and 95% CI of Breast Cancer Risk According to Glycemic Index and Glycemic Load Pattern Scores with Hormone Receptor Status

		ER ^b +			ER-		PR ^b +		PR-	
		Controls (n)	Cases (n)	Multivariate- adj. model ^c	Cases (n)	Multivariate- adj. model	Cases (n)	Multivariate- adj. model	Cases (n)	Multivariate- adj. model
GI pattern score	All subjects	357	249		109		222		136	
	First tertile	119	40	1	22	1	38	1	24	1
	Second tertile	119	66	1.46 (0.82-2.60)	28	0.86 (0.39-1.90)	54	1.26 (0.70-2.29)	40	1.24 (0.60-2.58)
	Third tertile	119	143	2.21 (1.22-4.02)	59	1.53 (0.69-3.38)	130	2.07 (1.14-3.77)	72	1.89 (0.87-4.08)
	p for trend ^a			0.008		0.293		0.014		0.14
	Premenopausal	228	169		41		159		51	
	First tertile	70	28	1	12	1	28	1	12	1
	Second tertile	71	44	1.46 (0.71-3.01)	9	0.76 (0.25-2.35)	38	1.18 (0.57-2.44)	15	1.09 (0.35-3.44)
	Third tertile	87	97	2.12 (1.03-4.38)	20	0.80 (0.26-2.41)	93	1.93 (0.94-3.96)	24	2.97 (0.84-10.54)
	p for trend ^a			0.039		0.696		0.064		0.849
GL pattern score	All subjects	357	249		109		222		136	
	First tertile	119	38	1	17	1	35	1	20	1
	Second tertile	119	58	1.69 (0.94-3.02)	30	1.74 (0.77-3.97)	51	1.55 (0.85-2.83)	37	2.12 (0.99-4.54)
	Third tertile	119	153	3.11 (1.76-5.49)	62	2.92 (1.31-6.50)	136	2.95 (1.64-5.29)	79	3.46 (1.63-7.35)
	p for trend ^a			<0.001		0.013		<0.001		0.003
	Premenopausal	228	169		41		159		51	
	First tertile	65	29	1	9	1	28	1	10	1
	Second tertile	80	41	1.21 (0.60-2.44)	11	0.86 (0.28-2.63)	38	1.11 (0.55-2.27)	14	1.20 (0.43-3.39)
	Third tertile	83	99	2.18 (1.10-4.32)	21	1.30 (0.45-3.78)	93	2.03 (1.01-4.10)	27	1.80 (0.66-4.92)
	p for trend ^a			0.017		0.635		0.032		0.236
GI pattern score	Postmenopausal	129	80		68		63		85	
	First tertile	54	9	1	8	1	7	1	10	1
	Second tertile	39	17	3.65 (1.00-13.35)	19	4.27 (1.08-16.91)	13	3.73 (0.90-15.56)	23	3.90 (1.11-13.73)
	Third tertile	36	54	13.18 (3.42-50.80)	41	8.97 (2.22-36.25)	43	14.24 (3.36-60.25)	52	8.29 (2.24-30.75)
	p for trend ^a			<0.001		0.002		<0.001		0.002

^aTests for trend were conducted by assigning the median value to each quartile of dietary pattern score as a continuous variable; ^bER, Estrogen receptor; PR, progesterone receptor; ^cadjusted for total energy intake (continuous), dietary fiber intake (log-transformed), age (continuous), body mass index (continuous), age at menarche (≤ 13 , 14, 15, and ≥ 16), menopausal status (premenopausal, postmenopausal), alcohol (never, ever), smoking (never, ever), parity (yes, no), family history of breast cancer (yes, no), education ($\leq$ middle school, $\geq$ high school), physical activity (log-transformed) and postmenopausal hormone use for postmenopausal women

had an increased risk of breast cancer in both the age- and energy-adjusted model [OR (95%CI): 3.31 (2.25-4.87), p for trend<0.001; 3.93 (2.65-5.82), p for trend<0.001, respectively] and the multivariate-adjusted model [OR (95%CI): 1.97 (1.14-3.42), p for trend=0.014; 2.66 (1.57-4.49), p for trend<0.001, respectively]. Among premenopausal women, no statistically significant effects of the GI pattern on breast cancer risk were found when comparing the highest tertile with the lowest tertile in the multivariate-adjusted model, and the tertile trend of the GL pattern score was marginally significant (p for trend=0.043). Although both the GI and GL patterns were positively associated with breast cancer risk among postmenopausal women, a stronger association was observed for the GL pattern score in the multivariate-adjusted model [OR (95%CI): 3.31 (1.06-10.39), p for trend=0.031; 9.24 (2.93-29.14), p for trend<0.001, respectively]. The overall relationship between breast cancer risk and the dietary GI/ GL values was similar to that for the GI and GL pattern scores.

The associations between the GI and GL pattern scores and breast cancer risk were analyzed after stratification by hormone receptor status (Table 4). The risk of breast cancer was increased with increasing tertile of the GI pattern score only in women who had ER+ or PR+ cancer, while the risk of breast cancer was increased with increasing tertiles of the GL pattern score in all subgroups. Furthermore, the

results differed based on hormone receptor status. The GI and GL pattern scores were positively associated with the risk of breast cancer in premenopausal women with ER+ or PR+ cancer, whereas the risk of breast cancer, although not statistically significantly related to the GI pattern score, was elevated with increasing GI or GL pattern scores in all subgroups of postmenopausal women. Patients with ER+/PR+ cancer and ER-/PR- cancer showed trends similar to women with ER+ or PR+ cancer and ER- or PR- cancer, respectively (data not shown).

Discussion

The effects of the GI and GL dietary patterns determined by RRR on breast cancer risk were investigated in the present study. Breast cancer incidence risk was elevated with increasing factor loadings of the GI and GL patterns.

Breast cancer risk was increased across the tertiles of GI and GL patterns in both premenopausal and postmenopausal women, but the increase was not statistically significantly related to the GI pattern and showed a marginally significant trend with respect to the GL pattern among premenopausal women. Breast cancer risk was highly associated with postmenopausal status and a high GL pattern score. Previous studies using simple GI and GL values have obtained inconsistent results. GI and GL had no association with breast cancer risk among

French postmenopausal women in a prospective cohort analysis (Lajous et al., 2008), but breast cancer risk was positively associated with both GI and GL among premenopausal women in Italian prospective cohort study (Sieri et al., 2007). Wen et al. (2009) reported that premenopausal Chinese women with high GLs had a higher risk of breast cancer. A meta-analysis revealed that only the GL had a positive association with breast cancer risk (Gnagnarella et al., 2008). Another meta-analysis that included only cohort studies was stratified based on menopausal status because the heterogeneity, but only a non-significant increase in breast cancer risk was observed in both premenopausal and postmenopausal women (Mulholland et al., 2008).

Korean meals are comprised of steam-cooked rice with various side dishes that are usually composed of large amounts of vegetables. It was hypothesized that the GI and GL pattern scores might have different effects on breast cancer risk because the high intake of grain typically accompanies a high intake of vegetables and other foods that contain preventive nutrients. Thus, the GI and GL patterns were extracted using the RRR method considering all food groups. The majority of the factor score variation in the GI and GL pattern was explained by grain intake in the present study. This result might be related to the high amount of grain intake by Koreans. The average amount of grain intake by Korean women was 260.4g and constituted 68.6% of carbohydrate intake in 2008 according to the KNHANES (Korea Health Statistics, 2009). White rice, the most frequently consumed food in Korea, accounted for 70% of carbohydrate intake from grains. Thus, the GI and GL pattern scores were mostly affected by white rice intake in the present study. Similar to the results for simple GI and GL values, high factor scores for the GI and GL patterns were associated with an increased risk of breast cancer. There was a previous study that compared the GI and GL dietary patterns derived by RRR and the simple GI and GL values in the estimation of breast cancer risk (McCann et al., 2007). The GI and GL patterns were not associated with breast cancer risk in either premenopausal or postmenopausal women, and simple the GI and GL values yielded results similar to those of the RRR-derived patterns, suggesting that the GI and GL patterns derived by RRR do not provide much new information compared to the GI and GL values. Breast cancer risk decreased with higher combined pattern scores of GI and GL among postmenopausal women and increased with high GL pattern scores in premenopausal women in the study. Although the effects of the GI and GL pattern scores derived by RRR on the risk of breast cancer might not be significantly different from the effect of the simple dietary GI and GL values, the pattern scores might give more precise results by removing the confounding effects of foods and because the GI and GL pattern scores affect breast cancer risk differently because food items vary in different countries.

Breast cancer risk was increased across the tertiles of the GI and GL pattern in all hormone receptor status subgroups in postmenopausal women, although this increase was not statistically significant for the GI pattern, while the risk was positively associated with only ER+

and PR+ patients among premenopausal women. The underlying mechanism might be related to insulin-like growth factor-I (IGF-I). A high intake of carbohydrates increases the risk of breast cancer via elevation of the IGF-I level, which promotes cell proliferation and inhibits cell death (Kaaks, 1996), while long-term low carbohydrate intake reduces the postprandial rise in gut hormones and insulin through suppression of free fatty acids (Jenkins et al., 2002). IGF-I can synergistically increase cell growth and proliferation via the activation of ER (Yee and Lee, 2000; Mawson et al., 2005; Lanzino et al., 2008; Richardson et al., 2011; Wang et al., 2012). Thus, large amounts of high GI and GL food intake can increase breast cancer risk, especially for ER+ premenopausal women. However, information was limited in previous studies. The GI and GL were positively associated with ER+/PR- breast cancer risk in a Swedish cohort, though there was no subgroup analysis based on menopausal status (Larsson et al., 2009), and two other studies were conducted after stratification by hormone receptor status using only postmenopausal women. A marginally significant positive association between GI and ER- breast cancer was found in a Danish cohort (Nielsen et al., 2005), and dietary GL was associated with increased risk of ER- breast cancer in a French cohort (Lajous et al., 2008). An elevated IGF-I concentration was found to be related to increased breast cancer risk in both premenopausal and postmenopausal women, but a positive association was shown only for ER+ breast cancer patients (Key et al., 2010). Thus, it seems that the association between breast cancer and GI or GL differs based on menopausal status and hormone receptor status, but further studies are needed to find clear associations.

Biases might have been introduced because the present study was conducted with a case-control design. Cases were recruited among patients who were admitted for breast cancer surgery, while the controls were selected from among individuals who underwent health screening examinations. Thus, even though the controls were age-matched to the cases, the control population might have had a healthier lifestyle, especially with respect to the selection of food items. Furthermore, the small sample sizes in the subgroup analysis limited the statistical power. Nevertheless, our data are unique because we focused on a population with a high carbohydrate intake and a high intake of various vegetables to analyze the relationship between the breast cancer risk and the GI or GL pattern score.

In summary, the GI and GL patterns derived by RRR were positively associated with breast cancer. The association was shown only in women with ER+ or ER+/PR+ cancer among premenopausal women and in all subgroups of hormone receptor status among postmenopausal women. Postmenopausal women with high GL pattern scores showed a strong association with breast cancer risk.

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