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Review Article

Molecular epidemiology of genetic susceptibility to gastric cancer: focus on single nucleotide polymorphisms in gastric carcinogenesis

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Abstract: Gastric cancer is a disease of gene-environment interactions, as suggested by the varying geographic patterns of its incidence. Even in areas with high rates of *Helicobacter pylori* infection, only a small proportion of infected individuals develop gastric cancer. Genetic susceptibility to gastric cancer can be investigated by common genetic variants, such as single nucleotide polymorphisms (SNPs), in various genes that regulate multiple biological pathways. The susceptibility to gastric carcinogenesis has a substantial influence on the population attributable risk by modulating the effects of environmental risk factors. Despite recent progress in the field of the molecular epidemiology of cancer, a re-evaluation of gastric cancer susceptibility and potentially functional SNPs in candidate genes is necessary, given the inconsistency of previous reported studies. This review focuses on genetic variants that contribute to the etiology of gastric cancer, particularly those SNPs involved in inflammatory response, metabolism of chemical carcinogens, DNA repair, and tumor suppression. In the future, well-designed large multicenter population-based studies will be needed to validate current findings and provide the rationale for identifying at-risk subpopulations for primary prevention of gastric cancer.

Key words: Gastric cancer, Meta-analysis, Genetic polymorphism

INTRODUCTION

Gastric cancer is a global health problem with a high rate of tumor incidence and mortality. It is the second most common cause of death from cancer, with an estimated 700,000 deaths each year worldwide [1]. Although surgery remains the major therapeutic approach in the management of early-stage gastric cancer, chemotherapy and radiation therapy have a limited effect on survival in the late stage of this malignancy. Therefore, primary prevention is still considered the best option for controlling this life-threatening disease.

The etiology of gastric cancer has a significant environmental component characteristic of the geographically varied incidence in the disease distribution, with high-risk areas in East Asia, East Europe, and parts of Central and South America [1]. Migrant populations have been found to have significantly lower cancer risks after they move from high-risk regions to low-risk regions [2-4]. Several environmental factors, including *Helicobacter pylori* infection, consumption of salted and nitrated foods, and cigarette smoking, have been found to be associated with the risk of developing gastric cancer, whereas fresh fruits and vegetables or the micronutrients contained in fruits and vegetables have been found to be protective against gastric cancer [5].

In addition to these environmental factors, genetic factors also play an important role in gastric cancer etiology, as demonstrated by the fact that only a small proportion of individuals exposed to the known environmental risk factors develop gastric cancer. In recent years, multiple gene deregulations have been found in gastric

cancer, which provide potential targets for therapeutic intervention [6]. Meanwhile, molecular epidemiological studies have described some relatively common genetic variants, such as single nucleotide polymorphisms (SNPs), as biomarkers for genetic susceptibility to gastric cancer development. These genetic variants may modulate the effects of environmental factors by regulating multiple biological pathways in response to the exposure during gastric carcinogenesis, thus exerting an effect on population attributable risks. Although the absolute risk associated with each of these variants is low, combined analysis of multiple genetic variants may help to identify individuals at high risk.

In this review, we summarize a number of published association studies discussing several well-characterized genetic variants or SNPs involved in the etiology of gastric cancer, with particular emphasis on their functional relevance. We also incorporate meta-analyses published in recent years to reflect most updated opinions on the associations between SNPs and gastric cancer risks. For some genes for which meta-analyses are not available, we searched MEDLINE by the names of the genes and gastric cancer in publications in English to select relevant reports and included some additional articles by a manual search of original studies on related topics. Analyses were performed with the Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC) and the Review Manager (v.4.2; The Cochrane Collaboration, Oxford, England) as described elsewhere [7].

MOLECULAR EPIDEMIOLOGICAL STUDIES

1. *H. pylori* infection

H. pylori infection is associated with the pathogenesis of diverse gastric diseases, ranging from simple asymptomatic gastritis to the most serious gastric neoplasia. When *H. pylori* infection challenges gastric mucosa, it induces a vigorous inflammatory response by stimulating gastric mucosal production of several inflammatory cytokines, such as interleukin-1 beta (*IL-1β*) and tumor necrosis factor alpha (TNF-α), which may contribute to mucosal resistance to injury [8]. Mounting evidence also suggests that concomitant inhibition of acid secretion may extend the area of *H. pylori* colonization, resulting in damage-induced inflammation of the corpus mucosa, leading to an early onset of gastric atrophy and subsequent malignant transformation [8]. Therefore, genetic polymorphisms in genes that code for crucial inflammatory molecules may alter the inflammatory response to *H. pylori* infection and contribute to malignant transformation of gastric mucosa.

IL-1B and IL-1RN. The genes of the *IL-1* family, *IL-1B* and *IL-1* receptor antagonist (*IL-1RN*), are clustered on the human chromosome 2q, encoding *IL-1β* and *IL-1* receptor antagonist (*IL-1ra*), respectively. *IL-1β* is a potent pro-inflammatory cytokine that not only has multiple important biologic effects but also regulates inflammatory reaction and immune response through its effect on the expression of various genes and surface receptors [9, 10]. *IL-1ra* is an anti-inflammatory cytokine that is inducible in most cells. It shares 26% amino acid homology with *IL-1β* and competes for *IL-1* receptor binding without agonist activities, thereby modulating the pro-inflammatory effects of *IL- 1β* [10, 11]. *IL-1B-511* and *IL-1B-31* are two diallelic polymorphisms, representing a C-T base transition at positions −511 and −31 base pairs (bp) of the genes from the transcriptional start site, which may influence gene expression by regulating the binding of transcription factors [12]. Likewise, the *IL-1RN* gene contains a variable number of 86-bp tandem repeats in the second intron, resulting in a short allele (*IL-1RN*2*, with two repeats) or long allele (*IL-1RN*L*, with three to six repeats), which may also affect its protein expression [13, 14]. Early investigation by El-Omar et al. showed an association of gastric cancer risk with the genotypes carrying *IL-1B-511T*, *IL-1B-31T*, and *IL-1RN*2/*2*, with odds ratios (OR) of 2.5 (95% CI = 1.6-3.8), 2.6 (95% CI = 1.7-3.9), and 3.7 (95% CI = 2.4-5.7) for the homozygotes, respectively [15]. However, subsequent epidemiological studies did not generate consistent results for the association between these genetic polymorphisms and gastric cancer risk. For example, the carriers of the *IL-1B-31C* allele in a Mexican population had an increased risk of distal gastric cancer (OR = 7.63, 95% CI = 1.7-46.9) [16], whereas other studies did not find any association between *IL-1B* and *IL-1RN* polymorphisms and gastric cancer risk in an Asian population [17, 18]. Furthermore, the *IL-1B-511C/C* genotype may be an independent risk factor for gastric cancer in the Thai population [19]. These

inconsistent results may result from the variation in allele frequencies in different ethnic groups, tumor types, and study methodologies among these studies. Three recently published meta-analyses provided enhanced statistical power for assessing the association of *IL-1* polymorphisms with gastric cancer. Two of these meta-analyses found an association of IL1B-511T and IL1RN*2 with gastric cancer risk in Caucasians but not in Asians [20, 21], whereas the third found a null association in both Caucasian and Asian populations [22]. A possible explanation for this discrepancy is that the authors may have grouped studies with different ethnic groups in their analyses.

TNF-α. Tumor necrosis factor alpha (TNF-α), encoded by the *TNFA* gene, is another potent pro-inflammatory cytokine and acid inhibitor with increased expression in *H. pylori* infection [23-25]. Although the *TNFA* gene has multiple polymorphisms within the promoter region, most published studies have focused on *TNFA*-308 (G>A), *TNFA*-238 (G>A), and *TNFA*-857 (C>T) because the other SNPs are functionally silent. Previous reports demonstrated that the *TNFA*-308A and *TNFA*-857T alleles were associated with increased TNF-α production, as a result of increased promoter activity [26, 27]. El-Omar et al. found that pro-inflammatory genotypes of *TNFA* were associated with elevated gastric cancer risks [28], a finding supported by other studies [29-31]. However, other researchers could not reproduce these results and have suggested that polymorphisms of *TNFA* may not be significantly associated with gastric cancer risk [32-34]. Currently, this controversial problem is partly resolved by two meta-analyses that support an association of *TNFA*-308A and *TNFA*-857T alleles with increased risk of gastric cancer , especially in Caucasian populations [35, 36]. However, the association with the *TNFA*-238A allele has not been confirmed.

2. Metabolism of carcinogens

The bioactivation and detoxification of chemical carcinogens and tissue transformation by chemical carcinogens are important in human carcinogenesis. In humans, a large number of metabolic enzymes can be grouped into two categories: phase I and phase II enzymes. Phase I enzymes, such as the cytochrome P450 superfamily (CYP), usually activate chemicals and convert lipophilic chemical compounds into more readily excretable polar products through introducing electrophilic groups to the molecules. Phase II enzymes, such as the glutathione S-transferase (GST) superfamily, usually conjugate water-soluble moieties to lipophilic compounds, most often making chemicals very hydrophilic and thus eliminating biological activities, although they may also activate some chemical carcinogens [37-40]. Epidemiological studies have identified several chemicals in the etiology of gastric cancer , such as N-nitrosamines and alkylnitrosamides [41]. These chemicals, after entering the human body, may undergo enzymatic metabolism and change their bioactivities. Some enzymes, such as P450, are known to be inducible, and enzymatic differences can explain the variable susceptibility of individuals to carcinogens. Therefore, the overall balance between activation and detoxification may determine the ultimate carcinogenicity of many toxicants in humans.

CYP2E1. *CYP2E1* belongs to the *CYP2E* subfamily and catalyzes the activation of various nitrosamines and other low-molecular-weight carcinogens produced either exogenously or endogenously [42, 43]. It is one of the major cytochrome P450 isoenzymes that constitute approximately 7% of all CYP isoforms, with the highest constitutive expression in human liver and low expression in extrahepatic tissues [44, 45]. There are no sex-related differences in its distribution and activation [45], but genetic polymorphisms have been associated with inter-individual differences in enzymatic activities, which contribute to individual capacity of metabolizing carcinogens [46]. Kim et al. found that *CYP2E*1 had a significantly lower level of catalytic activity and protein expression in Japanese populations compared with Caucasian populations [47], suggesting an underlying difference in ethnic and/or geographical origins. There are at least 13 genetic polymorphisms that have been described for the human *CYP2E1* gene, according to the Human Cytochrome P450 Allele Nomenclature Committee (http://www.imm.ki.se/CYPalleles). The most frequently studied genetic polymorphism in gastric cancer is the *CYP2E1*2* (C2) allele, recognized by the RsaI digestion in the 5'-

flanking region of the gene (*CYP2E1*5B* -1053C>T). A previous study demonstrated that this genetic variant might affect the binding of trans-acting factors and alter the gene expression through transcriptional regulation [48]. Therefore, CYP2E1 is presumed to confer susceptibility to gastric cancer by interaction with carcinogens. Using a meta-analysis, Boccia et al. found that the C2 allele seemed to be associated with gastric cancer risk in Asians (OR = 1.44, 95% CI = 0.85-2.42) but not in Caucasians (OR = 0.42, 95% CI = 0.05-3.85) [49]. They pointed out that the lack of significance for the association in Caucasian populations might be a result of the lower prevalence of *CYP2E1* C2 carriers (only 5–10% compared with 25–50% for Asians) [49].

GSTM1. *GSTM1* is a main component of the GST family that facilitates the binding of glutathione (GSH), a nucleophilic tripeptide, to carcinogens, leading to detoxification of several known chemical compounds. The absence of *GSTM1* expression, due to an inherited homozygous deletion of the *GSTM1* gene in the general population, may confer an increased cancer risk because the deletion carriers have a low ability to detoxify several xenobiotics, causing a decreased defense against cellular damage [50, 51]. Because in vitro studies have shown that *H. pylori* causes oxidative damage in gastric epithelial cells [52], the *GSTM1*-null genotype probably facilitates *H. pylori*-caused oxidative damage and therefore may be considered a risk factor for gastric cancer. Through a search of the *GSTM1*-related articles, we found 25 studies [53-77] that have investigated the role of the *GSTM1*-null genotype in the gastric cancer etiology, but no meta-analysis had been reported. We performed a meta-analysis using this pool of 25 studies and found that the *GSTM1*-null genotype elevated the gastric cancer risk by 1.33-fold (**Table 1**). However, there was substantial heterogeneity among these 25 studies (P = 0.003). When we evaluated the source of heterogeneity by ethnicity (Chinese population: 11 studies of 1,107 cases and 2,206 controls; other Asians: 7 cases of 1,306 cases and 1,999 controls; Caucasians: 7 studies of 926 cases and 2,068 controls), we found no between-study heterogeneity in each subgroup of ethnicity (data not shown). The increased risk associated with the *GSTM1*-null genotype was significant in both Chinese (OR = 1.58, 95% CI = 1.35-1.85) and other Asian populations (OR = 1.17, 95% CI = 1.01-1.36) but not in Caucasians (OR= 1.03, 95% CI = 0.88-1.21).

3. Deoxynucleotide synthesis and DNA repair

Previous studies have found that high consumption levels of vegetables and fruits were associated with a reduced risk of gastric cancer [78, 79]. The protective effect of vegetables and fruits against gastric cancer is in part due to their levels of folate, which acts as the methyl group donor and plays an important role in the *de novo* DNA synthesis. Chronic folate deficiency has been associated with abnormal DNA methylation [80], DNA strand breaks, and chromosomal instability [81, 82]. Furthermore, folate depletion may impair DNA excision repair, as shown in rat colonic mucosa, whereas such a depletion does not affect mismatch repair [83]. Therefore, it is possible that diminished enzyme activities involved in folate metabolism and DNA strand break repair due to functional polymorphisms of the genes involved in the metabolism of folate may be associated with gastric cancer risk.

MTHFR. 5,10-Methylenetetrahydrofolate reductase (MTHFR) is coded by the *MTHFR* gene on chromosome 1p36.3 in humans [84]. It is a central regulatory enzyme in the folate metabolism pathway, which irreversibly reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate and carbon donor for the re-methylation of homocysteine to methionine. In *MTHFR*, there are up to 281 polymorphisms; among these, the 677C>T and 1298A>C nonsynonymous SNPs have been extensively studied. The 677C>T nucleotide change at codon 222 of *MTHFR* results in an alanine to valine substitution, leading to the thermolabile variant of *MTHFR* with a decreased enzymatic activity, and subsequently increased plasma homocysteine levels [85]. The 1298A>C polymorphism, corresponding to nucleotide 1286 of the open reading frame, results in a Glu-to-Ala substitution and does not appear to cause hyperhomocysteinemia in either the heterozygous or homozygous state [86]. The roles of the *MTHFR* 677C>T and 1298A>C SNPs in gastric cancer susceptibility have recently been summarized by Zintzaras et al. [87]. They found that *MTHFR* 677C>T was associated with gastric cancer risks in East Asians but not Caucasians, whereas the

Table 1 Summary of meta-analyses of gastric cancer risks (random effects)

Genes and variants	Studies included	Sample size (cases/controls)	Model	OR (95% CI)		References
				Asians	Caucasians	
IL-1B-31 (T>C)	39	6,863/8,434	Dominant	0.92 (0.71-1.18)	1.10 (0.81-1.50)	[20, 21]
	14	2,616/4,230	Dominant	0.91 (0.71-1.17)	1.11 (0.74-1.67)	[20, 21]
	35	5,503/7,865	Homozygotes	0.82 (0.63-1.06)	1.21 (0.88-1.65)	[22]
IL-1B-511 (C>T)	39	2,616/4,230	Dominant	1.16 (0.92-1.46)	1.42 (0.97-2.06)	[20, 21]
	14	2,953/3,350	Dominant	0.96 (0.90-1.15)	1.49 (1.20-1.85)	[20, 21]
	35	5,503/7,865	Homozygotes	1.03 (0.87-1.21)	1.32 (0.86-2.02)	[22]
*IL1RN*2*	39	6,863/8,434	Dominant	1.09 (0.78-1.52)	1.30 (1.09-1.54	[20, 21]
	23	3,901/6,449	Dominant	1.11 (0.77-1.61)	1.21 (0.99-1.47)	[20, 21]
	35	5,503/7,865	Homozygotes	0.84 (0.29-2.44)	1.37 (0.84-2.23)	[22]
TNFA-308 (G>A)	19	3,335/5,286	Recessive	1.77 (0.68-4.67)	1,55 (1.10-2.36)	[35, 36]
	24	4,399/6,855	Homozygotes	1.14 (0.70-1.84)	1.74 (1.21-2.51)	[35, 36]
*CYP2E1*2 (C2)*	13	2,066/2,754	Homozygotes	1.44 (0.85-2.42)	0.42 (0.05-3.85)	[49]
GSTM1 null	25	3,339/6,273	Null vs. non-null	1.58 (1.35-1.85)	1.03 (0.88-1.21)	(our meta-analysis)
MTHFR (677C>T)	8	1,584/2,785	Homozygotes	1.66 (1.30-2.11)	1.24 (0.16-9.64)	[87]
P53 R72P	12	1,665/2,358	Homozygotes	1.20 (0.88-1.63)	1.21 (0.92-1.58)	[104]
CDH1-160 (C>A)	10	1,962/2892	Dominant	0.82 (0.66-1.02)	1.40 (0.95-2.04)	[111]

1298A>C variant was associated with gastric adenocarcinoma only in East Asians.

XRCC1. X-ray repair cross complementing group 1 (XRCC1) is one of the proteins involved in the base excision repair (BER) pathway, which functions in the repair of single-strand breaks caused by exposure to ionizing radiation, alkylating agents, and metabolic toxins. Considerable evidence indicates that XRCC1 participates in BER through an interaction with a complex of DNA repair proteins, including poly(ADP-ribose) polymerase (PARP), DNA ligase3, and DNA polymerase-beta [88, 89]. Several common nonsynonymous SNPs in XRCC1 have been reported, including Arg399Gln in exon 10 and Arg194Trp in exon 6. Arg399Gln is located in the BRCT-I interaction domain of XRCC1 with poly(ADP-ribose) polymerase, whereas the Arg194Trp variant sits in the PCNA binding region. Although these two SNPs have been extensively studied in regards to their biological functions and association with cancer risk in varied human malignancies, only five studies have investigated these SNPs in association with gastric cancer risks, with conflicting results [90-94], underscoring the need for additional studies with a more rigorous design and large sample sizes.

4. Selected tumor-suppressor genes

TP53. The tumor protein 53 gene (*p53*) is one of the most frequently mutated tumor-suppressor genes in human carcinogenesis and plays a pivotal role in the cellular response to stress by inducing cell growth arrest or apoptosis. It is conceivable that functional variants in *TP53*, which differ in

their biological functions, may influence the initiation and progression of normal tissues to malignancies. The G>C change at codon 72 of the *p53* gene results in an Arg>Pro amino acid substitution (p53R72P), of which the 72R isoform seems to induce faster apoptosis, while the 72P isoform has been suggested to induce G1 arrest more effectively [95, 96]. Recently, Siddique and Sabapathy reported that *p53* 72P cells had a significantly higher DNA-repair capacity than did *p53* 72R cells, possibly because *p53* 72P was more efficient than *p53* 72R in activating several *p53*-dependent DNA-repair target genes [97]. Pietsch et al. also suggested that the 72R variant, when found in a mutant *p53*, may have enhanced tumor development (e.g., through increased inactivation of p73). In contrast, when found in the wild-type *p53*, the 72R variant may inhibit tumor development (e.g., through increased apoptotic ability) [98]. These results reflect the functional differences between the *p53* variants and suggest that their expression status may influence cancer risk. Previous studies of the association between *p53* codon 72 polymorphisms and gastric cancer risk have reported conflicting results [99-103]. A meta-analysis performed by Zhou et al. also failed to find any significant difference in the genotype distribution between gastric cancer patients and cancer-free controls (Arg/Arg OR = 0.96, 95% CI = 0.79-1.16; Pro/Pro OR = 1.21, 95% CI = 0.92–1.58; Pro/Arg OR = 0.95, 95% CI = 0.79-1.14) [104]. However, further stratified analysis revealed that patients with gastric cancer had a significantly lower frequency of Arg/Arg (OR = 0.84, 95% CI = 0.72-0.99) than non-cancer controls among Asians and that the genotype distribution differed by the location, stage, and histological differentiation of gastric cancer [104].

CDH1. The E-cadherin gene (CDH1) maps to chromosome 16q22.1 and encodes a calcium-dependent trans-membrane cellular adhesion protein, which interacts with cytoskeleton actin filaments through catenins in regulating intracellular signaling and which promotes tumor growth through the Wnt-signaling pathway [105]. Several studies have provided strong evidence of an extremely high incidence of CDH1 germline mutations in an inherited familial cancer syndrome dominated by diffuse gastric cancer [106, 107]. However, CDH1 mutations, including in-frame deletions and point mutations, were also identified in 50% of patients with sporadic diffuse gastric cancer [108]. Furthermore, an inhibition of CDH1 through loss of expression has been reported to be associated with risk of cancers in the esophagus, breast, and stomach [109]. These results suggest that CDH1 may act as a tumor suppressor in diffuse gastric cancer and that its loss of function may predispose to gastric cancer. Several polymorphisms have been identified in the coding regions of the CDH1 gene, and the 160C>A SNP located 160 bp upstream of the transcriptional start point has been shown to cause a 70% reduction in the transcriptional activity [110]. Therefore, it is likely that the CDH1-160C>A variant is associated with increased gastric cancer risks. In a meta-analysis, CDH1-160C>A was found to be associated with an increased gastric cancer risk among Caucasians (OR = 1.40; 95% CI = 0.95-2.04) but with a decreased risk among Asians (OR = 0.76; 95% CI = 0.55-1.05) [111].

CONCLUSIONS AND PERSPECTIVES

Gastric cancer is a disease of gene-environment interactions, as suggested by the varying geographic patterns of gastric cancer incidence. Genetic susceptibility can be investigated by common genetic variants, such as SNPs in the genes involved in the regulation of multiple biological pathways that play a role in gastric carcinogenesis. Such genetic susceptibility may substantially influence the population attributable risk by modulating the effects of environmental risk factors. Despite recent progress in the field of molecular cancer epidemiology, a re-evaluation of gastric cancer susceptibility and potentially functional polymorphisms in candidate genes is necessary, given the inconsistency of previous reports. It is not surprising that the same genetic polymorphisms have different effects on gastric cancer risk among different ethnic groups, which is likely due to diverse genetic background, lifestyles, and disease prevalence, among other factors. However, it also reminds us to be very cautious when we generalize findings from one population to another. In addition, detailed information about environmental exposure should be collected in future studies, because the low-penetrant genetic effects of common SNPs may largely depend on interaction with a particular environmental exposure in multiple stages of gastric carcinogenesis.

It should be admitted that our current knowledge of the genetic basis of gastric cancer etiology is still very limited. Most of the genetic polymorphisms described here have a relatively weak association with gastric cancer risk. Heterogeneity among published studies is frequently observed. However, combined analysis of multiple polymorphisms may be more discriminating than the use of a single locus genotype in identifying individuals with a higher gastric cancer risk. Well-organized, multicenter prospective studies with large sample sizes based on different ethnicities are of great value in identifying valuable genetic polymorphisms for the prediction of gastric cancer and provide the rationale for primary prevention of this malignancy. In the near future, genome-wide association approaches will provide us the opportunity to gain a comprehensive genetic view of the disease and allow us to identify novel disease-specific genotypes that have not been investigated to date, further increasing our knowledge of the functional relevance of SNPs in the etiology of gastric cancer.

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