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Kimchi and soybean pastes are risk factors of gastric cancer

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Abstract

AIM: This case-control study investigated the effects of kimchi, soybean paste, fresh vegetables, nonfermented alliums, nonfermented seafood, nonfermented soybean foods, and the genetic polymorphisms of some metabolic enzymes on the risk of gastric cancer in Koreans.

METHODS: We studied 421 gastric cancer patients and 632 age- and sex-matched controls. Subjects completed a structured questionnaire regarding their food intake pattern. Polymorphisms of cytochrome P450 1A1 (*CYP1A1*), cytochrome P450 2E1 (*CYP2E1*), glutathione *S*-transferase mu 1 (*GSTM1*), glutathione *S*-transferase theta 1 (*GSTT1*) and aldehyde dehydrogenase 2 (*ALDH2*) were investigated.

RESULTS: A decreased risk of gastric cancer was noted among people with high consumption of nonfermented alliums and nonfermented seafood. On the other hand, consumption of kimchi, and soybean pastes was associated with increased risk of gastric cancer. Individuals with the *CYP1A1* Ile/Val or Val/Val genotype showed a significantly increased risk for gastric cancer. Increased intake of kimchi or soybean pastes was a significant risk factor for the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c1, the *GSTM1* non-null, the *GSTT1* non-null, or the *ALDH2* *1/*1 genotype. In addition, eating soybean pastes was associated with the increased risk of gastric cancer in individuals with the *GSTM1* null type. Nonfermented alliums were significant in individuals with the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c2 or c2/c2, the *GSTT1* null, the *GSTT1* non-null, or the *ALDH2* *1/*2 or *2/*2 genotype, nonfermented seafood was those with the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c1, the *ALDH2* *1/*1 genotype or any type of *GSTM1* or *GSTT1*. In homogeneity tests, the odds ratios of eating kimchi for gastric cancer according to the *GSTM1* or *GSTT1* genotype were not homogeneous.

CONCLUSION: Kimchi, soybean pastes, and the *CYP1A1* Ile/Val or Val/Val are risk factors, and nonfermented seafood and alliums are protective factors against gastric cancer in Koreans. Salt or some chemicals contained in kimchi and soybean pastes, which are increased by fermentation, would play important roles in the carcinogenesis of stomach cancer. Polymorphisms of the *CYP1A1, CYP2E1, GSTM1, GSTT1*, and *ALDH2* genes could modify the effects of some environmental factors on the risk of gastric cancer.

Key words: Kimchi; Soybean pastes; Gastric cancer

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INTRODUCTION

Stomach cancer is the most common cancer in Koreans[1], and the second leading site of cancer occurrence worldwide[2]. Environmental factors including dietary habits are important in its development[3,4]. Salted, smoked, pickled, and preserved foods rich in salt, nitrite, and preformed *N*-nitroso compounds have been reported to be associated with an increased risk of gastric cancer. In contrast, high intake of fresh fruit, raw vegetables, and antioxidants significantly reduced the risk of gastric cancer[5].

Since Crane *et al*[6] suggested a causal relationship between intake of traditional Korean foods and gastric cancer, there have been debates whether kimchi and soybean paste are protective factors or risk factors for gastric cancer. Messina *et al*[7] suggested that there was an inconsistent relationship between intake of soybean foods and stomach cancer; the risk seemed to increase with intake of fermented soybean foods and decrease with intake of nonfermented soybean foods. Kimchi and soybean pastes have been reported as risk factors for gastric cancer in some epidemiological studies[3,6] and as protective factors against gastric cancer in

others[8].

Genetic polymorphisms of xenobiotic-metabolizing enzymes can affect the susceptibility to cancers. The association of susceptibility to gastric cancer has been investigated in relation to the genetic polymorphisms of metabolic enzymes such as cytochrome P450 1A1 (*CYP1A1*), cytochrome P450 2E1 (*CYP2E1*), glutathione *S*-transferase mu 1 (*GSTM1*), glutathione *S*-transferase theta 1 (*GSTT1*), and aldehyde dehydrogenase 2 (*ALDH2*)[9-13]. Some of these studies found significant associations between these genetic polymorphisms and susceptibility to gastric cancer, but these results were not replicated in other studies[10,14,15].

Changes in the activity of enzymes metabolizing environmental carcinogens may modify the effect of exposure to environmental factors such as dietary factors, and result in alterations in an individual's susceptibility to gastric cancer. Thus, genetic factors as well as environmental factors should be considered in epidemiological studies.

In this case-control study, we investigated the effects of kimchi and soybean pastes on gastric cancer and compared them with those of the ingredients of kimchi, such as fresh vegetables, nonfermented alliums, and nonfermented seafood, and those of nonfermented soybean foods. We also considered genetic polymorphisms of major metabolic enzymes and the interactions between the polymorphisms and intake of those food items in the present study.

MATERIALS AND METHODS

Subjects

Four hundred and twenty-one people with gastric cancer and 632 controls frequency-matched based on age (within 3 years) and sex were the subjects of this hospital-based case-control study. Cases of cancer were all histologically confirmed from February 1997 to June 2003 at Chungbuk National University Hospital and Eulji University Hospital, Korea. Gastric cancer patients who had coexisting chronic disease affecting dietary pattern or communication problems were excluded. Control subjects were selected from patients newly diagnosed with diseases other than cancers at the same hospitals. In order to increase comparability between cases and controls, controls were also selected from patients who were admitted to the Department of Orthopedic Surgery of the same hospitals from where the cases were chosen, because of bony fractures, osteoarthritis, or inflammatory bone diseases. Individuals with a history of cancer, chronic disease affecting their dietary intake pattern, or communication problems were not included in the control group. The distributions of age and gender of the study subjects are shown in Table 1. The mean ages of the cases and control groups were 60.0±11.2 and 59.4±10.7 years, respectively. Case group comprised 276 men and 145 women, and control group 414 men and 218 women. Among 421 cases included, 24 individuals (7.0%) had tumor in cardiac area.

This study was conducted in accordance with the recommendations outlined in the Declaration of Helsinki, and every subject provided written informed consent.

Exposure to environmental factors

Trained interviewers interviewed subjects with a structured questionnaire not later than 1 mo after the diagnosis of gastric cancer or benign diseases. This included questions on demographic factors and diet. Dietary data were collected using a semi-quantitative food frequency table previously evaluated for validity and reliability[16]. All subjects were asked about the average frequency of intake and portion size of food items for a 1-year period leading up to the interview. These items were classified into six food groups having similar ingredients. Those food groups and corresponding food items were as follows: 'kimchi' - Chinese cabbage kimchi, radish kimchi, white kimchi, and kimchi stew, 'soybean paste' - soybean paste stew, fermented soybean stew, and miso soup, 'fresh vegetables' - fresh Chinese cabbage, lettuce, cucumber, hot pepper, and carrot, 'nonfermented alliums' - nonfermented garlic, onion, and Welsh onion, 'nonfermented seafood' - nonfermented shrimp, shellfish, oyster, and anchovy, 'nonfermented soybean foods' - bean curd, soybeans boiled in soysauce, boiled soybean, and soymilk.

Analysis of genetic polymorphisms

Genomic DNA was isolated from peripheral leukocytes by proteinase K digestion and phenol/chloroform extraction. The A4889G polymorphism in exon 7 of *CYP1A1* gene was analyzed for each subject as described previously[17]. Briefly, the PCR were performed in 25 μL of a solution containing 50 ng of genomic DNA, 1× PCR buffer (50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 9.0), 1.5 mmol/L $MgCl_2$ and 0.1% Triton X-100), 5 pmoL of each primer, 80 μmol/L each dNTP, and 2.0 unit *Taq* polymerase (Promega, Madison, WI, USA). The primers used were 5'-GAA CTG CCA CTT CAG CTG TC-3' and 5'-GAA AGA CCT CCC AGC GGT CA-3'. Amplifications were carried out in a Thermocycler (Perkin Elmer, Cetus, UK) as follows: 5 min of denaturation at 94 ℃, then 35 cycles consisting of denaturation at 94 ℃ for 60 s, annealing at 53 ℃ for 90 s and extension at 74 ℃ for 30 s. The PCR products (187-bp fragments) were digested with *Hin*cII restriction enzyme at 37 ℃ overnight and subjected to electrophoresis on 12% polyacrylamide gels. PCR analysis resulted in the following genotype classification: a predominant homozygote (Ile/Ile), a heterozygote (Ile/Val), and a rare homozygote (Val/Val).

The 5'-flanking region polymorphism of the *CYP2E1* gene was analyzed by procedures described previously[18]. Briefly, PCR was performed using the primers 5'-CCA GTC GAG TCT ACA TTG TCA-3' and 5'-TTC ATT CTG TCT

Table 1 Age and gender distribution of cases and controls

Variables	Number of subjects (%)	
	Cases	Controls
Gender		
Male	276 (65.6)	414 (65.5)
Female	145 (34.4)	218 (34.5)
Age (yr)		
<39	18 (4.3)	27 (4.3)
40–49	54 (12.8)	81 (12.8)
50–59	115 (27.3)	173 (27.4)
60–69	152 (36.1)	228 (36.1)
≥70	82 (19.5)	123 (19.4)

TCT AAC TGG-3'. Initial denaturation was performed at 94 ℃ for 5 min, followed by 35 thermal cycles consisting of denaturation for 1 min at 94 ℃, annealing for 1 min at 53 ℃ and extension for 30 s at 74 ℃. The 410-bp PCR product was digested with *Rsa*I at 37 ℃ overnight and subjected to electrophoresis on 2% agarose gels. The genotypes of *CYP2E1* were classified as follows: a predominant homozygote (c1/c1), a heterozygote (c1/c2), and a rare homozygote (c2/c2).

A multiplex PCR method[19] was used to simultaneously detect the presence or absence of the *GSTM1* and *GSTT1* genes with slight modification. The primers used were 5'-GAA GGT GGC CTC CTC CTT GG-3' and 5'-AAT TCT GGA TTG TAG CAG AT-3' for *GSTM1*, 5'-TTC CTT ACT GGT CCT CAC ATC TC-3' and 5'-TCA CCG GAT CAT GGC CAG CA-3' for *GSTT1*, and 5'-CAA CTT CAT CCA CGT TCA CC-3' and 5'-GAA GAG CCA AGG ACA GTT AC-3' for β-globin, the internal reference gene. After initial denaturation for 5 min at 94 ℃, a thermal cycle consisting of denaturation for 60 s at 94 ℃, annealing for 60 s at 58 ℃ and extension for 60 s at 74 ℃ was repeated 35 times. PCR products were separated on 2% agarose gels with ethidium bromide. *GSTM1* and *GSTT1* genotypes were not scored unless the PCR product of the β-globin gene was evident.

The *Mbo*II polymorphism of *ALDH2* was identified using a PCR-RFLP method[20] with slight modification. Briefly, PCR was performed using the primers 5'-CCA CAC TCA CAG TTT TCT CTT-3' and 5'-AAA TTA CAG GGT CAA CTG CT-3'. We used the same PCR conditions as in the *CYP1A1* gene analysis. The 134-bp amplicon was digested with *Mbo*II restriction enzyme at 37 ℃ overnight and subjected to electrophoresis on 15% polyacrylamide gels. The genotypes of ALDH2 were identified as a predominant homozygote (*1/*1), a heterozygote (*1/*2) and a rare homozygote (*2/*2).

Data analysis

Exposures to dietary factors were categorized into 'high' and 'low' intake groups based on median of intake in controls. For statistical analysis, the SAS System for Windows, Release 6.12 was used. *P*-value less than 0.05 was considered significant. Unconditional logistic analyses were performed to estimate odds ratios and 95%CI for high intake amount of food groups. To test for any increasing or decreasing trend of the risk of gastric cancer according to an increase of drinking amount, an unconditional logistic model including age and sex as independent variables was used.

Table 2 Mean±SE of intake amount of selected food items in cases and controls (unit: g/wk)

Food group	Cases	Controls	P^1
Kimchi	861.5±34.7	655.4±21.8	<0.0001
Soybean pastes	661.3±28.2	570.7±24.0	0.0155
Fresh vegetables	232.8±13.0	242.5±10.8	0.5681
Nonfermented alliums	74.3±6.6	99.9±6.8	0.0071
Nonfermented seafood	17.0±3.2	14.7±1.5	0.5125
Nonfermented soybean foods	208.9±14.4	229.7±12.3	0.2808

[1]*P*-value was estimated using a Student's *t*-test.

Odds ratios and 95%CI according to genotype of the *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, and *ALDH2* genes were estimated for food groups using unconditional logistic models including age and sex as independent variables. Homogeneities of the odds ratios according to the *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, and *ALDH2* genotypes were evaluated using the Breslow-Day test[21].

RESULTS

Average intake amounts of kimchi and soybean paste were significantly higher, and that of nonfermented alliums was significantly lower in gastric cancer cases than in controls. However, there was no significant difference in the intake amount of fresh vegetables, nonfermented seafood and soybean food (Table 2).

A decreased risk of gastric cancer was noted among people with high consumption of nonfermented alliums and nonfermented seafood. On the other hand, consumption of kimchi and soybean pastes was associated with increased risk of gastric cancer. The odds ratio (95%CI) of high consumption of kimchi was 1.57 (1.22, 2.01), and that of soybean paste was 1.62 (1.26, 2.09) (Table 3).

Individuals with the *CYP1A1* Ile/Val or Val/Val genotype showed a significantly increased risk for gastric cancer, and the adjusted odds ratio (95%CI) was 1.34 (1.04, 1.73). No genetic polymorphism of *CYP2E1*, *GSTM1*, *GSTT1*, or *ALDH2* was significant as an independent factor (Table 4).

Increased intake of kimchi or soybean pastes was a significant risk factor for the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c1, the *GSTM1* non-null, the *GSTT1* non-null, or the *ALDH2* *1/*1 genotype. In addition, eating soybean pastes was associated with the increased risk of gastric cancer in individuals with the *GSTM1* null type. Among the environmental protective factors, nonfermented alliums were significant in individuals with the *CYP1A1* Ile/Ile, the

Table 3 Distribution of cases and controls according to the intake of food groups

Food group	Number (%)		OR[1] (95%CI[2])	*P*
	Cases	Controls		
Kimchi				
Low	166 (39.4)	318 (50.3)	1.00	0.0004
High	255 (60.6)	314 (49.7)	1.57 (1.22, 2.01)	
Soybean pastes				
Low	162 (38.5)	319 (50.5)	1.00	0.0002
High	259 (61.5)	313 (49.5)	1.62 (1.26, 2.09)	
Fresh vegetables				
Low	217 (51.5)	311 (49.2)	1.00	0.4830
High	204 (48.5)	321 (50.8)	0.92 (0.72, 1.17)	
Nonfermented alliums				
Low	250 (59.4)	318 (50.3)	1.00	0.0046
High	171 (40.6)	314 (49.7)	0.70 (0.54, 0.89)	
Nonfermented seafood				
Low	254 (60.3)	317 (50.2)	1.00	0.0012
High	167 (37.9)	315 (49.8)	0.66 (0.51, 0.85)	
Nonfermented soybean foods				
Low	227 (53.9)	314 (49.7)	1.00	0.2160
High	194 (46.1)	318 (50.3)	0.85 (0.66, 1.10)	

[1]Odds ratio adjusted for age and sex. [2]Confidence interval.

Table 4 Distribution of genetic polymorphisms of the *GSTM1*, *GSTT1*, *CYP1A1*, *CYP2E1*, and *ALDH2* genes in cases and controls

Genotype	Number (%)		Total (%)	OR[1] (95%CI[2])
	Cases	Controls		
CYP1A1				
Ile/Ile	246 (58.9)	415 (65.8)	661 (63.0)	1.00
Ile/Val or Val/Val	172 (41.1)	216 (34.2)	388 (37.0)	1.34[a] (1.04, 1.73)
CYP2E1				
c1/c1	268 (64.4)	400 (63.5)	668 (63.9)	1.00
c1/c2 or c2/c2	148 (35.6)	230 (36.5)	378 (36.1)	0.96 (0.74, 1.24)
GSTT1				
Non-null	229 (57.3)	367 (59.8)	596 (58.8)	1.00
Null	171 (42.7)	247 (40.2)	418 (41.2)	1.11 (0.86, 1.44)
GSTM1				
Non-null	149 (37.3)	254 (41.4)	403 (39.7)	1.00
Null	251 (62.7)	360 (58.6)	611 (60.3)	1.18 (0.91, 1.53)
ALDH2				
*1/*1	286 (67.9)	462 (73.3)	748 (71.2)	1.00
*1/*2 or *2/*2	135 (32.1)	168 (26.7)	303 (28.8)	1.30 (0.99, 1.70)

[1]Odds ratio. [2]Confidence interval.

Table 5 Odds ratios (95%CI) for food groups according to polymorphisms of the *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, and *ALDH2* genes

Genotype		Kimchi	Soybean pastes	Fresh vegetables	Nonfermented alliums	Nonfermented seafood	Nonfermented soybean foods
CYP1A1	Ile/Ile	1.89[b]	1.78[b]	0.92	0.60[b]	0.56[b]	0.78
		(1.37, 2.61)	(1.29, 2.46)	(0.67, 1.26)	(0.44, 0.83)	(0.40, 0.77)	(0.56, 1.07)
	Ile/Val or	1.13	1.34	0.85	0.91	0.89	0.96
	Val/Val	(0.75, 1.70)	(0.89, 2.02)	(0.57, 1.28)	(0.61, 1.38)	(0.59, 1.34)	(0.63, 1.44)
CYP2E1	c1/c1	1.74[b]	1.77[b]	0.91	0.74	0.57[b]	0.84
		(1.27, 2.40)	(1.29, 2.43)	(0.67, 1.24)	(0.54, 1.01)	(0.42, 0.78)	(0.61, 1.15)
	c1/c2 or	1.27	1.37	0.91	0.63[a]	0.87	0.87
	c2/c2	(0.84, 1.93)	(0.90, 2.09)	(0.60, 1.38)	(0.41, 0.96)	(0.57, 1.33)	(0.57, 1.33)
GSTM1	Null	1.15[2]	1.51[a]	0.84	0.69[a]	0.64[b]	0.84
		(0.83, 1.59)	(1.08, 2.10)	(0.61, 1.16)	(0.50, 0.95)	(0.46, 0.89)	(0.61, 1.17)
	Non-null	2.31[b]	1.73[b]	1.00	0.71	0.64[a]	0.82
		(1.51, 3.53)	(1.14, 2.61)	(0.66, 1.50)	(0.47, 1.08)	(0.42, 0.96)	(0.54, 1.24)
GSTT1	Null	1.05[2]	1.38	0.94	0.70	0.64[a]	0.79
		(0.71, 1.56)	(0.93, 2.04)	(0.63, 1.39)	(0.47, 1.04)	(0.43, 0.96)	(0.53, 1.17)
	Non-null	2.01[b]	1.85[b]	0.89	0.67[a]	0.64[b]	0.87
		(1.43, 2.84)	(1.32, 2.61)	(0.64, 1.24)	(0.48, 0.94)	(0.45, 0.90)	(0.62, 1.22)
ALDH2	*1/*1	1.67[b]	1.64[b]	1.01	0.75	0.66[b]	0.81
		(1.34, 2.26)	(1.22, 2.22)	(0.75, 1.36)	(0.56, 1.01)	(0.49, 0.89)	(0.60, 1.10)
	*1/*2 or	1.24	1.57	0.68	0.61[a]	0.68	1.00
	*2/*2	(0.77, 1.99)	(0.98, 2.51)	(0.43, 1.08)	(0.38, 0.97)	(0.42, 1.10)	(0.62, 1.61)

[1]Odds ratios and 95%CI were adjusted for age and sex. [2]Odds ratio was significantly different from that of the other genotype in a homogeneity test. [a]$P<0.05$. [b]$P<0.01$ *vs* others.

CYP2E1 c1/c2 or c2/c2, the *GSTT1* null, the *GSTT1* non-null, or the *ALDH2* *1/*2 or *2/*2 genotype, nonfermented seafood was those with the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c1, the *ALDH2* *1/*1 genotype or any type of *GSTM1* or *GSTT1* (Table 5).

In homogeneity tests, the odds ratios of eating kimchi for gastric cancer according to the *GSTM1* or *GSTT1* genotype were not homogeneous (Table 5).

DISCUSSION

In this present study, a decreased risk of gastric cancer was noted among people with a high consumption of nonfermented seafood and alliums. Eating fish has been reported to decrease the risk of gastric cancer in Japanese women[22], and in Swedes[23]. However, effects of fish intake on the risk of gastric cancer varied by preparation method. Pan-fried fish decreased, whereas stewed or broiled fish increased the risk of gastric cancer in Koreans[4]. Alliums have been repeatedly reported to decrease the risk of gastric cancer[24]. Alliums have been shown to suppress the growth of *Helicobacter pylori*[25], and *N*-nitrosodimethylamine-induced forestomach tumor in mice[26]. Some chemicals in alliums inhibit the expression of carcinogen-activating cytochrome P450 enzymes but induce GSTs[27]. Diallyl sulfide, which is abundant in alliums, has been suggested as the key protective material[28]. Intake of fresh vegetables, which has been reported to reduce the risk of gastric cancer[22,29], showed an odds ratio smaller than 1, but was not statistically significant.

Eating kimchi and soybean pastes was associated with

increased risk of gastric cancer in this present study (Table 3). The odds ratios for gastric cancer of kimchi and soybean pastes were less than 2, but those food items are very popular among the Koreans. Therefore, the risks attributable for gastric cancer by the intake of kimchi and soybean pastes would be relatively high among the Korean population. Fermented Korean foods, such as kimchi and soybean pastes, have been reported to show high nitrate concentrations[30,31]. During fermentation of kimchi, nitrate contents decrease but secondary amine increases continuously[32], especially in Chinese cabbage kimchi made with fermented shrimp sauce[30]. Nitrosodimethylamine increased in every kind of kimchi after simulated gastric digestion of kimchi[33]. Increases in the risk of gastric cancer associated with a high intake of fermented soy-based foods have been reported in epidemiologic studies among the Koreans[3,6], Japanese[34,35], Taiwanese[36], and Chinese[37]. We did not find any statistical significance for risks associated with nonfermented soybean foods as reported by Lee *et al*[36] and Hoshiyama *et al*[34]. Fermented soybean pastes also show a high nitrate level[31].

After dietary nitrate is absorbed, about 25% is actively secreted into the saliva and 5% of ingested nitrate is reduced to nitrite by oral bacteria. Since most saliva is swallowed, about 80% of gastric nitrite in the normal acidic stomach arises from the reduction of ingested or endogenous nitrate[38]. Gastric nitrosation, which is carried out by nitrite, may produce unstable *N*-nitroso compounds that do not reach extra-gastric sites and act directly in the stomach to initiate gastric cancer, or may produce stable *N*-nitroso compounds that induce cancer at other sites[38,39].

Many epidemiological studies have reported a relationship between a high salt diet and gastric cancer[40-45]. Koreans have one of the highest rates of 24-h urinary sodium excretion in the world[45], and one of the highest rates of mortality from gastric cancer. It should be noted that kimchi and soybean pastes, which were significant risk factors of gastric cancer in this study, also have very high salt contents.

A few epidemiological studies on gastric cancer have included genetic polymorphisms in the analysis, and fewer studies have tested gene and environmental interactions. The results of epidemiological studies on the effects of genetic polymorphisms on gastric cancer are not always consistent. In spite of the expression of *CYP1A1* in gastric mucosa, no studies have been identified that assess the potential influence of *CYP1A1* polymorphisms in gastric cancer risk[46]. Increased risks of developing gastric cancer have been reported for the *CYP2E1* c1/c2 or c2/c2[13], *GSTM1* null[9,10], *GSTT1* null[12], and *2-allele containing *ALDH2* genotypes[11] independently, or in combination with environmental factors. However, these significant associations were not found in other studies[10,14,15]. In this present study, we could find an increased risk of gastric cancer in individuals with the *CYP1A1* Ile/Val or Val/Val genotype. This result is concordant with the previous studies that cigarette smoking is a risk factor of stomach cancer, and the *CYP1A1* genotype would be involved in the gastric carcinogenesis by cigarette smoking[47].

In this present study, kimchi and soybean pastes showed very similar interactions with the genetic polymorphisms, and were significant risk factors in individuals with the *CYP1A1* Ile/Ile, the *CYP2E1* c1/c1, the *GSTM1* non-null, the *GSTT1* non-null, and the *ALDH2* *1/*1 genotypes. This fact leads to a possibility that kimchi and soybean pastes contain some common carcinogens which are metabolized by the same metabolic enzymes. Though *CYP2E1* activity for the metabolism of chlorzoxazone has been reported to be lower in individuals with *CYP2E1* c2/c2 type than in those with other genotypes[48], *CYP2E1* activity for the metabolism of *N*-nitroso compound would be low in individuals with *CYP2E1* c1/c1 type. Therefore, hepatic *CYP1A1* or *CYP2E1* activity and first-pass clearance would be low in individuals with *CYP1A1* Ile/Ile genotype or *CYP2E1* c1/c1 type. In that case, the blood level of the unmetabolized carcinogens and, in turn, exposure of extrahepatic organs to the carcinogen may be increased[49]. *N*-nitroso compounds originating from kimchi and soybean pastes would not be rapidly metabolized in the hepatic tissue of individuals with *CYP1A1* Ile/Ile or *CYP2E1* c1/c1 genotypes, and the risk of gastric cancer may be increased by the increased exposure of gastric mucosa to *N*-nitroso compounds.

On the contrary, in hepatic tissue of individuals with *GSTM1* non-null or *GSTT1* non-null genotype, rapid glutathione conjugation of activated carcinogens would occur. Since glutathione conjugates are water-soluble, plasma concentration of the glutathione-conjugated carcinogens would be increased. The high plasma concentration may increase exposure of gastric tissue to glutathione conjugated carcinogens and, in turn, the risk of gastric cancer in individuals with *GSTM1* non-null or *GSTT1* non-null genotype.

In homogeneity tests, the odds ratios of eating kimchi for gastric cancer according to the *GSTM1* or *GSTT1* genotype were not homogeneous. Because homogeneity was tested for 36 times and the *P*-value was 0.05, about two tests would be expected to be statistically significant by chance.

Because the interval between exposure to dietary carcinogens and the development of gastric cancer could be 20 years or more, it would be desirable to test the causal relationships between the historical dietary intake patterns and present gastric cancer development. However, it is almost impossible to get an unbiased information on such past dietary intake patterns. We therefore assessed the average frequencies of intake and portion size of six food groups in a 1-year period leading up to the interview. There is a possibility that the very symptoms of gastric cancer might change the food intake pattern or nutritional state of patients with gastric cancers that have been neglected for years. Therefore, the diet-related results of this study should be carefully interpreted.

Tumors located at cardiac area have been reported to have different etiological factors from non-cardiac gastric cancers. We did not exclude cardiac gastric cancers from the case group of this present study. Although the proportion of cardiac cancer (7.0%) was not so high, we cannot rule out the possibility of selection bias.

In summary, kimchi, soybean pastes, and the *CYP1A1*

Ile/Val or Val/Val are risk factors, and nonfermented seafood and alliums are protective factors against developing gastric cancer. Salt or some chemicals contained in kimchi and soybean pastes, which are increased by fermentation, would play important roles in the carcinogenesis of stomach cancer. Polymorphisms of the *CYP1A1*, *CYP2E1*, *GSTM1*, *GSTT1*, and *ALDH2* genes could modify the effects of some environmental factors on the risk of gastric cancer.

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