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SYSTEMATIC REVIEWS

Gene-diet interactions in gastric cancer risk: A systematic review

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Abstract

AIM: To conduct a systematic review of the published epidemiological studies investigating the association of the interactions between gene variants and dietary intake with gastric cancer risk.

METHODS: A literature search was conducted in PubMed, EMBASE, and MEDLINE for articles published between January 2000 and July 2013, and 38 studies were identified. Previous studies included various dietary factors (*e.g.*, fruits and vegetables, soybean products, salt, meat, and alcohol) and genetic variants that are involved in various metabolic pathways.

RESULTS: Studies suggest that individuals who carry high-risk genetic variants and demonstrate particular dietary habits may have an increased risk of gastric cancer compared with those who do not carry high-risk genetic variants. Distinctive dietary patterns and variations in the frequency of genetic variants may explain the higher incidence of gastric cancer in a particular re-gion. However, most previous studies have limitations, such as a small sample size and a retrospective case-control design. In addition, past studies have been unable to elucidate the specific mechanism in gene-diet interaction associated with gastric carcinogenesis.

CONCLUSION: Additional large prospective epidemiological and experimental studies are required to identify the gene-diet metabolic pathways related to gastric cancer susceptibility.

Key words: Gastric cancer; Gene; Diet; Interaction

Core tip: Gene-diet interactions related to gastric carcinogenesis may provide a unique environment for cancer growth or suppression in each individual. Gene-diet interactions may explain the large variation in gastric cancer incidence in different populations and the inconsistent findings of previous gene or diet studies. Therefore, this review provides an overview of the published epidemiological studies that have investigated the interactions between gene variants and dietary factors associated with gastric cancer risk.

INTRODUCTION

Although the incidence of gastric cancer has steadily declined in past decades, gastric cancer is the second leading cause of death from cancer worldwide[1,2]. Evidence has indicated that environmental factors such as Helicobacter
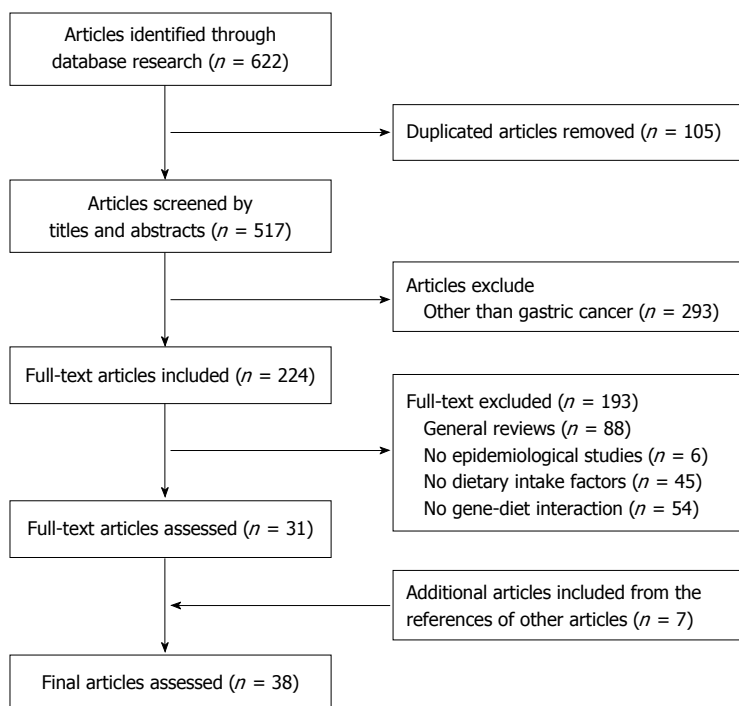
Figure 1 **Study flow chart depicting the literature search and study selection.**

pylori (*H. pylori*) colonization, cigarette smoking, and diet may play an important role in gastric carcinogenesis[3]. It has been reported that high intake of fresh fruits and vegetables has a protective effect against gastric cancer, whereas salted, smoked, pickled, and preserved foods rich in salt, nitrites, and preformed N-nitroso compounds are associated with an increased risk of gastric cancer[4,5]. Polymorphisms in genes may also contribute to the etiology of gastric cancer by altering the activity of enzymes that are involved in diverse molecular processes, such as DNA synthesis and repair (*e.g.*, *MTHFR*), carcinogen-metabolism (*e.g.*, *GST* and *NAT*), the inflammatory response (*e.g.*, *IL-1B*), tumor suppression (*e.g.*, *p53*), and so on[6].

The incidence of gastric cancer varies geographically; high-risk areas include East Asia (especially China and Japan), Eastern Europe, and parts of Central and South America[7]. Gastric cancer is thought to result from a combination of environmental factors and the accumulation of generalized and specific genetic alterations[8]. Therefore, gene-diet interactions, which provide a unique environment for cancer growth or suppression in each individual, may explain the large amount of variation in gastric cancer in different populations and the inconsistent findings of gene or diet studies[8,9]. In this present study, we reviewed previous studies that have investigated the interactions between dietary intake and gene polymorphisms associated with gastric cancer risk in diverse populations in epidemiological studies.

MATERIALS AND METHODS

The studies were identified in a search of the electronic databases of PubMed, MEDLINE, and EMBASE from January 2000 to July 2013. The search strategy used combinations of the following terms: gastric cancer, stomach cancer, gene, polymorphism, and diet. The following inclusion criteria were used for selecting the studies: (1) measurement of gastric cancer incidence; (2) measurement of dietary factors; (3) epidemiological study with a case-control or cohort study design; and (4) assessment of the interaction effect of dietary factors and genetic variants on gastric cancer risk.

We assessed the relevance of the studies using a hierarchical approach based on the title, the abstract, and the full-text article. The references of the retrieved papers were also examined to identify additional papers; an additional seven articles were included. The identified studies were screened by two authors independently. The study flow chart depicting the literature search and study selection is presented in Figure 1. We identified a total of 38 eligible studies, which were assessed by two reviewers. In terms of gene-diet interactions, many genes and their polymorphisms were examined. Therefore, we summarized previous studies based on the metabolic pathways of genetic variants. The following data were extracted from each eligible study as follow: (1) study (year) and country; (2) study design (number of cases and controls, source of control); (3) exposure [gene (polymorphisms), diets/nutrients]; and (4) outcome (gene, diets/nutrients, interaction).

RESULTS

In this review, we identified 38 studies that investigated the gene-diet interactions. The studies were mostly performed in Asia (*n* = 23), followed by the Europe (*n* = 9) and America (*n* = 6). In Asia, studies performed among

Chinese people were most common ($n = 11$), followed by Korean ($n = 8$), Japanese ($n = 3$), and Indian ($n = 1$) populations. In Europe, two nested case-control studies were conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. An additional seven independent studies were conducted in Poland ($n = 3$) and Italy ($n = 4$). In America, Mexico was the most popular study location ($n = 3$), followed by Brazil ($n = 2$) and the United States ($n = 1$). The incidence rates of gastric cancer in the studies were measured in a hospital-setting or in the general population in a specific region of a country.

The studies examined various dietary factors (*e.g.*, fresh fruits and vegetables, meat, salted and preserved foods, and alcohol) and polymorphisms in many genes. We summarized the findings of the previous studies in Tables 1-3, according to the role of the genetic polymorphisms that have been studied in association with gastric cancer. Table 1 presents the interactive effect between DNA synthesis and repair-related genetic polymorphisms (*e.g.*, *MTHFR*, *hOGG1*, and *XRCC*) and various dietary factors on gastric cancer risk. Table 2 shows the effect of diet on gastric cancer risk according to the carcinogen metabolism-related genetic polymorphisms (*e.g.*, *CYP2E1*, *GSTT1*, *GSTM1*, *SULT1A1*, and *ALDH2*). Finally, Table 3 presents the effect of diet on gastric cancer risk according to the other selected genetic variants (*e.g.*, *IL-1B*, *IL-10*, and *p53*).

DISCUSSION

This review summarizes the previous studies that have investigated the gene-diet interactions according to the roles of the genetic polymorphisms that have been studied in association with gastric cancer.

Effect of DNA synthesis and repair-related genetic polymorphisms and dietary factors on gastric cancer risk

Polymorphisms of genes associated with DNA synthesis and repair enzymes may contribute to an increased risk of gastric carcinogenesis by altering the function or efficiency of DNA synthesis and repair[10].

Genetic variation in one-carbon metabolism may affect normal patterns of DNA methylation and synthesis and therefore determine susceptibility to gastric cancer[11]. Methylenetetrahydrofolate reductase (MTHFR) irreversibly converts 5,10-methylene-tetrahydrofolate to 5-methyltetrahydrofolate, which is the main circulating form of folate and a methyl group donator[6]. A meta-analysis by Boccia *et al*[12] revealed a higher risk of gastric cancer among individuals with the *MTHFR* 677TT genotype compared with those with wild-type homozygotes, because of reduced enzyme activity[13]. Several studies have investigated the association between dietary factors (*e.g.*, fruits, vegetables, folate, and alcohol) and *MTHFR* polymorphisms and have reported significant interactions[14-19]. In a population-based case-control study in China, individuals carrying the *MTHFR* 677TT genotype who had low folate intake had a higher gastric cancer risk compared with those with the CC genotype (*P* for interaction < 0.05)[15]. Another population-based case-control study in Mexico also reported that *MTHFR* 677TT carriers with high folate intake had a lower risk of diffuse-type gastric cancer, whereas those with low folate intake had a higher risk of intestinal-type gastric cancer compared with C allele carriers[14]. Stolzenberg-Solomon *et al*[18] found that alcohol consumption increased gastric cancer risk among *MTHFR* 677TT carriers in China. The increased gastric risk can be explained by DNA hypomethylation caused by the decrease in *MTHFR* enzyme activity among the individuals carrying the T allele who consume few fruits and vegetables and large amounts of alcohol[17]. This dietary habit may impair folate metabolism, particularly in those with folate deficiencies[20]. In contrast, some studies have found no association between *MTHFR* polymorphisms and either folate intake[11,21] or alcohol intake[16,21] and gastric cancer risk. It has been suggested that the differences in folate status between different populations may have caused the inconsistent findings on the role of *MTHFR* genetic variants in gastric carcinogenesis[17]. In addition to *MTHFR* polymorphisms, Zhang *et al*[11] also investigated the modifying effect of polymorphisms of methionine synthesis reductase (*MTRR*) and methionine synthase (*MTR*), but found no interactions.

Human oxoguanine glycosylase 1 (*hOGG1*) is responsible for repairing 8-hydroxy-deoxyguanosine residue, which is the major form of oxidative DNA damage induced by reactive oxygen species (ROS)[22]. *hOGG1* Ser-Cys substitution at codon 326 results in decreased DNA repair activity, and thus might increase gastric cancer risk[23]. Tsukino *et al*[23] reported that high cruciferous vegetable intake had a protective effect against gastric cancer only among individuals carrying the Ser/Ser genotype (*P* for interaction = 0.053) and that high salt intake was positively associated with gastric cancer risk only among Cys carriers (*P* for interaction = 0.001). These results may suggest that the protective effect of dietary antioxidant compounds and other natural compounds (*e.g.*, phenols, flavonoids, and isothiocyanates) against gastric cancer is stronger among subjects with the *hOGG1* Ser/Ser genotype[23]. Takezaki *et al*[24] also found that a greater risk of gastric cancer associated with the frequent consumption of pickled vegetables, meat, and alcohol among the subjects carrying the Cys/Cys genotype than among the Ser carriers, but these interactions had only borderline significance. Oxidative damage due to dietary factors may induce carcinogenesis in the stomach, and it is more pronounced in Cys/Cys carriers, who have less ability to repair DNA damage[24].

Several other genetic variants related to DNA repair pathways were also examined. In a population-based case-control study in Poland, Huang *et al*[25] investigated four DNA repair genes (*e.g.*, *XRCC1*, *XPD*, *MGMT*, and *XRCC3*), which represent four repair pathways. The risk associated with low fruit or vegetable intake tended

Table 1 Interactive effect between DNA synthesis and repair-related genetic polymorphisms and diet on gastric cancer risk

Ref.	No. case/control (control)	Gene (polymorphism)	Diet/nutrient	Outcome		
				Gene	Diet/nutrient	Interaction
Takezaki *et al*[24], 2002, China	101/198 (Population)	*hOGG1* (Ser326Cys)	Meat, soybean, vegetable, garlic, tea, alcohol	No assoc	Pickled vegetable (freq. *vs* non-freq): OR = 2.53 (1.52-4.21)	The positive assoc between pickled vegetable (*P* interaction = 0.093) or meat (*P* interaction = 0.083) and GC risk was stronger in Cys/Cys carriers than in Ser carriers; a frequent alcohol consumption (≥ 2 times/wk) increased GC risk in Cys/Cys carriers (*P* interaction = 0.086)
Stolzenberg-Solomon *et al*[18], 2003, China	90/398 (Population)	*MTHFR* (C677T, A1298C) *MTRR* (A66G)	Alcohol	No assoc	Unknown	Alcohol drinkers increased GC risk among those with *MTHFT* 677TT carriers (*P* interaction = 0.03)
Tsukino *et al*[23], 2004, Japan	142/271 (Hospital)	*hOGG1* (Ser326Cys)	Salt, fruit, vegetable, Vt C, β-carotene	No assoc	Unknown	The positive assoc between salt and GC risk was observed only in Cys allele carriers (*P* interaction = 0.01); the protective effect of cruciferous vegetable on GC risk was stronger among Ser/Ser genotype carriers (*P* interaction = 0.053)
Huang *et al*[25], 2005, Poland	281/390 (Population)	*XRCC* (Arg399Gln) *XPD* (Lys751Gln) *MGMT* (Ile143Val, Leu84Phe) *XRCC3* (Thr241Met)	Fruit/vegetable	No assoc	Fruit (low *vs* high): OR = 2.2 (1.3-3.6)	The positive assoc between low fruit or vegetable intake was modified by selected polymorphisms in *XRCC1*, *XPD*, *MGMT* (*P* interaction = 0.1-0.2)
Nan *et al*[26], 2005, South Korea	110/220 (Hospital)	*hMLH1* promoter	Cereal, potato, fruit, vegetable, mushroom, butter/cheese/margarine, protein, Vt C, P, K, Zn, Ca, alcohol	Unknown	Unknown	High vegetables increased GC risk and high potato intake decreased GC risk among cases with *hMLH1* promoter hypermethylation; high intake of protein, P, K, Zn, Vt C, and Ca was associated with higher GC risk without hypermethylation of the *hMLH1* gene promoter; high alcohol consumption was associated with a higher GC risk among those with hypermethylation of the *hMLH1* gene promoter
Graziano *et al*[19], 2006, Italy	162/164 (Population)	*MTHFR* (C677T)	Alcohol	677TT *vs* CC: OR = 2.95 (1.57-5.55)	Unknown	Alcohol drinking modified the association between *MTHFR* C677T and GC risk (*P* interaction = 0.09)
Lacasaña-Navarro *et al*[21], 2006, Mexico	201/427 (Hospital)	*MTHFR* (C677T)	Folate, alcohol	677TT *vs* CC: OR = 1.62 (1.00-2.59)	No assoc	No interaction
Boccia *et al*[16], 2007, Italy	102/254 (Hospital)	*MTHFR* (C677T, A1298C)	Fruit, vegetable, alcohol	677TT *vs* CC for diffuse GC: OR = 2.92 (1.19-5.58)	Alcohol (high *vs* low): OR = 3.74 (1.13-12.45)	Low fruit/vegetable consumers increased GC risk among individuals with 677TT genotype
Mu *et al*[17], 2007, China	206/415 (Population)	*MTHFR* (C677T, A1298C)	Fruit, vegetable	677TT *vs* CC: OR = 2.80 (1.41-5.56)	No assoc	*MTHFR* 677TT genotype showed a stronger positive association among low fruit/vegetable intake subjects compared with high intake groups
Zhang *et al*[11], 2007, Poland	305/427 (Population)	*MTHFR* (2 SNPs) *MTR* (1 SNP) *MTRR* (7 SNPs)	Folate	No assoc	No assoc	No interaction
Galván Portillo *et al*[14], 2009, Mexico	248/478 (Population)	*MTHFR* (C677T)	Folate, choline, Vt B6, Vt B12, methionine	677TT *vs* C allele: OR = 0.23 (0.06-0.84)	Folate (*P* = 0.001)	Among individuals with *MTHFR* 677TT genotype, low folate intake increased, but high folate intake decreased diffuse GC risk (*P* interaction = 0.055)
Duan *et al*[29], 2012, China	400/400 for rs751402; 403/403 for rs2296147 (Population)	*ERCC5* (rs751402, rs2296147)	Alcohol	rs751402 (AA *vs* GG): OR = 1.99 (1.20-3.31); rs2296147 (CC *vs* TT): OR = 2.17 (1.04-4.54)	Unknown	Alcohol drinking substantially increased GC risk for subjects carrying rs2296147 CC homozygous variants, but their interaction was not statistically significant
Gao *et al*[15], 2013, China	264/535 (Population)	*MTHFR* (C677T)	Folate	677TT *vs* CC: OR = 2.08 (1.28-3.66)	Folate (high *vs* low): OR = 0.54 (0.34-0.83)	*MTHFR* 677TT carriers increased GC risk among subjects with low folate intake (*P* interaction = 0.005)

ERCC5: Excision repair cross-complementing group 5; *hOGG1*: Human 8-oxoguanine DNA glycosylase 1; *hMLH1*: Human mutL homolog 1; *MTHFR*: Methylenetetrahydrofolate reductase; *MGMT*: O-6-methylguanine-DNA methyltransferase; *MTR*: 5-methyltetrahydrofolate-homocysteine methyltransferase; *MTRR*: 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *XPD*: Xeroderma pigmentosum D; *XRCC*: X-ray repair complementing defective repair in Chinese hamster cells; Freq: Frequent; GC: Gastric cancer; No assoc: No association; OR: Odds ratio; Vt: Vitamin; P: Phosphorous; K: Potassium; Zn: Zinc; Ca: Calcium.

Table 2 Interactive effect between carcinogen metabolism-related genetic polymorphisms and diet on gastric cancer risk

Ref.	No. case/ control (control)	Gene (polymorphism)	Diet/Nutrient	Outcome		
				Gene	Diet/nutrient	Interaction
Nishimoto *et al*[58], 2000, Brazil	332/528 (Hospital)	*CYP2E1* (RsaI C/A)	Meat	No assoc	The frequency of meat consumption was higher in case only among Japanese, not Brazilians	No interaction
Setiawan *et al*[33], 2000, China	143/433 (Population)	*GSTT1* (null) *GSTM1* (null)	Salt, fruit, alcohol	*GSTT1* null *vs* normal: OR = 2.5 (1.01-6.22)	Fruit (*P* < 0.001) Alcohol (*P* = 0.051)	High salt intake increased GC risk only among *GSTT1* null carriers.
Gao *et al*[42], 2002, China	98/196 (Population)	*CYP2E1* (RsaI)	Meat, soybean, vegetable (pickled or raw), tomato, garlic, tea, alcohol	No assoc	Unknown	No interaction
Gao *et al*[46], 2002, China	153/223 (Population)	*GSTM1* (null) *GSTT1* (null)	Tea, alcohol	No assoc	Tea drinking was a protective effect on GC risk: OR = 0.38 (0.24-0.62)	Tea consumption decreased GC risk among those with *GSTT1* null genotype; frequent alcohol intake increased GC risk in those with *GSTM1* positive genotype.
Boccia *et al*[39], 2005, Italy	76/260 (Hospital)	*SULT1A1* (His/His)	Fruit, vegetable, grilled/ barbecued meat, alcohol	His/His *vs* Arg/Arg: OR = 3.32 (1.17-9.45)	Frequency of GC was higher among those with high fruit intake (*P* = 0.043)	Among individuals carrying *SULT1A1* His/His genotype, high fruit or grilled/barbequed meat intake increased GC risk; alcohol intake increased GC risk among those with His/His genotype.
Nan *et al*[35], 2005, South Korea	421/632 (Hospital)	*CYP1A1* (Ile/Val) *CYP2E1* (c1/c2) *GSTM1* (null) *GSTT1* (null) *ALDH2* (*1/*2)	Kimchi, soybean paste, vegetable, allium, seafood, soybean food	*CYP1A1* Val carriers *vs* Ile/ Ile: OR = 1.34 (1.04-1.73)	Kimchi (high *vs* low): OR = 1.57 (1.22-2.01); Soybean pastes (high *vs* low): OR = 1.62 (1.26-2.09); Non-fermented alliums (high *vs* low): OR = 0.70 (0.54-0.89); Non-fermented seafood (high *vs* low): OR = 0.66 (0.51-0.85)	High intake of kimchi or soybean pastes was associated with increased GC risk among carriers with *CYP1A1* Ile/Ile, *CYP2E1* c1/c1, *GSTT1* positive, or *ALDH2* *1/*1 genotype; non-fermented alliums were associated with a decreased GC risk among carriers of *CYP1A1* Ile/Ile, *CYP2E1* c1/c2 or c2/c2, *GSTM1* null, *GSTT1* positive, or *ALDH2* *1/*2 or *2/*2 genotype; non-fermented seafood was associated with a reduced GC risk among carriers with *CYP1A1* Ile/Ile, *CYP2E1* c1/c1, *ALDH2* *1/*1 genotype.
Boccia *et al*[59], 2007, Italy	107/254 (Hospital)	*CYP1A1* (*2A) *CYP2E1* (*5A or *6) mEH (rapid, slow, very slow) *GSTM1* (null) *GSTT1* (null) *NAT2* (slow) *SULT1A1* (Arg/His, His/His)	Alcohol, fruit/ vegetable, grilled meat, meals salt addition	*GSTT1* null and *NAT2* slow acetylators: OR = 3.00 (1.52-5.93)	Alcohol (< 7 g/d *vs* ≥ 7 g/d): OR = 2.10 (1.22-3.60)	Alcohol drinkers carrying the variant allele of *CYP2E1* (*5A or *6 alleles) had an increased GC risk compared to those drinking without the variant allele (*P* for heterogeneity = 0.001)
Kobayashi *et al*[40], 2009, Japan	149/296 (Hospital)	*NAT2* (4 SNPs) *CYP1A1* (Ile462Val) *CYP1A2* (5'UTR)	Grilled/ barbecued meat, HCA	No assoc	No assoc	No interaction
Malik *et al*[60], 2009, India	108/195 (Population)	*GSTM1* (null) *GSTT1* (null) *GSTP1* (1313Ile/Val) *GSTM3* (intron 6 3-bp del) *CYP1A1* (6235T/C) *CYP2E1* (RsaI-1091C/T)	High salted tea	*GSTM1* null *vs* normal: OR = 1.98 (1.22-3.21); *CYP2E1* RsaI c2 *vs* c1: OR = 2.18 (1.12-4.24); *GSTM3* intron 6 3-bp del B *vs* A: OR = 0.50 (0.27-0.92)	Salted tea (high *vs* low): OR = 14.78 (8.22-27.23)	No interaction

Piao *et al*[43], 2009, South Korea	2213/1699 (Population)	*GSTM1* (null) *GSTT1* (null)	Alcohol	No assoc	No assoc	No interaction
Zhang *et al*[36], 2009, South Korea	471/471 (Hospital)	*NAT2* acetylator	Meat, Vt B6, Fe, nut, stew, Kimchi, soybean paste, soybean food, allium, seaweeds, alcohol	No assoc	High intake of stews, kimchi, soybean paste, sodium, well-done meat, and alcohol increased GC risk; high intake of nuts, non-fermented soybean foods, non-fermented alliums decreased GC risk.	High intake of kimchi, stews, soybean paste, and alcohol were increased GC risk in slow/intermediate acetylators.
Shin *et al*[44], 2011, South Korea	445/370 (Hospital)	*ALDH2* (*1/*2)	Alcohol	No assoc	Ex-drinker *vs* never-drinker: OR = 1.68 (1.07-2.64)	There was an interaction between drinking status and *ALDH2* genotype (*ALDH**1/*1 *vs* ALDH2 *1/*2, *P* interaction = 0.048).
Duell *et al*[41], 2012, Europe	364/1272 (EPIC study; nested case-control)	*ADH1A* (2 SNPs) *ADH1B* (5 SNPs) *ADH1C* (9 SNPs) *ADH7* (10 SNPs) *ALDH2* (2 SNPs)	Alcohol	Allelic OR *ADH1A* rs1230025: OR = 1.30 (1.07-1.59); *ADH1C* rs283411: OR = 0.59 (0.38-0.91); *ALDH2* rs16941667: OR = 1.34 (1.00-1.79)	Alcohol (high *vs* low): OR = 2.37 (1.37-4.10)	Alcohol intake modified the association between *ALDH1A* rs1230025 and GC risk.
Zhang *et al*[61], 2012, China	618/1147 (Population)	*GSTP1* (Ile105Val)	Alcohol	Ile/Ile *vs* Val/Val: OR = 3.32 (1.79-6.17)	Alcohol (drinker *vs* nondrinker): *P* < 0.002	Alcohol drinking increased GC risk among Val/Val carriers compared with Ile/Ile carriers
Matsuo *et al*[45], 2013, Japan	697/1372 (Hospital)	*ALDH2* (Glu504Lys)	Alcohol, fruit/vegetable		Alcohol (heavy *vs* non-drinker): OR = 1.72 (1.17-2.52)	A significant interaction between alcohol drinking and *ALDH2* Lys allele (*P* = 0.0054)
Eom *et al*[37], 2013, South Korea	477/477 (Hospital)	*CYP1A2* (3 SNPs) *CYP2E1* (3 SNPs) *EPHX1* (3 SNPs) *GSTM1* (null) *GSTT1* (null)	Aflatoxin B1	*CYP1A2* (CT *vs* CC): OR = 0.72 (0.52-0.98)	Aflatoxin B1 (low *vs* high): OR = 1.94 (1.43-2.63)	No interaction

CYP2E1: Cytochrome P450, family 2, subfamily E, polypeptide 1; *CYP1A1*: Cytochrome P450, family 1, subfamily A, polypeptide 1; *EPHX1*: Microsomal epoxide hydrolase 1; *GSTP1*: Glutathione S-transferase P1; *GSTT1*: Glutathione S-transferase T1; *GSTM1*: Glutathione S-transferase M1; *SULT1A1*: sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1; *ADH*: Alcohol dehydrogenase; *ALDH2*: Aldehyde dehydrogenase 2 family; *NAT2*: N-acetyltransferase 2; Fe: Iron; Vt: Vitamin; GC: Gastric cancer; No assoc: No association; HCA: Heterocyclic amine.

to be modified by selected polymorphisms in *XRCC1*, *XPD*, and *MGMT* (*P* for interaction = 0.1-0.2)[25]. Additionally, Nan *et al*[26] found that high vegetable intake and low potato intake were associated with an increased risk of gastric cancer caused by hypermethylation of the *hMLH1* promoter, which is correlated with the loss of gene expression in South Korea. It is assumed that pickled vegetables are a major source of vegetables in Korean diets; thus, high salt consumption may affect gastric carcinogenesis[27]. In this study, high intake of butter, cheese, and margarine was associated with a lower risk of gastric cancer regardless of hypermethylation of the *hMLH1* promoter, which is in agreement with the relatively low incidence of gastric cancer in countries that consume large amounts of these foods[28]. Duan *et al*[29] investigated two polymorphisms in excision repair cross-complementing group 5 (*ERCC5*) promoter region in China and found their genetic effect on increased gastric cancer risk, especially for the diffuse subtype. They also found that alcohol drinking appeared to elevate the risk

of gastric cancer among variant carriers, but their interaction effects were not statistically significant.

Effect of carcinogen metabolism-related genetic polymorphisms and dietary factors on gastric cancer risk

Potential carcinogens are activated by phase I enzymes [*e.g.*, cytochrome P450 (CYP)] or detoxified by phase II enzymes [*e.g.*, glutathione S-transferases superfamily (GST), N-acetyltransferase (NAT) and sulfotransferase (SULT)]. Genetic polymorphisms of these enzymes may alter enzyme activity and thus affect susceptibility to gastric cancer[6,30].

Salt and salted food consumption is known to elevate gastric cancer risk directly by damaging the gastric mucus or indirectly through correlating with *H. pylori* infection[31,32]. Setiawan *et al*[33] reported a positive association between high salt intake and gastric cancer among *GSTT1* null carriers in China. *GSTM1* and *GSTT1* genes exhibit homozygous deletion (null) genotype polymor-

Table 3 Interactive effect between other genetic polymorphisms and diet on gastric cancer risk

Ref.	No. case/control (control)	Gene (polymorphism)	Diet/nutrient	Outcome		
				Gene	Diet/nutrient	Interaction
Mu *et al*[47], 2005, China	206/415 (Population)	*GSTM1* (null) *GSTT1* (null) *GSTP1* (Ile/Val) *p53* codon 72 (Arg/Pro)	Green tea	Multi-genetic index ($\geqslant$ 3 *vs* 0-1): OR = 2.21 (1.02-4.79)	Green tea (high *vs* low): OR = 0.39 (0.17-0.91)	Among individual carrying *p53* codon 72 Pro/Pro genotype, no green tea drinking increased GC risk compared with those with Arg carriers and green tea drinking
Sul *et al*[52], 2006, United States	155/134 (Hospital)	*p53* codon 72 (Pro/Arg)	Na, calorie, fiber, fat, Vt C, alcohol	No assoc	Unknown	Possible interactions were observed between Vt C or fat intake and Pro/Pro genotype on GC risk
Ko *et al*[49], 2009, South Korea	84/336 (Korean Multi-Center Cancer Cohort; nested case-control)	*IL-1B* (4 SNPs) *IL-2* (2 SNPs) *IL-4* (2 SNPs) *IL-8* (3 SNPs) *IL-10* (3 SNPs)	Soybean product	No assoc	No assoc	Low intake of soybean product increased GC risk among carriers of *IL-10* gene variants (-592 GG/GA, -819 TC/CC, or -1082 AG/GG)
Wright *et al*[54], 2009, Poland	279/414 (Population)	*SLC23A1* (4 SNPs) *SLC23A2* (9 SNPs)	Vt C	No assoc	Fruit/juice ($P < 0.001$)	No interaction
López Carrillo *et al*[48], 2012, Mexico	158/317 (Hospital)	*IL-1B* (-31C/T)	Capsaicin	No assoc	Unknown	*IL-1B*-31 C allele carriers infected with *H. pylori* (CagA+) strains with moderate/high consumption of capsaicin showed an increased GC risk compared to T carriers (P interaction between Cap consumption and *IL-1B*-31C carrier = 0.04)
Oliveira *et al*[50], 2012, Brazil	200/246 (Population)	*IL-1RN* (VNTR) *TNF-β* (A252G)	Alcohol	*IL-1RN* (VNTR) L/2+2/2 *vs* LL; OR = 2.53 (1.66-3.80)	Drinker *vs* non-drinker: OR = 3.09 (1.91-5.02)	No interaction
Agudo *et al*[53], 2013, Europe	365/1284 (EPIC study, nested case-control)	*HFE* (9 SNPs)	Fe	H63D (G allele *vs* CC) (dominant): OR = 1.73 (1.20-2.51) for non-cardia; OR = 1.93 (1.25-2.98) for intestinal type	No assoc	No interaction
Song *et al*[55], 2013, South Korea	3245/1700 (Hospital)	*PRKAA1* and *PTGER4* (rs13361707) *ZBTB20* (rs9841504)	Alcohol	rs13361707 (TT *vs* CC): OR = 1.68 (1.41-2.01)	No assoc	No interaction
Zhang *et al*[56], 2013, China	401/420 (Hospital)	*EGFR* (6 SNPs)	Salty food, alcohol	rs2072454 (T allele *vs* C allele): OR = 0.77 (0.61-0.97)	Salty food ($P < 0.001$); Alcohol drinking ($P < 0.006$)	No interaction

GSTM1: Glutathione S-transferase M1; *GSTT1*: Glutathione S-transferase T1; *GSTP1*: Glutathione S-transferase P1; *p53*: Tumor protein p53; *IL*: Interleukin; *SLC23A1*: Solute carrier family 23 (ascorbic acid transporter) member 1; *HFE*: Hemochromatosis; *PRKAA1*: 5′-AMP activated protein kinase catalytic subunit alpha-1; *PTGER4*: Prostaglandin E receptor 4; *TNF-β*: Tumor necrosis factor beta; *ZBTB20*: Zinc finger and BTB domain containing protein 20; *EGFR*: Epidermal growth factor receptor; Fe: Iron; Vt: Vitamin; GC: Gastric cancer; No assoc: No association; Na: Sodium.

phisms. Individuals carrying one of these variants have no enzyme activity, and thus are more susceptible to carcinogens[34]. In South Korea, Nan *et al*[35] found that high intake of kimchi and soybean pastes fermented with salt and other chemicals is a risk factor for gastric cancer among individuals carrying *CYP1A1* Ile/Ile and *CYP2E1* c1/c1, as well as the *GSTM1*-positive, *GSTT1*-positive, or *ALDH2* *1/*1 genotypes. N-nitroso compounds from kimchi and soybean pastes would not be rapidly metabolized in individuals with the *CYP1A1* Ile/Ile or *CYP2E1* c1/c1 genotypes, and the increased exposure of the gastric mucosa to N-nitroso compounds may elevate the risk of gastric cancer[35]. High plasma concentrations of glutathione-conjugated carcinogens in individuals with the *GSTM1*-positive genotype or the *GSTT1*-positive genotype may increase the risk of gastric cancer[35]. In

addition, Zhang *et al*[36] found that high consumption of salted foods was associated with a higher risk of gastric cancer in slow/intermediate acetylators than in rapid *NAT2* acetylators in Koreans. It has been suggested that the slow/intermediate *NAT*2 acetylator genotype may have less capacity to detoxify the carcinogens in the diet and thus may increase susceptibility to gastric cancer in individuals who consume large amounts of foods containing those carcinogens[36]. Eom *et al*[37] investigated the interactions between dietary intake of aflatoxin B1 and the polymorphisms of aflatoxin B1 metabolic enzymes (*CYPA2, CYP2E1, EPHX1, GSTM1,* and *GSTT1*), but found no interactions.

Prolonged cooking of meat at a high temperature produces several potent carcinogens including heterocyclic amines (HCAs)[38]. Boccia *et al*[39] reported that the

positive association between gastric cancer risk and high consumption of grilled/barbecued meat in Italy was more pronounced among *SULT1A1* His/His carriers compared with Arg/Arg carriers. It is possible that low enzyme activity in the individuals with *SULT1A1* His/His genotype may result in less detoxification of HCAs from high consumption of grilled/barbequed meat[39]. However, Kobayashi *et al*[40] did not find any interaction between the consumption of grilled or barbequed meat and polymorphisms in *NAT2, CYP1A1*, and *CYP1A2*. The authors assumed that the relatively low intake of HCAs among the Japanese might have affected the findings.

The increased acetaldehyde levels induced by heavy alcohol drinking may lead to DNA damage and subsequently increase gastric cancer risk[41]. Several studies have investigated the differential role of alcohol on gastric cancer risk according to polymorphisms in various genes (*e.g., GSTT1, GSTM1, CYP2E1, SULT1A1,* and *ALDH2*)[33,36,39,41-45]. In the EPIC study, Duell *et al*[41] investigated 29 polymorphisms in alcohol metabolism-related genes, alcohol intake, and gastric cancer risk. They found that genetic variants at the *ADH1* and *ALDH2* loci may influence gastric cancer risk and that alcohol consumption may modify the effect of *ADH1* rs1230025. Similarly, Matsuo *et al*[45] reported that heavy drinking was associated with an increased risk of gastric cancer among *ALDH2* Lys allele carriers in a Japanese population. Boccia *et al*[39] found that alcohol intake increased gastric cancer risk among individuals with the *SULT1A1* His/His genotype who had a low *SULT1A1* enzyme activity. They hypothesized that high alcohol consumption may elevate gastric cancer risk more among individuals with low enzyme efficiency in their detoxification reactions.

Tea consumption has a protective effect against gastric carcinogenesis[32]. Gao *et al*[46] found that regular tea consumption among those with the *GSTM1* or the *GSTT1* null genotype was associated with decreased gastric cancer risk in China. This result suggests that the protective effect of tea consumption against gastric cancer is independent of the detoxification mechanisms involving *GSTM1* and *GSTT1*. However, Mu *et al*[47] found no interactions between tea consumption and these polymorphisms. Unexpectedly, Boccia *et al*[39] reported that the positive association between the *SULT1A1* His/His genotype (compared with the Arg/Arg genotype) and gastric cancer risk was more pronounced among individuals with high fruit intake in Italy. The authors assumed that the His/His genotype was possibly associated with unknown risk factors, such as heavy contamination with herbicides or pesticides related to gastric cancer risk.

Effect of other selected genetic polymorphisms and dietary factors on gastric cancer risk

Individual differences in the inflammatory response may contribute to the variation in the malignant transformation of the gastric mucosa, which may be modulated by genetic variants of inflammation-related cytokines[6]. López-Carrillo *et al*[48] reported that moderate to high cap-

saicin consumption synergistically increased the risk of gastric cancer in genetically susceptible individuals (*IL-1B*-31C allele carriers) infected with the more virulent *H. pylori* (CagA-positive) strains in Mexico. They suggested that capsaicin consumption, *H. pylori* infection, and *IL-1B*-31C genotypes may affect gastric carcinogenesis via the same metabolic pathway (*e.g.*, an increased inflammatory response and an altered gastric acidic environment). In South Korea, Ko *et al*[49] investigated several inflammation-related polymorphisms and found that *IL-10* genetic variants and low intake of soybean products increased gastric cancer risk compared with the same variants combined with high consumption of soybean products. Soybeans are a major source of isoflavones (*e.g.*, genisten and daidzein), which have anti-inflammatory and anti-oxidative effects. In those who consume fewer soybeans, *IL-10* genetic variants may allow infection with more virulent *H. pylori* strains and increase gastric inflammation[49]. Oliveira *et al*[50] investigated the modifying effects of alcohol on the association between genetic polymorphisms anti- or pro-inflammatory cytokines and gastric cancer risk in Southeast Brazilians but found no significant interactions.

The tumor protein 53 gene (*p53*) is the most frequently studied tumor suppressor gene[51]. It has been reported that the *p53* codon 72 Arg/Arg genotype may induce apoptosis with faster kinetics and suppress transformation more efficiently than the Pro/Pro variant[47]. Sul *et al*[52] reported that the *p53* codon 72 Pro/Pro genotype combined with low vitamin C intake showed a strong positive relationship with distal gastric cancer. Vitamin C, an important anti-oxidant, inhibits carcinogenesis by neutralizing ROS that can damage DNA. Additionally, Mu *et al*[47] also reported that the *p53* codon 72 Pro/Pro genotype was more strongly associated with an increased risk of gastric cancer among non-green-tea drinkers compared with green-tea drinkers who were Arg carriers. They also found that individuals with a high multi-genetic index (*e.g., GSTM1, GSTT1, GSTP1*, and *p53* codon 72 genotype) who consumed green tea were at higher risk of developing gastric cancer in China, suggesting that the combination of multiple genes from different pathways may contribute to the development of gastric cancer[47].

Some studies have investigated the modifying effect of some dietary factors on the roles of other genetic variants in gastric carcinogenesis, but did not find any significant interactions[53-56]. Because iron overload can increase oxidative stress and DNA damage, Agudo *et al*[53] investigated the interaction between the Hemochromatosis (*HFE*) gene mutation and iron overload in gastric carcinogenesis. In the EPIC study, individuals carrying the mutation of *HFE* polymorphism (H63D) had an increased risk of non-cardia and intestinal-type gastric cancer due to iron overload, but they found no interaction with iron intake[53]. In addition, it has been suggested that the common genetic variation in *SLC23A1* and *SLC23A2* could impact gastric cancer risk based on the role of ascorbic acid in the stomach, but Wright *et al*[54] found no association between *SLC23A2* and ascorbic acid intake.

Limitations of studies investigating gene-diet interactions and gastric cancer risk

Previous studies investigating the gene-diet interaction effects on gastric cancer have several limitations. First, a majority of the studies were case-control studies, which are susceptible to both recall and selection bias. In particular, hospital-based controls may not adequately represent the prevalence of genetic variants or dietary habits in the general population because some of them may be related to their diseases. Second, many studies are underpowered to detect the interactions between genetic polymorphisms and dietary factors because they have a relatively small sample size or effect size. The lack of statistical power may explain why the results of the analysis of the interactions between polymorphisms and dietary status did not reach statistical significance. Third, the dietary data may not be entirely accurate because information about dietary intake was based on a questionnaire that assessed the average intake frequencies and portion size. In addition, exposure to dietary carcinogens may not develop into gastric cancer for 20 years or more, and recent dietary habits might not reflect the past eating habits accurately. Fourth, the etiology of gastric cancer varies according to the histological type (diffuse *vs* intestinal) and the anatomic location (cardia *vs* non-cardia)[57]. Although some studies have reported differential gene-diet interactions according to the subtype of gastric cancer[14], most studies did not conduct stratified analyses. Given these limitations, the findings from these studies should be interpreted with caution.

Different dietary habits and frequencies of genetic polymorphisms are observed in diverse populations. In addition, previous studies also provide some evidence of possible gene-diet interaction effects on gastric cancer risk, indicating differential effects of dietary factors on gastric carcinogenesis in genetically susceptible individuals. It may explain the geographical variations in gastric cancer and the inconsistent findings from previous studies investigating the role of either diet or gene in gastric carcinogenesis. However, additional large prospective studies are required to confirm these findings. We speculate that findings from gene-diet interaction studies may provide a basis for identifying at-risk subpopulations and promoting primary prevention of gastric cancer.

COMMENTS

Background
The incidence of gastric cancer varies geographically, which implies that environmental and genetic factors play a role in gastric carcinogenesis. Overall, this review summarized 38 research studies conducted on gene-diet interaction associated with gastric cancer risk.

Research frontiers
This study is related with genetics, nutrition, and cancer field. It may be helpful to understand the general mechanism of cellular processes (*e.g.*, DNA synthesis) and genetic transitions (*e.g.*, *p53* gene), which significantly affects the development of cancer. Also, it is important to understand the role of nutrition related with cancer risk.

Innovations and breakthroughs
The previous research studies have shown that the alteration in DNA synthesis,

the effects of carcinogen metabolism-related genetic polymorphisms and other selected polymorphisms with dietary intake may increase the risk of gastric cancer in diverse populations. This evidence suggests the modifications in genetic variants, particularly from dietary intake, are associated with gastric carcinogenesis.

Applications
Future studies may include a larger study population to determine consistent findings compared with the previous studies. This review may be expanded to further investigation on a specific role of genetic variants with dietary intake in additional regions associated with gastric cancer risk.

Terminology
Genetic variation is the phenotypic and genotypic differences among individuals in a population. Polymorphism is one of two or more variants of a particular DNA sequence. Genotype is the genetic constitution of an organism or cell.

Peer review
Indeed, genetic variants interacting with dietary intake are possibly associated with gastric cancer risk among individuals in different regions. This review may be useful to understand the increase risk of gastric cancer from the alterations in genetic variants and their interaction with nutrition.

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