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Interaction between dietary potassium intake and *TNF-α* rs1800629 genetic polymorphism in gastric cancer risk: a case–control study conducted in Korea

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Abstract

Mineral consumption has been suggested to have an impact on gastric cancer (GC) prevention. However, the protective effect of potassium against gastric carcinogenesis remains inconclusive. The causal link between inflammation and cancer is well established. Notably, potassium intake and potassium channels may play certain roles in regulating the production of TNF-α (*TNF-α*). We aimed to determine whether dietary potassium intake is related to the risk of GC. We further observed whether this association was modified by *TNF-α* rs1800629. We designed a case–control study comprising 377 GC cases and 756 controls. Information on dietary potassium intake was collected using a semiquantitative food frequency questionnaire. Genotyping was performed by the Affymetrix Axiom Exom 319 Array platform. Unconditional logistic regression models were used to assess associations. A significantly reduced GC risk was found for those who consumed higher dietary potassium levels (OR = 0·63, 95 % CI = 0·45, 0·89, *P* for trend = 0·009). In the dominant model, we observed a non-significant association between *TNF-α* rs1800629 and GC risk (OR = 1·01, 95 % CI = 0·68, 1·49). In females, those who were homozygous for the major allele (G) of rs1800629 with a higher intake of dietary potassium exhibited a decreased risk of GC (OR = 0·40, 95 % CI = 0·20, 0·78, *P* interaction = 0·041). This finding emphasises the beneficial effect of potassium intake on GC prevention. However, this association could be modified by *TNF-α* rs1800629 genotypes. A greater protective effect was exhibited for females with GG homozygotes and high potassium intake.

Key words: **Potassium: *TNF-α* rs1800629: Gastric cancer: Case–control study**

According to data from 2020, gastric cancer (GC) is responsible for the fifth and fourth greatest incidence and mortality rates worldwide, respectively[1]. The prevalence rate of GC varies geographically[2]. The highest incidence rate of GC was recorded in East Asia[2,3]. Although South Korea has experienced a decreasing trend in incidence and mortality since 1999[4], GC remains a significant concern.

Several studies have been conducted to explore various risk factors associated with GC development[5]. Although infection with *Helicobacter pylori (H. pylori)* has been well recognised in relation to GC progression, the role of other risk factors in the aetiology of GC still needs to be determined[6]. A healthy diet is indicated to be a key source of important vitamins and minerals, and its importance has drawn much attention in recent years[7].

Previous epidemiological studies documented that minerals may have certain roles in GC pathogenesis. For example, sodium consumption has a detrimental effect on GC even with the intake of intermediate levels[8]. A higher haem iron intake was reported to be associated with an elevated GC risk, whereas non-haeme iron was suggested to be a protective factor against GC risk[9]. A beneficial effect against gastric carcinogenesis was also found for Ca and Mg[10].

Potassium is an essential mineral that is mainly derived from dietary sources such as fruits, vegetables, beans and lentils. The Western diet is a consequence of the global spread of the Western lifestyle, which is characterised by low fruit and vegetable consumption and high processed food consumption. Consequently, there is an imbalance in Na and K intake, where high Na and low K intake have been reported[11]. To date, few studies have been conducted to elucidate the link between low potassium consumption and cancer. Potassium intake was found to be a preventive nutrient for colorectal cancer[12,13]. Similarly, an

Abbreviations: GC, gastric cancer.

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appropriate potassium intake served as a protective factor against lung cancer risk[14]. In contrast, available evidence regarding a protective effect of potassium against other cancers is limited, and GC is no exception. To the best of our knowledge, only one study has been conducted to explore the association of potassium with GC. However, a non-significant association was observed[8], whereas potassium was suggested to have a preventive effect on GC development by a nutrition survey[15]. Thus, there is a paucity of evidence related to the relationship of potassium intake with GC risk. In addition to dietary factors such as dietary potassium intake, it is necessary to focus on inflammation-related factors that are strongly related to gastric carcinogenesis.

It has been reported that there are positive correlations between inflammatory cytokines specifically in individuals with *H. pylori* infection and GC risk[16]. *TNF-α* is one of the proinflammatory cytokines that stimulates other cytokines and mediates the cytokine cascade causing inflammation[17]. There is a causal association between the production of *TNF-α* and cancer tumorigenesis[18]. The regulation of *TNF-α* production occurs at the level of transcription, and polymorphisms in the *TNF-α* promoter region are indicated in relation to *TNF-α* production[19]. The association between *TNF-α* promoter polymorphisms and GC risk was indicated in a previous meta-analysis[20]. One of the *TNF-α* promoter polymorphisms is the G (guanine) > A (adenine) (rs1800629) SNP located at position -308, which is associated with *TNF-α* production[19]. In detail, a higher transcriptional activity was observed for the A allele compared to the G allele[21,22]. For example, in comparison with the presence of the G allele at -308 of the *TNF-α* promoter, the presence of the A allele increased the transcriptional level twofold[22]. Notably, a previous study emphasised that *TNF-α* production may be regulated by potassium (K^+) and K^+ channels by activated human culture-derived macrophages[23]. Furthermore, differences in genetic variants and dietary patterns may account for different GC risks among individuals. Thus, the discrepancy in GC susceptibility may be explained by the interaction between genes and diet[24]. Based on this biological mechanism, we hypothesised that there may be an interaction between dietary potassium intake and *TNF-α* rs1800629 in gastric carcinogenesis.

To our knowledge, the potential effect of dietary potassium intake on gastric carcinogenesis has been reported in a few previous studies, and the findings have been ambiguous. Additionally, an interactive effect between potassium intake and *TNF-α* rs1800629 on gastric carcinogenesis has not been investigated thus far. Therefore, we aimed to examine whether potassium intake is related to GC risk. Moreover, we wanted to observe whether the *TNF-α* rs1800629 SNP modifies this association.

Materials and methods

Study population

We recruited participants from the National Cancer Center (NCC) Hospital in Korea between March 2011 and December 2014 to conduct a case–control study. The details of participant recruitment are described elsewhere[25,26]. Cases were identified as those who were diagnosed with GC within 3 months preceding enrollment, except participants with chronic diseases and who were pregnant or breastfeeding. Subjects without a history of cancer or chronic diseases who visited the Cancer Prevention and Detection Center in NCC for health-screening examinations were identified as controls. We used age (±5 years) and sex to match controls and cases at a ratio of 2:1. A total of 756 controls and 377 cases with available information on genotypes were included for analysis in our study. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Institutional Review Board of the National Cancer Center Korea (IRB No. NCC2021–0181). Written informed consent was obtained from all subjects/patients.

Data collection

The assessment of dietary intake of participants within 12 months prior to the interview was performed with a 106-item semiquantitative FFQ. The semiquantitative FFQ has been reported to be valid and reliable[27] and contains nine categories for food consumption frequency and three categories for portion size. Total energy and potassium intake were determined by using a Computer Aided Nutritional analysis program (CAN-PRO 5·0, Korean Nutrition Society). Dietary potassium (mg/d) for each participant was calculated by summing the amount of potassium obtained from consumed foods. Additionally, information on demographics and lifestyle was collected using a self-administered questionnaire.

Genotype identification

Detailed information on the genotyping and quality control steps is mentioned elsewhere[28,29]. Briefly, we used peripheral blood to extract genomic DNA. Genotyping was performed using the Affymetrix Axiom Exom 319 Array (Afymetrix Inc.) platform with 318 983 variants. Genotype imputation was performed using the Asian population (n 504) in the 1000 Genome haplotypes phase III integrated variant set release GRch37/hg19 (https://www.1000genomes.org/) as a reference panel. Genetic markers with deviation from Hardy–Weinberg equilibrium P values < 1×10^{-10}, a minor allele frequency < 0·05, and a low call rate (< 98 %) were discarded. We used SHAPEIT (v2.r837) for phasing and IMPUTE2 (2·3·2) for SNP imputation. After filtering for an INFO score over 0·6, quality control criteria were applied. Finally, *TNF-α* rs1800629 was selected as a candidate SNP for the analysis of our study.

Statistical analyses

Potassium intake was energy-adjusted using the residual method[26]. We used the distribution of controls to classify potassium intake into tertiles. The comparison of general characteristics of cases with controls was performed by using the χ^2 test and t test for categorical and continuous variables, respectively. The calculation of OR and 95 % CIs was based on unconditional logistic regression models. The lowest tertile was considered the reference group. Furthermore, we determined the dose–response relationships of intake of dietary potassium in relation

to GC risk by using the median value of each tertile of potassium intake to identify a test for trend. We used a dominant model to analyse genetic association. We used tertile categories of potassium intake to examine the impact of the interaction between dietary potassium intake and *TNF-α* rs1800629 on GC risk. Statistical interaction was determined using a likelihood ratio test of models with and without the interaction term (potassium × SNP). SAS software (version 9.4, SAS Institute) was used for all statistical analyses, and a two-sided *P* value less than 0·05 was considered significant.

Results

Demographic characteristics of the study participants

In comparison with healthy individuals, GC patients were more likely to be infected with *H. pylori*, and a high proportion of patients were current smokers (92·6 % *v.* 61·4 % and 30·8 % *v.* 20·4 %, $P < 0·001$, respectively). Similarly, they exhibited a higher rate of first-degree family history of GC (20·4 % *v.* 12·6 %, $P < 0·001$). In contrast, lower proportions of physical activity, level of education, income and occupation were observed in cases than those in controls (36·1 % *v.* 56·1 %, 23·1 % *v.* 51·8 %, 23·3 % *v.* 32·7 % and 17·2 % *v.* 19·0 %, respectively, $P < 0·001$). GC cases consumed significantly lower amounts of dietary potassium than controls ($P < 0·001$) (Table 1).

Potassium intake and GC risk

In comparison with subjects in the low tertile group of potassium intake, subjects in the high tertile group showed a lower GC risk. This significant association was observed in both the univariate model and model adjusted for possible confounders; OR (95 % CI) were 0·56 (0·41, 0·77), *P* for trend < 0·001 and 0·63 (0·45, 0·89), *P* for trend = 0·009, respectively. Importantly, the significant inverse associations between dietary potassium intake and GC risk remained for both male (OR = 0·65 (0·42, 0·99), *P* for trend = 0·042) and female (OR = 0·54 (0·29, 0·99), *P* for trend = 0·048) populations in the fully adjusted model (Table 2).

Associations of the TNF-α rs1800629 polymorphism with GC risk

The three genotypes of *TNF-α* rs1800629 were GG, AG and AA and were in Hardy–Weinberg equilibrium ($P = 0·077$). A dominant model of the *TNF-α* rs1800629 SNP was used to examine its association with GC risk. We observed a non-significant association of *TNF-α* rs1800629 with gastric carcinogenesis. The OR (95 % CI) in the unadjusted and adjusted models were 0·98 (0·68, 1·41) and 1·01 (0·68, 1·49), respectively. Non-significant associations were also observed for both sexes; OR (95 % CI) were 1·19 (0·74, 1·92) and 0·73 (0·36, 1·49) for males and females, respectively (Table 3).

The interactive effect of the TNF-α rs1800629 polymorphism and potassium intake on gastric carcinogenesis

Table 4 presents the interactive effect of the *TNF-α* rs1800629 genetic polymorphism and potassium intake on gastric carcinogenesis. High potassium intake was found to be inversely associated with GC risk among subjects who carried the homozygous wild-type allele (GG) regardless of confounding adjustment (Model 3: OR = 0·63 (95 % CI: 0·43, 0·91)). Based on the sex stratification, this preventive effect seemed to be limited to females (OR = 0·40 (95 % CI: 0·20, 0·78)) with a significant interaction (*P* interaction = 0·041).

Discussion

In the present case–control study, we observed a negative association between potassium intake and GC risk. Additionally, *TNF-α* genetic polymorphism was observed to have an effect modification on this association. In detail, a protective effect of potassium against GC seemed to be greater in subjects who had higher potassium intake and carried the *TNF-α* rs1800629 homozygous wild-type allele (GG), especially among females.

The effect of a diet high in potassium on cancer prevention was investigated in some previous studies. Existing evidence supports the hypothesis that high potassium intake may contribute to reducing cancer risk. For example, a protective effect of potassium against lung cancer was emphasised in a study of 165 409 participants from the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial and the Women's Health Initiative[14]. Another study indicated that high potassium intake may be considered a preventative factor for colorectal cancer occurrence[12]. The aforementioned association was reinforced by a conclusion drawn from a meta-analysis of twenty-nine studies[13].

To date, available evidence indicating the role of potassium in GC prevention is limited. There was only a case–control study conducted to explore the potential effect of potassium on GC risk and found a non-significant association[8]. In contrast, high potassium intake was suggested to have a preventive effect on GC development in our study. This is in agreement with a previous nutrition survey[15]. Consistent findings were also observed in an *in vivo* study, which reported that the incidence of GC was reduced significantly due to prolonged oral treatment with potassium[30]. The possible biological mechanisms underlying this association may be proposed. First, intracellular ions and potassium can be released into the extracellular fluid by tumour necrosis. T-cell receptor-driven Akt-mTOR phosphorylation and effector programs may be impaired by an increase in intracellular potassium within T cells due to increased extracellular potassium. As a result, T-cell effector function is suppressed. Neoantigens, which are generated and recognised by tumour cells and T cells, respectively, and cancerous cells may be killed by T cells. In addition, T cells may produce chemicals that play a role in the regulation of immunity and protective effects against tumours[14]. Second, the effect of potassium on GC prevention may be linked to gastric acid secretion. Gastric acid is known to be associated with gastric carcinogenesis[30]. It is important to note that potassium ions have a critical role in activating and catalysing gastric H^+, K^+-ATPase, leading to the secretion of acid[31]. Third, potassium may serve as an anti-tumour agent because it is essential for folding and stabilising G-quadruplexes[32]. Fourth, pancreatic cells need

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Table 1. General characteristics of the study participants

	All (*n* 1133)					Men (*n* 743)					Women (*n* 390)				
	Controls (*n* 756)		Cases (*n* 377)			Controls (*n* 497)		Cases (*n* 246)			Controls (*n* 259)		Cases (*n* 131)		
	n	%	*n*	%	*P*-value*	*n*	%	*n*	%	*P*-value*	*n*	%	*n*	%	*P*-value*
Age (years)†															
Mean	53·8		53·9		0·947	54·8		55·0		0·758	51·9		51·6		0·826
SD	9·0		9·3			8·4		8·6			9·7		10·1		
Sex															
Male	497	65·7	246	65·3	0·870										
Female	259	34·3	131	34·7											
BMI (kg/m^2)															
Mean	24·0		23·9		0·389	24·5		24·2		0·288	23·1		23·1		0·984
SD	2·9		3·1			2·7		3·0			3·1		3·0		
<23	276	36·5	147	39·0	0·673	140	28·2	84	34·2	0·207	136	52·5	63	48·1	0·727
23–25	230	30·4	107	28·4		160	32·2	68	27·6		70	27·0	39	29·8	
≥25	249	32·9	122	32·4		197	39·6	94	38·2		52	20·1	28	21·4	
Missing	1	0·2	1	0·2		0	0	0	0		1	0·4	1	0·7	
H. pylori infection															
Negative	292	38·6	28	7·4	<0·001	175	35·2	16	6·5	<0·001	117	45·2	12	9·2	<0·001
Positive	464	61·4	349	92·6		322	64·8	230	93·5		142	54·8	119	90·8	
Missing	0	0	0	0		0	0	(0)			(0)		(0)		
First-degree family history of GC															
No	659	87·2	299	79·3	<0·001	424	85·3	190	77·2	0·006	235	90·7	109	83·2	0·030
Yes	95	12·6	77	20·4		71	14·3	55	22·4		24	9·3	22	16·8	
Missing	2	0·2	1	0·3		2	0·4	1	0·2		0	0	0	0	
Smoking status															
Non-smoker	344	45·5	151	40·0	<0·001	96	19·3	34	13·8	<0·001	248	95·8	117	89·4	0·038
Ex-smoker	258	34·1	110	29·2		251	50·5	103	41·9		7	2·7	7	5·3	
Current smoker	154	20·4	116	30·8		150	30·2	109	44·3		4	1·5	7	5·3	
Missing	0	0	0	0		0	0	0	0		0	0	0	0	
Alcohol intake															
Non-drinker	212	28·0	112	39·7	0·333	81	16·3	42	17·1	0·330	131	50·6	70	53·4	0·863
Ex-drinker	58	7·7	37	9·8		46	9·3	31	12·6		12	4·6	6	4·6	
Current-drinker	486	64·3	228	60·5		370	74·4	173	70·3		116	44·8	55	42·0	
Missing	0	0	0	0		0	0	0	0		0	0	0	0	
Regular exercise															
Yes	424	56·1	136	36·1	<0·001	279	56·1	100	40·6	<0·001	145	56·0	36	27·5	<0·001
No	329	43·5	241	63·9		215	43·3	146	59·4		114	44·0	95	72·5	
Missing	3	0·4	0	0		3	0·6	0	0		0	0	0	0	
Education n (%)															
Less than high school	109	14·4	126	33·4	<0·001	64	12·9	81	32·9	<0·001	45	17·4	45	34·4	<0·001
High school	225	29·8	163	43·2		124	24·9	106	43·1		101	39·0	57	43·5	
More than high school	392	51·8	87	23·1		281	56·5	58	23·6		111	42·9	29	22·1	
Missing	30	4·0	1	0·3		28	5·7	1	0·4		2	0·7	0	0	
Marital status															
Married	652	86·2	327	86·7	0·777	441	88·7	221	89·8	0·592	211	81·5	106	80·9	0·895
Others	103	13·6	49	13·0		55	11·1	24	9·8		48	18·5	25	19·1	
Missing	1	0·2	1	0·3		1	0·2	1	0·4		0	0	0	0	
Monthly income (10 000 Korean won/mo)															
<200	132	17·5	120	31·8	<0·001	74	14·9	78	31·7	<0·001	58	22·4	42	32·1	0·050
200–400	313	41·4	132	35·0		217	43·7	94	38·2		96	37·1	38	29·0	
≥400	247	32·7	88	23·3		153	30·8	50	20·3		94	36·3	38	29·0	
Missing	64	8·4	37	9·9		53	10·6	24	9·8		11	4·2	13	9·9	
Occupation															
Professional administrative	144	19·0	65	17·2	<0·001	108	21·7	54	22·0	0·004	36	13·9	11	8·4	0·006
Office, Sales, service	240	31·7	108	28·6		186	37·4	72	29·3		54	20·9	36	27·5	
Labourer, agricultural	117	15·5	98	25·9		100	20·1	78	31·7		17	6·6	20	15·3	
Others, unemployed	252	33·3	105	27·9		100	20·1	41	16·7		152	58·6	64	48·8	
Missing	3	0·4	1	0·4		3	0·7	1	0·3		0	0	0	0	
Histological subtype of gastric cancer															
Diffuse	–		149	39·5		–		70	28·5		–		79	60·3	
Intestinal	–		145	38·5		–		119	48·4		–		26	19·8	
Mixed	–		51	13·5		–		37	15·0		–		14	10·7	
Indeterminate	–		4	1·1		–		3	1·2		–		1	0·8	
Missing			28	7·4				17	6·9				11	8·4	
Total energy intake† (kcal/d)															
Mean	1796·8		2014·1		<0·001	1847·5		2125·7		<0·001	1699·5		1804·6		0·081
SD	569·4		638·3			561·4		661·6			573·1		534·5		

Table 1. (*Continued*)

	All (*n* 1133)					Men (*n* 743)					Women (*n* 390)				
	Controls (*n* 756)		Cases (*n* 377)			Controls (*n* 497)		Cases (*n* 246)			Controls (*n* 259)		Cases (*n* 131)		
	n	%	*n*	%	*P*-value*	*n*	%	*n*	%	*P*-value*	*n*	%	*n*	%	*P*-value*
Potassium intake† (mg/d)															
Mean	2583·4		2408·0		<0·001	2473·0		2346·3		0·023	2795·1		2523·9		0·003
SD	793·6		723·7			728·4		676·6			868·5		794·7		

* χ^2 test for categorical variables and *t* test for continuous variables were applied.
† Mean ± SD was presented for continuous variables.

Table 2. Association of *tertiles* of dietary potassium intake with GC risk

					Model 1		Model 2		Model 3	
Potassium (mg/d)	No. of controls	%	No. of cases	%	OR	95 % CI	OR	95 % CI	OR	95 % CI
All (*n* 1133)										
T1 (<2199·96)	252	33·3	167	44·3	1·00		1·00		1·00	
T2 (2199·96–2785·23)	252	33·3	116	30·8	0·70	0·52, 0·93	0·70	0·52, 0·96	0·71	0·51, 0·98
T3 (≥2785·23)	252	33·4	94	24·9	0·56	0·41, 0·77	0·61	0·44, 0·84	0·63	0·45, 0·89
P for trend					<0·001		0·003		0·009	
Men (*n* 743)										
T1 (<2145·42)	165	33·2	107	43·5	1·00		1·00		1·00	
T2 (2145·42–2696·47)	166	33·4	80	32·5	0·74	0·52, 1·07	0·77	0·53, 1·11	0·79	0·54, 1·17
T3 (≥2696·47)	166	33·4	59	24·0	0·55	0·37, 0·81	0·56	0·38, 0·84	0·65	0·42, 0·99
P for trend					0·002		0·005		0·042	
Women (*n* 390)										
T1 (<2340·75)	86	33·2	59	45·0	1·00		1·00		1·00	
T2 (2340·75–3054·34)	86	33·2	43	32·8	0·73	0·45, 1·19	0·80	0·47, 1·35	0·78	0·44, 1·37
T3 (≥3054·34)	87	33·6	29	22·2	0·49	0·29, 0·83	0·55	0·31, 0·98	0·54	0·29, 0·99
P for trend					0·008		0·043		0·048	

GC, gastric cancer.
Model 1: unadjusted model; Model 2: adjusted for age, BMI, first-degree family history of GC, smoking status, alcohol consumption, regular exercise and marital status; Model 3: additionally adjusted for *H. pylori* infection. In the total subjects, models 2 and 3 were additionally adjusted for sex.

Table 3. *TNF* rs1800629 genetic polymorphisms and risk of GC in the dominant model

		No (%)				OR (95 % CI)					
		Controls		Cases		Model 1		Model 2		Model 3	
	Genotypes	*n*	%	*n*	%	OR	95 % CI	OR	95 % CI	OR	95 % CI
All	GG	652	86·2	326	86·5	1·00		1·00		1·00	
	AG/AA	104	13·8	51	13·5	0·98	0·68, 1·41	1·04	0·71, 1·50	1·01	0·68, 1·49
Men	GG	434	87·3	210	85·4	1·00		1·00		1·00	
	AG/AA	63	12·7	36	14·6	1·18	0·76, 1·84	1·19	0·76, 1·89	1·19	0·74, 1·92
Women	GG	218	84·2	116	88·6	1·00		1·00		1·00	
	AG/AA	41	15·8	15	11·4	0·69	0·37, 1·30	0·81	0·41, 1·58	0·73	0·36, 1·49

GC, gastric cancer.
Model 1: unadjusted model; Model 2: adjusted for age, BMI, first-degree family history of GC, smoking status, alcohol consumption, regular exercise and marital status; Model 3: additionally adjusted for *H. pylori* infection. In the total subjects, models 2 and 3 were additionally adjusted for sex.

potassium to secrete insulin. As a result, hypokalaemia may lead to impaired insulin secretion and glucose intolerance[33]. A higher risk of diabetes can be attributable to lower potassium intake, which was well recognised in previous studies[34,35]. Notably, epidemiological studies are robust enough to support the causal link between diabetes and GC occurrence[36–38]. Thus, it has been established that diabetes may be a mediator for the link between low potassium intake and increased GC progression.

H. pylori is known to be an aetiology for gastric carcinogenesis. *H. pylori* and host genetic factors impact the inflammatory response and epithelial cell physiology and increase GC risk[39]. The *TNF-α* gene is a major cytokine related to *H. pylori* infection[40]. It is reported to be related to chronic inflammation,

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Table 4. Interactive effect of the *TNF-α* rs1800629 polymorphism and potassium intake on gastric carcinogenesis

TNF rs1800629	GG			AG/AA		*P* interaction
All	**Low (<2199.96)**	**Moderate (2199.96–2785.23)**	**High (≥2785.23)**	**Low (<2199.96)**	**Moderate (2199.96–2785.23)**	**High (≥2785.23)**	
No. of controls/cases	215/142	216/102	221/82	37/25	36/14	31/12	
Model 1 [OR (95% CI)]	1.00	0.72 (0.52–0.98)	0.56 (0.40–0.78)	1.02 (0.59–1.77)	0.59 (0.31–1.13)	0.59 (0.29–1.18)	0.856
Model 2 [OR (95% CI)]	1.00	0.72 (0.52–1.00)	0.60 (0.42–0.85)	1.04 (0.59–1.84)	0.63 (0.32–1.23)	0.69 (0.33–1.45)	0.853
Model 3 [OR (95% CI)]	1.00	0.71 (0.50–1.01)	0.63 (0.43–0.91)	0.97 (0.53–1.78)	0.68 (0.34–1.39)	0.65 (0.30–1.40)	0.989
Men	**Low (<2145.42)**	**Moderate (2145.42-2696.47)**	**High (≥2696.47)**	**Low (<2145.42)**	**Moderate (2145.42-2696.47)**	**High (≥2696.47)**	
No. of controls/cases	142/89	143/66	149/55	23/18	23/14	17/4	
Model 1 [OR (95% CI)]	1.00	0.74 (0.50–1.09)	0.59 (0.39–0.89)	1.25 (0.64–2.44)	0.97 (0.48–1.99)	0.38 (0.12–1.15)	0.539
Model 2 [OR (95% CI)]	1.00	0.75 (0.50–1.12)	0.60 (0.39–0.92)	1.20 (0.60–2.40)	1.04 (0.50–2.19)	0.38 (0.12–1.26)	0.551
Model 3 [OR (95% CI)]	1.00	0.76 (0.50–1.17)	0.70 (0.45–1.10)	1.23 (0.59–2.58)	1.20 (0.55–2.61)	0.39 (0.12–1.29)	0.365
Women	**Low (<2340.75)**	**Moderate (2340.75-3054.34)**	**High (≥3054.34)**	**Low (<2340.75)**	**Moderate (2340.75-3054.34)**	**High (≥3054.34)**	
No. of controls/cases	73/54	67/40	78/22	13/5	19/3	9/7	
Model 1 [OR (95% CI)]	1.00	0.81 (0.48–1.37)	0.38 (0.21–0.69)	0.52 (0.18–1.55)	0.21 (0.06–0.76)	1.05 (0.37–3.00)	0.015
Model 2 [OR (95% CI)]	1.00	0.86 (0.49–1.51)	0.42 (0.22–0.80)	0.58 (0.18–1.81)	0.29 (0.08–1.08)	1.38 (0.45–4.25)	0.026
Model 3 [OR (95% CI)]	1.00	0.79 (0.43–1.45)	**0.40 (0.20–0.78)**	0.41 (0.12–1.39)	0.30 (0.08–1.19)	1.19 (0.35–4.01)	**0.041**

Model 1: unadjusted model; Model 2: adjusted for age, BMI, first-degree family history of GC, smoking status, alcohol consumption, regular exercise and marital status; Model 3: additionally adjusted for *H. pylori* infection. In the total subjects, models 2 and 3 were additionally adjusted for sex.
OR, odds ratio; CI, confidence interval.

autoimmunity, tumour progression and metastasis[41]. The role of *TNF-α* has been indicated to be associated with not only polymorphisms in the genes in relation to regulation of *TNF-α* production and effect but also polymorphisms in *TNF* itself[42]. *TNF-α* promoter polymorphisms were documented to affect the expression of this gene and are associated with GC susceptibility[39]. One of the *TNF-α* promoter polymorphisms is the G (guanine) > A (adenine) (rs1800629) polymorphism, which suggests an impact on the *TNF-α* level and susceptibility to GC[19]. However, the detrimental effect of *TNF-α* rs1800629 on GC development is still controversial. It was considered a potential contributor to gastric tumorigenesis and was associated with *H. pylori* infection in a previous study[39]. However, a significant association was limited to Caucasians, and a non-significant association was found for East Asians[19]. We found a similar association between *TNF-α* rs1800629 and GC risk, which is in agreement with a previous study in Korea[40].

TNF-α production is associated with cancer progression[18]. Promoter polymorphisms were indicated in relation to elevated *TNF-α* production[19]. Macrophages are known to play an important role in immunity and inflammation due to bioactive molecule secretion. A previous study suggested certain roles of K^+ and K^+ channels in the regulation of *TNF-α* production by activated human culture-derived macrophages[23]. Thus, we hypothesised that there is an interactive effect of potassium intake with *TNF-α* rs1800629 on GC carcinogenesis. Our findings suggest a difference in the protective effect of potassium against gastric carcinogenesis according to host genetic factors. A significant effect seems to be observed in those carrying the homozygous wild-type allele of *TNF-α* rs1800629 (GG). Importantly, a biological interaction between potassium intake and *TNF-α* rs1800629 was found in our study. Possible mechanisms for the interaction may be explained as follows. Potassium was indicated to regulate *TNF-α* production. In detail, phorbol myristate acetate-induced cytokine production may be inhibited by the effect of blockade of K^+ channels through mechanisms regarding translation or post-translation. This effect is duplicated with an increase in extracellular K^+[23]. Additionally, potassium plays a role in *TNF*-induced apoptosis and gene induction. *TNF* receptor triggering leads to reduced intracellular spermine, which impacts the activity of potassium channels and intracellular potassium concentrations, enhances the activity of caspases and increases cell death[43]. Another possible mechanism can be proposed. Potassium cyanate is thought to induce apoptosis in colorectal cancer cell lines. Notably, potassium cyanate is a mediator of *TNF-α* release in these cells via activation of nuclear factor kappa B[44]. Overall, our study suggests a biological interaction between potassium intake and *TNF-α* rs1800629. However, a significant interaction was found only for females. Higher expression of inflammatory genes was observed in females than in males due to sex hormones[45]. Thus, different eating habits and sex hormones may account for the difference in the interactive effect between males and females[46]. This interaction should be elucidated in further studies.

This study is one of few studies aiming to determine the protective effect of high potassium intake on the progression of GC. Importantly, our study represents the first attempt to demonstrate an impact of an interactive effect between

potassium intake and genetic polymorphisms in proinflammatory genes on GC risk. Additionally, we used a validated and reliable semiquantitative FFQ to collect information on nutrient intake. Information on general characteristics, especially possible confounders, was collected by trained personnel. As a consequence, the quality of our data was relatively higher. Although the associations for subtypes of GC were not assessed in our study due to the limited number of cases, cases in our study well reflect the trend in Asia, where the majority of cases are non-cardia GC[6]. Furthermore, the statistical power of genotype associations may be affected by the small number of variant allele carriers. Although we tried to tackle case–control study-related limitations, selection bias and recall bias may occur. Finally, although there would be a possibility to have effect from other genes, except *TNF-α*, that might be helpful in reaching an effective conclusion. However, we did not consider the effect from other probable genes or combinations of genes in our current study.

In conclusion, our study emphasised a protective effect of high potassium intake against GC carcinogenesis. Additionally, we drew a concept regarding an interaction between dietary potassium intake and *TNF-α* rs1800629. In detail, the preventative effect of potassium depended on the individual's genetic background. A greater effect seems to be exhibited for *TNF-α* rs1800629 homozygous wild-type allele carriers, especially females. This evidence suggests that we should consider individual genotypes to develop strategies for GC prevention.

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