Molecular Epidemiology of Gastric Cancer: Current Status and Future Prospects

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ABSTRACT

Gene-environment interaction appears to contribute to the etiology of gastric cancer, as suggested by the varying geographic patterns of gastric cancer incidence. Even in areas with a high rate *Helicobacter pylori (H. pylori)* infection, only a small proportion of infected individuals develop gastric cancer. It is likely that genetic factors, particularly relatively common genetic variants, such as single nucleotide polymorphisms (SNPs), may modulate the effects of environmental risk factors by regulating multiple biologic pathways involved in gastric carcinogenesis. Thus, common genetic variants can pose a substantial influence on the population attributable risk, even though the absolute risk associated with each of these variants may be low. Remarkable progress has been made in the field of molecular epidemiology, but it appears that an initial view on the magnitude of the effects of inherited variants was overestimated. Nevertheless, evidence suggests that genetic variants may contribute to the etiology of gastric cancer, particularly those SNPs in genes that are involved in inflammatory response, metabolism of chemical carcinogens, DNA repair, and tumor suppression. Although previous molecular epidemiologic studies of potentially functional polymorphisms in candidate genes and gastric cancer susceptibility lack consistency, they have advanced our knowledge of the role of genetic susceptibility in the etiology of gastric cancer. Future, well-designed large population-based studies will validate current findings and provide the rationale for identifying at-risk subpopulations for primary prevention of gastric cancer.

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Although the incidence of gastric cancer has steadily declined in past decades, this disease remains a significant global health problem. Worldwide, cancer of the stomach ranks fourth in frequency (after cancers of the lung, breast, and colon and rectum), with an estimated 934,000 new cases per year in 2002, and it is the second most common cause of cancer death (approximately 700,000 deaths annually).[1] Although diagnostic and therapeutic advances have occurred during the past 10 years, the prognosis of late-stage gastric cancer continues to be bleak, and conventional treatments have little effect on survival.[2] Accordingly, prevention remains the best strategy for controlling this life-threatening disease.

The etiology of gastric cancer involves a strong environmental component, and its global distribution is characterized by a wide geographic variation in incidence. Particularly high-risk areas include East Asia (especially China and Japan), Eastern Europe, and parts of Central and South America.[1] First-line evidence of environmental risk factors is drawn from migration studies, in which populations from high-risk regions of the world were found to have a markedly diminished risk when they moved to lower-risk areas.[3–5]

Since 1991, sufficient evidence has emerged to support the hypothesis that *Helicobacter pylori (H. pylori)* colonization might play a major role in the development of gastric cancer, and it has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO).[6] Dietary factors, such as the consumption of salted and nitrated foods, are also believed to be responsible for the high incidence and mortality of gastric cancer observed primarily in Asian countries.[7,8] On the other hand, risk of gastric cancer is dramatically decreased in populations whose diet includes a high intake of fruits and vegetables,[9] which may be partly attributable to the consumption of antioxidant micronutrients.[10] Tobacco smoking is also considered a known risk factor for gastric cancer.[11]

In addition to the aforementioned modifiable environmental factors, genetic

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factors also appear to play an important role in the etiology of gastric cancer. Data show, for example, that in certain regions of the world where nearly 100% of the populace tests positive for *H. pylori,* only a small fraction of those infected develop gastric cancer.[12] This observation suggests that genetic variations in susceptibility may constitute an underlying mechanism of gastric carcinogenesis.

Family-based genetic analysis revealed the presence of rare, highly penetrant mutations in several genes, such as *E-cadherin,* that may confer a high individual risk, but they account for only a small percentage of gastric cancer.[13,14]

In contrast, relatively common genetic variants, such as single nucleotide polymorphisms (SNPs), may modulate the effects of environmental risk factors by regulating multiple biologic pathways involved in gastric carcinogenesis. Thus, common genetic variants can contribute substantially to population attributable risk, even though the absolute risk associated with each of these variants may be low. Remarkable progress has been made in this field of study, but it appears that initial theories might have overestimated the magnitude of the effects of inherited variants.

This review summarizes a number of published association studies using several well-characterized variants or SNPs in genes involved in multiple biologic pathways related to the etiology of gastric cancer. Emphasis is placed on the functional relevance of each genetic variant or SNP, rather than the hypothesis-driven selection of disease-related biologic pathways. Although the significance of most SNPs is still largely unknown, some are more likely to be a-priori disease-causing entities than others. One implication is that SNPs that cause amino acid substitutions (ie, nonsynonymous) or that are located at regulatory regions (ie, promoters) may influence disease outcomes by affecting the expression and functions of proteins.

Because relatively small, single studies published to date may not have been sufficiently powered to detect the effect of genetic polymorphisms in low-penetrance genes, we performed a meta-analysis by incorporating data available from numerous published studies to better address the association between SNPs and gastric cancer risk. We identified studies eligible for inclusion in this meta-analysis by conducting an electronic search of the literature (MEDLINE) to select relevant reports. Additional studies were identified by a manual search of references cited in original studies or review articles on similar topics. All analyses were performed with Statistical Analysis System software (v.9.1.3; SAS Institute, Cary, NC) and Review Manage Software (v.4.2; Oxford, England) as described elsewhere.[15]

MOLECULAR EPIDEMIOLOGIC STUDIES

Mucosal Protection Against *H. Pylori* Infection

H. pylori infection is associated with diverse clinical outcomes that range from simple asymptomatic gastritis to more serious conditions, such as peptic ulcer disease and gastric neoplasia. Key determinants of these outcomes are severity and distribution of the *H. pylori*-induced gastritis.[16]

When *H. pylori* challenges gastric mucosa, a vigorous inflammatory response is triggered that involves a complex network of inflammatory mediators, especially pro-inflammatory cytokines (eg, interleukin-1beta [IL-1β] and tumor necrosis factor-alpha [TNF-∝]), which may help eradicate *H. pylori* organisms. Concomitant inhibition of acid secretion, however, may extend the area of colonization, resulting in damage-induced inflammation of the corpus mucosa, leading to an early onset of gastric atrophy and malignant transformation.[16] Therefore, individual differences in the intensity of the inflammatory response may contribute to variation in the likelihood of malignant transformation of gastric mucosa, which may be modulated by polymorphisms in genes that code for key inflammatory molecules.

IL1B and IL1RN

IL-1β, encoded by the IL1B gene, is a potent pro-inflammatory cytokine and an inhibitor of gastric acid secretion. Thus, it plays a key role in modulating the inflammatory response to *H. pylori* infection.[17] The interleukin-1–receptor antagonist (IL-1ra), encoded by the IL1RN gene, is an anti-inflammatory cytokine that competitively binds to the IL-1β receptors, thereby modulating the pro-inflammatory effects of IL-1β.[18] Inter-individual variation in IL-1β and IL-1ra protein levels appears to be determined by functional polymorphisms in transcription regulatory regions of their respective genes.[19–21] Case-control studies of diverse ethnic populations have been conducted to determine the roles these polymorphisms play in the development of gastric cancer.[22–48]

As shown in Table 1, the IL1B-511T and IL1RN-S alleles, which are reportedly associated with increased levels of IL-1β production, have been found to confer an increased risk of gastric cancer. However, significant between-study heterogeneity was revealed in the meta-analysis, regardless of which genetic model was used, suggesting that confounders or cofactors may play important roles in determining gastric cancer risk. In subgroup analysis, a significantly elevated risk (assuming a dominant model; OR = 1.37, 95% CI = 1.13–1.67, $P = .54$ for the heterogeneity test) associated with the IL1RN-S allele was only evident among studies conducted in the United States[24,33,44,45,47] but not in Europe (assuming a dominant model; OR = 1.25, 95% CI = 0.93–1.69, $P = .0002$ for the heterogeneity test),[22,27,35,38,40,42,43] nor in Asia (assuming a dominant model; OR = 1.11, 95% CI = 0.75–1.64, $P = .0002$ for the heterogeneity test).[23,25,26,29,31,34,37,39,41,46] Further, a significantly elevated risk (assuming a dominant model; OR = 1.78, 95% CI = 1.01-3.13, $P < .0001$ for the heterogeneity test) associated with the IL1RN-S allele was only evident among studies of intestinal gastric cancer[31,33,35,40,42,47] but not for diffuse gastric cancer (assuming a dominant model; OR = 1.18, 95% CI = 0.87–1.62, $P = .27$ for the heterogeneity test).[31,33,35,40,47] These results suggested that histologic types of the disease might contribute to the study heterogeneity. Therefore, different genetic backgrounds and local environmental factors between populations must be taken into account in such association studies.

TNF-∝

TNF-∝, encoded by the TNF-∝ gene, is another potent pro-inflammatory cytokine and acid inhibitor highly expressed in *H. pylori*-induced gastritis, albeit the acid inhibitory properties are weaker than IL-

1β.[49–51] Several polymorphisms have been reported in the TNF-∝ promoter, but the majority of published studies have focused on the G→A SNP at position –308, because most of the other SNPs are functionally silent.

The TNF-∝-308A allele is thought to increase transcriptional activity of TNF-∝[52] and was found to be associated with a higher concentration of TNF-∝ in patients with malignant tumors.[53,54] However, evidence from our meta-analysis with 2,789 cases and 4,497 controls[24,27,29,35,38,42,45,46,48,55–61] is not supportive (Table 1), suggesting that these results need to be verified by additional large, well-designed studies.

Metabolism of Carcinogens

Inherited polymorphisms in metabolic enzymes contribute to variability in the metabolism of xenobiotics and carcinogens, a well-recognized mechanism underlying the initiation of multiple cancers. However, the metabolic system is rather nonspecific to permit high efficiency in dealing with a wide spectrum of substrates. A large number of metabolic enzymes can be grouped into two families. Phase I enzymes (like the cytochrome P450 superfamily, CYP) catabolize oxidative reactions that introduce electrophilic groups to the molecules and make them more reactive, usually leading to carcinogen activation. Phase II enzymes (like the glutathione S-transferases superfamily, GST) introduce a hydrophilic group into the intermediate molecules, usually resulting in detoxification of activated carcinogens.

CYP2E1

CYP2E1, the only member of the CYP2E subfamily identified so far, catalyzes various exogenous *N*-nitrosamines, including *N*-nitroso-dialkyiamines and tobacco-smoke-related nitrosamine.[62] Considerable evidence supports the view that carcinogenic *N*-nitrosamine derivatives are important in the etiology of human cancers, including gastric cancer. However, large inter-individual variation in the activity of CYP2E1 has been observed, suggesting that genetic polymorphisms may play a role in individual capacity of metabolizing carcinogens. The -1053C→T SNP located in the 5′-flanking region of the CYP2E1 gene was reported to affect its binding of trans-acting factors and change its transcriptional regulation, resulting in different expression levels of the CYP2E1 mRNA.[63] Although relatively few published studies have investigated this SNP and risk of gastric cancer, there clearly is a dominant protective effect of the variant allele without between-study heterogeneity as shown in Table 1.[64–72]

GSTM1

GSTM1 is a main component of the GST families that facilitate 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

Table 1. Summary of meta-analyses of published studies on selected variants and gastric cancer risk.

Genes and variants	Models[a]	No. of Cases/Controls	OR (95% CI)	References
IL1B-31 (T→C)	Homozygote comparison	1883/3220	0.95 (0.76–1.18)	22, 23, 25, 26, 29, 30,
	Dominant model	3476/5788	0.96 (0.80–1.14)	32-38, 40, 41, 43–48
	Recessive model	3476/5788	0.98 (0.83–1.16)	
IL1B-511 (C→T)	Homozygote comparison	1813/2370	1.19 (0.93–1.53)	22, 24, 26-35, 37,
	Dominant model	3663/4594	1.10 (0.92–1.32)	39–42, 44, 46, 48
	Recessive model	3663/4594	1.15 (0.94–1.40)	
IL1RN (L→S)[b]	SS vs. LL	2799/4355	1.42 (0.90–2.25)	22–27, 29, 31, 33-35,
	Dominant model	3749/5905	1.23 (1.02–1.48)	37–47
	Recessive model	3749/5905	1.33 (0.82–2.15)	
TNF-∝-308 (G→A)	Homozygote comparison	2279/3721	1.27 (0.91–1.77)[c]	24, 27, 29, 35, 38,
	Dominant model	2789/4497	1.06 (0.87–1.28)	42, 45, 46, 48, 55–61
	Recessive model	2789/4497	1.23 (0.89–1.72)[c]	
	Homozygote comparison	792/930	0.92 (0.59–1.42)[c,d]	64–72
CYP2E1-1053 (C→T)	Dominant model	1248/1762	0.78 (0.67–0.92)[c]	
	Recessive model	995/1368	0.98 (0.64–1.50)[c,d]	
GSTM1 null genotype	Null genotype vs. non-null genotype	3339/6273	1.33 (1.16–1.52)	72, 74–97
P53 R72P (G→C)	Homozygote comparison	534/731	0.86 (0.66–1.11)[c]	121–128
	Dominant model	1077/1387	0.98 (0.82–1.18)[c]	
	Recessive model	1077/1387	0.81 (0.65–1.00)[c]	
	Homozygote comparison	740/722	1.04 (0.51–2.11)	131–136
CDH1-160 (C→A)	Dominant model	1287/1240	1.05 (0.81–1.37)	
	Recessive model	1287/1240	0.99 (0.52–1.87)	

a Homozygote comparison: variant homozygotes were compared with wild-type homozygotes; dominant model: a single variant allele was assumed to have a dominant effect; ie, both heterozygotes and variant homozygotes were at risk, compared with wild-type homozygotes; recessive model: only variant homozygotes (having both variant alleles) were at risk, compared with variant heterozygotes and wild-type homozygotes. [143]

b S: ILRN*2; L: other alleles.

c The fixed model ($P > .05$ for heterogeneity test); otherwise, the random model was used.

d *CYP2E1*-1053 (C→T): recessive model/homozygote comparison [64–68, 70–71]

because of the resultant low ability to detoxify several xenobiotics, causing a decreased defense against cellular damage, such as oxidative stress. In vivo studies have shown that *H. pylori* causes oxidative damage in gastric epithelial cells,[73] and the GSTM1 null genotype is very likely to be associated with compromised antioxidant capacity in situ, especially in the presence of *H. pylori* infection, and therefore may be considered a risk factor for gastric cancer.

Twenty-five studies have investigated the role of the GSTM1 null genotype in gastric cancer susceptibility, and the meta-analysis showed a significant overall 1.33-fold increased risk.[72,74–97] However, there was substantial heterogeneity among these 25 studies (P = .003). When we evaluated the source of heterogeneity by ethnicity (Chinese populations, 11 studies of 1,107 cases and 2,206 controls; other Asian populations, 7 studies of 1,306 cases and 1,999 controls; white populations, 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 white populations (OR = 1.03, 95% CI = 0.88–1.21). Furthermore, we used the Egger's test to provide statistical evidence for the funnel plot symmetry on any publication bias.[98] In the linear regression analysis, the intercept values were all significantly deviated from zero for both overall and subgroup tests (data not shown), suggesting some publication bias may be a source of possible bias in the observed associations between the GSTM1 null genotype and gastric cancer risk.

Deoxynucleotide Synthesis and DNA Repair

Studies showed that high consumption of vegetables and fruits was associated with a reduced risk of gastric cancer,[99,100] partly due to a sufficient supplement of folate.[101,102] An important function of folate is to provide methyl groups required for intracellular methylation reactions and de novo deoxynucleotide synthesis. Chronic folate/methyl deficiency in vivo and in vitro has been associated with abnormal DNA methylation,[103,104] DNA strand breaks, and chromosomal instability.[105,106] Moreover, folate depletion may impair DNA excision repair in rat colonic mucosa but not mismatch repair.[107] Therefore, it is conceivable that diminished activity of enzymes involved in folate metabolism and DNA strand break repair due functional polymorphisms may confer an increased risk of gastric cancer.

MTHFR

5,10-Methylenetetrahydrofolate reductase (MTHFR) is a central regulatory enzyme in folate metabolism. It catalyzes the reduction of 5,10-methylenetetrahydrofolate (methylene-THF) to 5-methyltetrahydrofolate (methyl-THF), the predominant circulatory form of folate and carbon donor for the remethylation of homocysteine to methionine. Two main non-synonymous SNPs (nsSNPs), 677C→T and 1298A→C of the MTHFR gene, have been identified. For example, the 677C→T nucleotide change at codon 222 results in an alanine-to-valine substitution that was found to induce a thermolabile variant of the MTHFR enzyme with a reduced activity.[108] The roles of the MTHFR 677C→T and 1298A→C SNPs in gastric cancer susceptibility were recently summarized by Zintzaras et al.[109] In that meta-analysis, the MTHFR 677C→T, not the 1298A→C variant, was shown to be associated with gastric cancer risk in all genetic models tested.[109]

XRCC1

Among the main DNA maintenance mechanisms operating in mammals, base excision repair (BER) is the primary guardian against damage that results from cellular metabolism, including reactive oxygen species, methylation, deamination, and hydroxylation. The x-ray repair cross complementing group 1 gene (XRCC1), one of the over twenty genes that participate in the BER pathway, encodes a scaffolding protein that functions in the repair of single-strand breaks (SSBs).[110] Both biologic and biochemical evidence indicates a direct role of XRCC1 in BER, because it interacts with a complex of DNA repair proteins, including poly(ADP-ribose) polymerase (PARP), DNA ligase 3 (LIG3), and DNA polymerase-β.[110,111]

Several common nsSNPs in the XRCC1 gene have been reported, including Arg399Gln in exon 10 and Arg194Trp in exon 6. The Arg399Gln is located in the region of the BRCT-I interaction domain of XRCC1 with poly(ADP-ribose) polymerase, while the Arg194Trp variant occurs in the PCNA binding region. These two SNPs have been extensively investigated both in their functions and associations with cancer risk.[15] For gastric cancer, however, only five studies have been reported, with conflicting results.[112–116] This suggests the need for more rigorously designed studies with large sample sizes.

Selected Tumor Suppressor Genes

TP53

The tumor protein 53 gene (TP53 or p53), the most frequently studied tumor suppressor gene, plays a number of roles in carcinogenesis in response to cellular stresses.[117] TP53 is the most frequently mutated gene in human cancers, and some of these mutations have been correlated to specific carcinogen exposures and clinical phenotypes. Therefore, it is conceivable that functional genetic variants in the TP53 gene may be associated with the development of certain cancers. One well-known common nsSNP results in a non-conservative change of an arginine (R72) to a proline (P72) at amino acid 72 in a proline-rich region of p53, which may be important for the growth suppression and apoptotic functions of this protein.[118,119]

Recently, Pietsch reviewed the existing evidence of biochemical and biologic differences between the R72 and P72 isoforms of p53.[120] The R72 variant, when found in a mutant form of p53, may enhance tumor development (eg, through increased inactivation of p73), but, when found in the wild-type form of p53, it may better inhibit tumor development (eg, through increased apoptotic ability), whereas the P72 variant may facilitate enhanced growth arrest.[120] Several groups performed association studies on the p53 R72P SNP and gastric cancer risk.[121–128] As shown in Table 1, the 72PP variant homozygote was associated with a borderline decreased gastric cancer risk in a recessive model without between-study heterogeneity, suggesting a role for

the p53 R72P SNP in regulating growth arrest in the initiation of gastric cancer.

E-Cadherin

The E-cadherin gene (CDH1) encodes a transmembrane cellular adhesion protein acting as a mediator of homophilic recognition signals, leading to cell-cell contact inhibition. Significant familial clustering of diffuse gastric cancer was found to be attributable to germline mutations in CDH1.[129] The majority of CDH1 mutation carriers were considered susceptible to this inherited cancer syndrome dominated by diffuse gastric cancer,[129] suggesting a central role for this gene as a tumor suppressor in diffuse gastric cancer.

Mutation-specific genetic testing for the CDH1 gene is now available, mainly for missense mutations and intragenic in-frame deletions.[129] The hypothesis that decreased expression without mutations in CDH1 in the general population may contribute to gastric cancer risk with a low penetrance has led to a wave of association studies of the CDH1 promoter variant and gastric cancer risk. A C→A SNP located at 160 bp upstream from the CDH1 transcription start site was identified, and the A allele was found to be correlated to a reduced transcriptional factor binding strength and transcriptional activity.[130] However, epidemiologic studies failed to demonstrate an association between the promoter CDH1 variant and gastric cancer susceptibility (Table 1).[131–136]

CONCLUSIONS AND PERSPECTIVES

In summary, evidence suggests that genetic variants may contribute to the etiology of gastric cancer, particularly those SNPs in genes that are involved in inflammatory response, metabolism of chemical carcinogens, DNA repair, and tumor suppression. Although previous molecular epidemiologic studies of potentially functional polymorphisms in candidate genes and gastric cancer susceptibility lack consistency, they have advanced our knowledge of the role of genetic susceptibility in the etiology of gastric cancer. For the association of low-penetrance genetic variants and gastric cancer risk, heterogeneity among published studies poses a great challenge, underscoring a need for more careful study design, study execution, and data analysis.

Heterogeneity between studies may arise from the disease itself due to different histological types and anatomic locations that may involve different etiologies and genetic predispositions.[137] Lauren proposed categorizing gastric cancers as either intestinal or diffuse types in 1965.[138] This method of classification is still useful, because it reflects a fundamental difference in gastric cancer subtypes with regard to their etiology and tumor biologic behaviors.[139] However, new disease classifications based on genetic markers rather than traditional morphologic features are warranted in the future to improve the designs of genetic and molecular epidemiologic studies.

Another source of the heterogeneity is the prevalence of confounders or cofactors. As high-throughput genotyping methods become available technically mature, and more affordable, genome-wide association approaches will be conducted more frequently in the years to come, which may provide the opportunity to develop a comprehensive genetic view of the disease.

The ability to perform related data mining and statistical analyses in terms of networking of the genes presents a challenge. Knowledge of the functional relevance of SNPs will be more critical when the issues of multiple testing can be dealt with using more sophisticated methods.

Currently, most published studies have failed to present sufficient information on environmental exposure in the early stages of the genome-wide studies. This is obviously contrary to the notion of "common variants and common disease," the basis of the HapMap project and genome-wide scan strategy,[140–141] because the low-penetrant genetic effects of common SNPs may largely depend on interaction with a particular environmental exposure in multiple stages of gastric cancer carcinogenesis, such as *H. pylori* infection (eg, pro-inflammation genes and DNA repair genes) and dietary factors (eg, carcinogens, metabolic genes, and folate metabolic genes).

A critical area for further development in molecular epidemiologic studies on gastric cancer susceptibility would be the incorporation of novel technologic advances for refining the assessment of continuous, daily exposure to dietary factors. It is also important to develop phenotypic assays that can provide overall measurements of well-defined biologic pathways to assess correlations or associations between genetic variants and the phenotypes in appropriate tissues.

Another important aspect of epidemiologic studies is the ability to form improved multicenter research consortia,[142] which may be more advantageous compared with individual studies, not only in terms of study sample sizes but also finance, data quality, and generalizable findings and conclusions.

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The authors declared no known financial interests or personal or professional relationships that could be perceived as presenting a potential conflict of interest that might have a bearing on the material in this paper.