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ARTICLE

Cell proliferation-related genetic polymorphisms and gastric cancer risk: systematic review and meta-analysis

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Apart from *Helicobacter pylori* infection and lifestyle factors, host genetic susceptibility has been suggested to contribute to individual variation in gastric cancer risk as well. Aiming to evaluate the associations between host cell proliferation-related genetic polymorphisms and gastric cancer susceptibility, we reviewed the related studies published until 15 September 2008 and quantitatively summarized the associations of the most widely studied polymorphisms (*TP53* Arg72Pro, *L-myc Eco*RI) using meta-analysis. Fifty-five eligible studies were included in this review. Twenty-three polymorphisms significantly related to gastric cancer risk in at least one study were identified. Polymorphisms determining higher levels of growth factors, which are important for tissue repair, were recently observed to be associated with reduced risk of gastric cancer. In the meta-analysis, *TP53* 72Pro was associated with increased risk of diffuse gastric cancer among Asians (OR, 1.44; 95% CI, 1.04–1.99), but decreased risk of intestinal gastric cancer among Caucasians (OR, 0.56; 95% CI, 0.36–0.89). This review suggests that cell proliferation-related genetic polymorphisms could be candidate biomarkers of gastric cancer risk, but current evidence for the use for risk stratification is still very limited. Modestly significant associations in meta-analyses stratified by population or type of gastric cancer may be observed by chance because of the limited number of studies and small sample size. Larger studies are warranted to clarify the effect of cell proliferation-related genetic polymorphisms on gastric carcinogenesis.
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Keywords: gastric cancer; genetic polymorphism; cell proliferation

Introduction

Despite a worldwide decline in incidence, gastric cancer (GC) still is the second most common cause of cancer-related mortality.[1] It is well accepted that *Helicobacter pylori* infection is a key risk factor for GC. However, only a small fraction of the infected people develop GC or its precursors.[2–4] Such clinical diversity suggests that factors other than bacterial infection alone determine gastric carcinogenesis. Apart from virulence factors of the pathogen and other environmental and lifestyle risk factors, host genetic susceptibility is also likely to contribute.[5–7] In recent years, host genetic polymorphisms involved in inflammatory response, carcinogen metabolism, antioxidant protection, mucosal protection and cell proliferation regulation have been widely studied as potential biomarkers to predict GC risk. However, the findings are frequently heterogeneous.[8–10] In this article, we provide a systematic review of studies addressing the association of cell proliferation-related polymorphisms with GC suscepti-

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bility. For the most widely studied polymorphisms, we also quantitatively summarized associations with GC using meta-analysis.

Materials and methods

Literature search

Studies investigating associations of host genetic polymorphisms and GC risk were identified by searching for articles in the MEDLINE database and Chinese BioMedical Literature Database. Articles published until 15 September 2008 were considered. Different combinations of the key words 'gastric cancer', 'stomach cancer', 'polymorphism(s)' and 'susceptibility' were used to screen for potentially relevant studies. Additional studies were also identified using cross-referencing.

Inclusion and exclusion criteria

Polymorphisms related to GC risk were divided into several groups according to their biological roles: mucosal protection and inflammation response, carcinogen metabolism, oxidative damage and DNA reparation, tumor invasion (cell adhesion and angiogenesis) and the regulation of cell proliferation. Cell proliferation-related genetic polymorphisms were selected for this review. Case–control or cohort studies presenting original data on associations between the genetic polymorphisms and GC were included. If the effect of a polymorphism was reported in duplicate, the article published in English or published earlier was included. Exclusion criteria include: (i) articles not in English or Chinese; (ii) review articles; (iii) articles which were not cases–control or cohort studies addressing GC susceptibility; (iv) articles focusing on polymorphisms other than cell proliferation-related.

Data extraction and statistical analysis

Data extraction and analysis followed standard methods for systematic review and meta-analysis[11,12] as described elsewhere.[13] Briefly, for all studies, we extracted the following data from the original publications: first author and year of publication; genes and relevant polymorphisms; characteristics of the study design and the study population, association according to tumor location and histological types, case–control matching criteria and covariates controlled for (the latter are presented in Supplementary Tables only). Adjusted odds ratios (ORs) were extracted from the studies where available and included in tabular presentation. For some studies, crude ORs had to be calculated from the reported frequencies of genotype by disease status.

Meta-analyses were carried out using Comprehensive Meta-Analysis (V2.0, Biostat, Englewood, NJ, USA) for the most widely studied polymorphisms, which were evaluated in at least five studies. Dominant models were used to represent the effect of the polymorphism, and corresponding ORs (adjusted ORs were used where available) from the included studies were summarized. Random effects models were used in meta-analysis, taking into account the possibility of heterogeneity between studies, which was evaluated with the Q test ($P<0.10$ was considered indicative of statistically significant heterogeneity) and the I^2 statistic (values of 25, 50 and 75% are considered to represent low, medium and high heterogeneity, respectively). The Begg rank correlation method and the Egger weighted regression method were used to statistically assess publication bias ($P<0.05$ was considered indicative of statistically significant publication bias). Stratified analyses were conducted according to the ethnicity of the study population (Asian or Caucasian) and histological type of GC (Lauren's classification: diffuse type or intestinal type).

Results

The literature search identified 61 original articles[14–74] on associations between cell proliferation-related genetic polymorphisms and GC (flow diagram of study identification shown in Figure 1). Of these, six articles[69–74] were excluded from this review because of duplication reporting of results. From 55 included studies, 54 were hospital-based ($n=46$) or population-based ($n=8$) case–control studies, and only one was a cohort study-based nested case–control study.[34] Forty polymorphisms in 27 genes were assessed in included studies and 23 of them were significantly related to GC in at least one study. On the basis of their biological roles, the involved polymorphisms were categorized in two groups: cell cycle and apoptosis regulators (Table 1 and Supplementary Table 1) and cell growth factors-related (Table 2 and Supplementary Table 2) polymorphisms.

There were 43 studies focusing on the relationships between cell cycle regulators-related polymorphisms and GC susceptibility (Table 1). Inconsistent associations were observed for tumor protein p53 (*TP53*) Arg73Pro, the most widely studied polymorphism. Meta-analysis of the 14 included studies showed that, overall, the Pro allele at codon 72 of *TP53* was not significantly associated with GC (OR, 1.08; 95% confidence interval (CI), 0.91–1.27) (Figure 2).[14–23,25–28] However, when stratified by ethnicity and histological type of GC, we found that among Asians, the Pro allele acted as risk factor of GC and this association was particularly pronounced in diffuse GC (OR, 1.44; 95% CI, 1.04–1.99) but absent in intestinal GC (OR, 1.07; 95% CI, 0.64–1.80). No substantial difference was observed between hospital-based (OR, 1.26; 95% CI, 1.03–1.53) and population-based studies (OR, 1.13; 95% CI, 0.87–1.47) among Asians. Among Caucasians, the Pro allele was associated with a reduced risk of intestinal GC (OR, 0.56; 95% CI, 0.36–0.89), and no significant association was found with diffuse GC (OR, 0.74; 95% CI, 0.48–1.16).

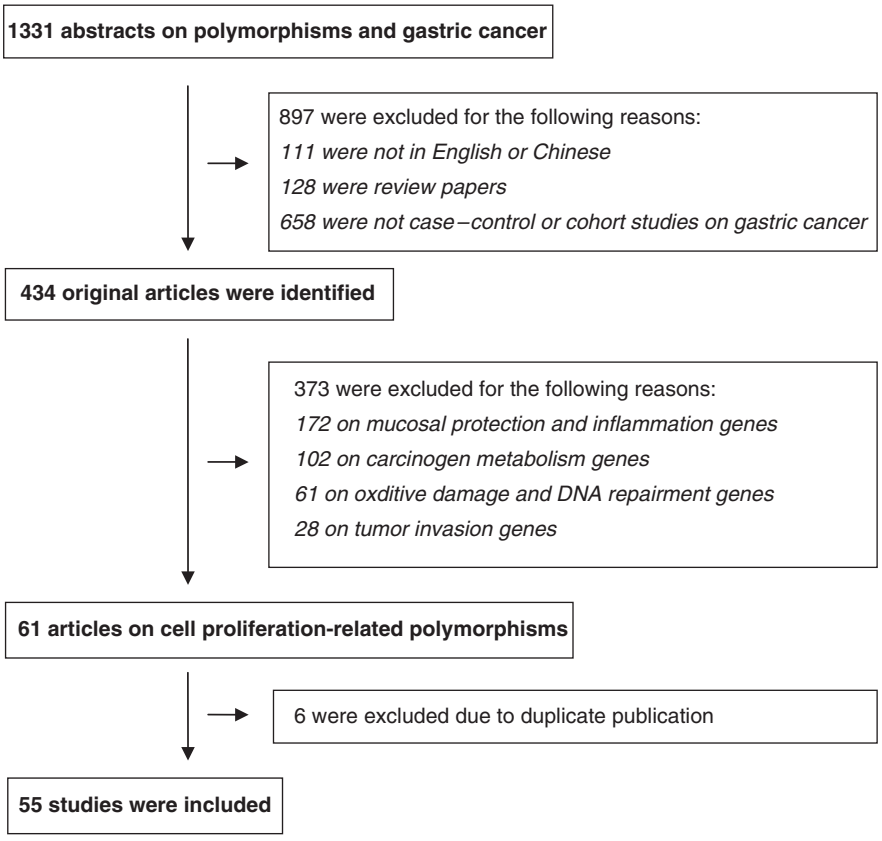


Figure 1 Flow diagram of study identification (until 15 September 2008).

However, only six out of the 14 included studies reported associations by histological type of GC (four in Asian populations[15,20,26,27] and two in the Caucasian populations[16,25]), and therefore the summarized results have to be interpreted with caution. One study on this polymorphism shown in Table 1 was excluded from the meta-analysis because the genotype frequencies and ORs were not reported by the original article.[24] No evident publication bias was observed as assessed by Begg rank correlation method ($P=0.83$) and Egger weighted regression method ($P=0.82$).

Polymorphisms of functional regulators of *TP53*, *TP53BP2* (tumor protein p53 binding protein 2) and *MDM2* were also found to be related to the development of GC in studies from Korea and Japan, respectively.[29,30] An SNP (exon 2 4G>A) in *TP73,* which encodes a homology of p53, showed significant association in Chinese[32] but not in Japanese.[14] Four studies were carried out on the 870G>A variant in *Cyclin D*;[33–36] a significantly reduced risk of GC was observed for AA genotype in one study[36] carried out in the Chinese population. H-RAS was reported to stabilize p21 by promoting the formation of p21–cyclin D1 complexes that prevent subsequent degradation; Harvey retrovirus-associated DNA sequences (H-RAS) 81C allele was associated with an increased risk of GC (OR, 3.7; 95% CI, 2.2–6.0) in a study from China.[38]

Meta-analysis showed inconsistent results for the S allele of an *Eco*RI polymorphism in the second intron of *L-myc* (*MYCL1*) (Figure 3). Of the four included Asian studies, one showed a significant increase in risk, the other three presented non-significant associations in opposite directions.[39,40,42,45] Diverse results were also found in the two studies involving Caucasians.[43,44] One study on this polymorphism shown in Table 1 was excluded from meta-analysis because the allele frequencies were not reported by the original article.[41] The results of Begg rank correlation analysis ($P=0.13$) and Egger weighted regression analysis ($P=0.49$) did not indicate significant publication bias.

Genotypes inhibiting apoptosis were reported to increase GC risk. For example, *Survivin* -31C allele was associated with an increased risk compared with GG genotype in studies from China.[46,47] Gene variants in transcription factors participating in cell cycle regulation, such as peroxisome proliferator-activated receptor γ (PPAR-γ), eukaryotic translation release factor 3 , krüppel-like factor 6 and RUNX3, were also identified as potential predictors of GC.[49–54]

Table 1 Association between cell cycle and apoptosis regulators gene polymorphisms and gastric cancer susceptibility

		Study design and population			*Association with GC*	
Polymorphism (SNP ID)	*First author, publish year*	*No. of cases/controls*	*Population*	*Setting*	*Groups compared*	*OR (95% CI)*
(a) TP53 and its functional regulators						
TP53 Arg72Pro (rs1042522)	Hamajima, 2002	144/241	Japanese	Hospital	*Pro *vs* Arg/Arg	1.1 (0.7–1.7)[a]
	Hiyama, 2002	117/116	Japanese	Hospital	*Pro *vs* Arg/Arg	1.1 (0.6–1.8)[a]
					Diffuse	2.1 (1.0–4.6)[a]
					Intestinal	0.7 (0.4–1.3)[a]
	Zhang, 2003	120/277	British	Hospital	*Pro *vs* Arg/Arg	0.7 (0.5–1.1)[a]
					Diffuse	0.9 (0.5–1.6)[a]
					Intestinal	0.6 (0.4–1.1)[a]
	Shen, 2004	324/317	Chinese	Population	Pro/Pro *vs* *Arg	0.7 (0.5–1.1)[a]
	Wu, 2004	89/192	Chinese	Hospital	Pro/Pro *vs* Arg/Arg	1.3 (0.6–3.2)
	Xi, 2004	48/288	Chinese	Population	*Pro *vs* Arg/Arg	1.6 (0.8–3.1)[a]
	Lai, 2005	51/59	Chinese	Hospital	*Pro *vs* Arg/Arg	1.4 (0.6–2.9)[a]
					Diffuse	2.0 (0.8–5.0)[a]
					Intestinal	0.6 (0.2–1.8)[a]
	Lai, 2005	123/126	Chinese	Hospital	*Pro *vs* Arg/Arg	1.3 (0.8–2.2)[a]
	Perez-P, 2005	65/182	Mexican	Hospital	*Pro *vs* Arg/Arg	0.5 (0.3–0.9)[a]
	Mu, 2005	206/415	Chinese	Population	*Pro *vs* Arg/Arg	1.2 (0.7–2.0)
	Khayat, 2005	54/54	Brazil	Hospital	*Pro *vs* *Arg	1.2 (0.5–2.7)[a]
	Belyavskaya, 2006	30/125	Russian	Hospital	*Pro *vs* Arg/Arg	0.6 (0.3–1.4)[a]
					Diffuse	0.2 (0.1–1.1)[a]
					Intestinal	0.5 (0.1–1.9)[a]
	Chung, 2006	84/43	Korean	Hospital	*Pro *vs* Arg/Arg	1.1 (0.6–2.0)[a]
					Diffuse	0.7 (0.3–1.8)[a]
					Intestinal	2.1 (0.9–5.0)[a]
	Yi, 2006	292/216	Korean	Hospital	*Pro *vs* Arg/Arg	1.3 (0.9–1.9)[a]
					Diffuse	1.3 (0.9–2.0)[a]
					Intestinal	1.3 (0.9–2.1)[a]
	Sul, 2006	155/134	American	Hospital	Pro/Pro *vs* *Arg	1.0 (0.5–2.1)
TP53BP2						
rs1538140 C>T					CC *vs* *T	1.5 (1.1–2.1)
rs1982610 A>T					AA *vs* *T	1.5 (1.0–2.1)
rs1222158 G>A					GG *vs* *A	1.6 (1.1–2.2)
rs2242188 A>T	Ju, 2005	233/390	Korean	Hospital	AA *vs* *T	1.5 (1.0–2.2)
rs745697 G>T					GG *vs* *T	1.0 (0.7–1.5)
rs1153942 G>T					TT *vs* *G	1.2 (0.6–2.2)
rs1222155 G>A					GG *vs* *A	1.1 (0.8–1.6)
MDM2 309T>G (rs2279744)	Ohmiya, 2006	410/438	Japanese	Population	GG *vs* *T	1.5 (1.0–2.1)
	Cho, 2008	239/299	Korean	Hospital	GG *vs* TT	0.8 (0.5–1.5)
					Diffuse	0.7 (0.4–1.3)[a]
					Intestinal	0.8 (0.4–1.3)[a]
p73 exon 2 4G>A (rs9662633)	Hamajima, 2002	144/241	Japanese	Hospital	GG *vs* AA	0.7 (0.3–1.9)[a]
	Zhang, 2008	385/412	Chinese	Hospital	GG *vs* AA	1.7 (1.2–2.5)
					Diffuse	1.3 (1.2–2.8)
					Intestinal	1.1 (0.6–2.3)
(b) Other cell cycle and apoptosis regulators						
Cyclin D1 870G>A (rs603965)	Zhang, 2003	87/183	Chinese	Hospital	AA *vs* *G Cardia	1.5 (0.9–3.1)
	Geddert, 2005	286/253	German	Hospital	AA *vs* *G	0.7 (0.4–1.0)[a]
	Song, 2007	253/442	Korean	Hospital	AA *vs* *G	0.8 (0.6–1.2)[a]
	Jia, 2008	159/162	Chinese	Hospital	AA *vs* GG non-cardia	0.3 (0.2–0.7)
p16 540C>G (rs11515)	Lai, 2005	123/119	Chinese	Hospital	*G *vs* CC	0.4 (0.1–1.9)[a]
	Geddert, 2005	267/230	German	Hospital	*G *vs* CC	0.8 (0.5–1.3)[a]
$p21^{WAF1/CIP1}$ Arg31Ser (rs1801270)	Wu, 2004	89/192	Chinese	Hospital	*Ser *vs* Arg/Arg	1.1 (0.5–2.2)
	Xie, 2004	30/45	Chinese	Hospital	*Ser *vs* Arg/Arg	3.4 (1.0–13.8)[a]
	Xi, 2004	48/288	Chinese	Population	Ser/Ser *vs* Arg/Arg Intestinal	1.7 (0.7–3.9)
	Lai, 2005	123/119	Chinese	Hospital	*Ser *vs* Arg/Arg	0.7 (0.4–1.2)[a]
$p21^{WAF1/CIP1}$ 1718T>C (rs733590)	Xi, 2004	48/288	Chinese	Population	CC *vs* TT	1.7 (0.7–3.9)[a]
$p21^{WAF1/CIP1}$ 460G>C (rs730506)					CC *vs* GG	1.6 (0.7–3.9)[a]
H-RAS T81C (rs12628)	Zhang, 2008	90/448	Chinese	Population	*C *vs* TT	3.7 (2.2–6.0)
*L-myc Eco*R1	Ishizaki, 1990	60/100	Japanese	Hospital	*S *vs* LL	0.7 (0.3–1.5)[a]
	Kato, 1996	82/151	Japanese	Hospital	*S *vs* LL	
					Diffuse	1.2 (0.4–3.4)
					Intestinal	1.4 (0.5–4.0)
	Kato, 1997	284/284	Japanese	Hospital	LS *vs* LL	1.6 (1.0–2.3)
	Shibuta, 1998	61/107	Japanese	Hospital	*S *vs* LL	3.1 (1.3–7.2)
					Diffuse	2.9 (0.9–10.2)[a]
					Intestinal	2.8 (0.9–10.0)[a]
	Isbir, 2002	25/83	Turkish	Hospital	*S *vs* LL	4.6 (1.5–16.8)[a]
	Dlugosz, 2002	100/65	Caucasian	Hospital	*S *vs* LL	0.5 (0.2–1.1)[a]
					Diffuse	0.6 (0.2–1.4)[a]
					Intestinal	0.4 (0.2–1.1)[a]
	Nan, 2005	110/220	Chinese	Hospital	*S *vs* LL	1.6 (0.9–2.9)[a]
Survivin -31G>C (rs17884799)	Cheng, 2008	96/67	Chinese	Hospital	CC *vs* GG	4.8 (2.9–8.0)
	Yang, 2008	220/220	Chinese	Hospital	*C *vs* GG	1.4 (0.9–2.2)
					Cardia	1.0 (0.5–1.9)
					Non-cardia	2.0 (1.2–3.3)
DR4 626C>G (rs4871857)	Kuraoka, 2005	274/344	Japanese	Hospital	*G *vs* CC	1.1 (0.6–2.0)[a]
Erf3 GGC VNTR	Brito, 2005	278/200	Portuguese	Hospital	*10 *vs* *12	19.9 (1.2–333.9)
KLF6 -27G>A (rs3750861)	Cho, 2008	264/299	Korean	Hospital	AA *vs* GG	9.5 (1.7–52.3)
$PPAR_{\gamma}$ Pro12Ala (rs1801282)	Liao, 2006	104/104	Chinese	Hospital	*Ala *vs* Pro/Pro Non-cardia	2.5 (1.1–5.8)
	Tahara, 2007	215/201	Japanese	Hospital	Pro/Ala *vs* Pro/Pro	2.4 (1.0–5.7)
					Cardia	5.0 (0.5–51.4)
					Non-cardia	2.4 (1.0–5.7)
					Diffuse	2.2 (0.8–6.2)
					Intestinal	2.9 (1.1–7.7)
	Prasad, 2008	62/241	Indian	Hospital	*Ala *vs* Pro/Pro	2.1 (1.1–4.1)
RUNX3 364C>T	Hu, 2005	178/361	Chinese	Hospital	TT *vs* CC	1.1 (0.4–2.8)
LAPTM4B VNTR in 5′ UTR	Liu, 2007	214/350	Chinese	Hospital	*1 *vs* *2/2	2.4 (1.2–4.8)

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; VNTR, variable number tandem repeat.
*Allele carrier.
[a]Calculated based on genotype or allele frequency extracted from corresponding article.

Table 2 Association between growth factors gene polymorphisms and gastric cancer susceptibility

		Study design and population			*Association with GC*	
Polymorphism (SNP ID)	*First author, publish year*	*No. of cases/ controls*	*Population*	*Setting*	*Groups compared*	*OR (95% CI)*
EGF 5′UTR 61A>G (rs4444903)	Hamai, 2005	200/230	Japanese	Hospital	*A *vs* GG	0.6 (0.4–0.9)
					Diffuse	0.8 (0.5–1.4)[a]
					Intestinal	0.5 (0.3–0.7)[a]
	Goto, 2005	202/454	Japanese	Hospital	*A *vs* GG	1.0 (0.7–1.4)
	Jin, 2007	617/660	Chinese	Population	*A *vs* GG	0.8 (0.6–1.0)
EGF -1380G>A (rs11568835)	Jin, 2007	617/660	Chinese	Population	AA *vs* GG	0.9 (0.5–1.7)
EGF -1744A>G (rs3756261)					GG *vs* AA	1.2 (0.7–2.1)
HER2 Ile655Val (rs1801200)	Kuraoka, 2003	212/287	Japanese	Hospital	Val/Val *vs* Ile/Ile	3.3 (1.1–9.8)
TGFB1 -509C>T (rs1800469)	Jin, 2007	636/676	Chinese	Population	*T *vs* CC	0.7 (0.5–0.8)
	Li, 2008	167/193	Chinese	Hospital	TT *vs* CC	2.1 (1.1–3.8)
TGFB1 869T>C (rs1982073)	Jin, 2007	636/676	Chinese	Population	CC *vs* TT	0.9 (0.7–1.3)
	García-G, 2006	142/342	Spanish	Hospital	CC *vs* TT	1.1 (0.6–1.8)[a]
	García-G, 2007	404/404	Spanish	Hospital	CC *vs* TT	0.9 (0.6–1.1)
	Li, 2008	167/193	Chinese	Hospital	CC *vs* TT	4.0 (2.1–7.8)
TGFB1 915G>C (rs1800471)	García-G, 2006	142/342	Spanish	Hospital	*C *vs* GG	1.2 (0.7–2.2)[a]
	García-G, 2007	404/404	Spanish	Hospital	*C *vs* GG	1.4 (0.9–2.1)
TGFBR2 -875G>A (rs3087465)	Jin, 2007	636/676	Chinese	Population	*A *vs* GG	0.7 (0.5–0.9)
INS -23A>T (rs698)	Li, 2007	160/166	Chinese	Hospital	*T *vs* AA	1.4 (0.8–2.7)
IGF1R A>G (rs2229765)					GG *vs* AA	1.2 (0.7–2.3)
IGF-II 17200A>G (rs680)					GG *vs* AA	1.5 (0.8–2.9)
IGFBP1 643A>G (rs3793344)					GG *vs* AA	1.4 (0.7–2.6)
IGFBP3 -202A>C (rs2854744)	Zhang, 2004	120/267	British	Hospital	CC *vs* *A	2.1 (1.1–3.9)[a]
	Chen, 2008	576/647	Chinese	Hospital	CC *vs* AA	1.3 (0.7–2.1)
IGFBP3 Gly32Ala (rs2854746)	Chen, 2008	576/647	Chinese	Hospital	Ala/Ala *vs* Gly/Gly	2.4 (1.5–3.9)
MK -2669G>A (rs20542)	Lai, 2005	123/126	Chinese	Hospital	*A *vs* GG	1.3 (0.5–3.1)[a]
Pepsinogen C I/D	Liu, 2003	73/42	Chinese	Hospital	*6/6 *vs* others	2.9 (1.1–8.5)[a]
	Pinto-C, 2006	57/127	Portuguese	Population	*6 present *vs* absent	0.4 (0.2–0.8)

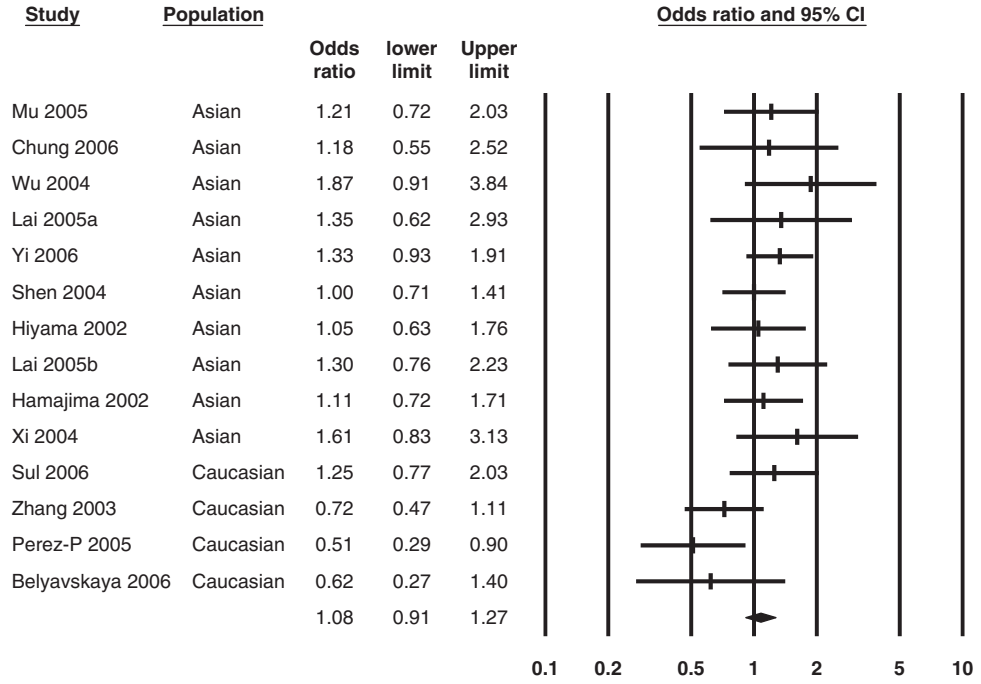
Abbreviations: GC, gastric cancer; OR, odds ratio; UTR, untranslated region; I/D, insertion/deletion.
*Allele carrier.
[a]Calculated based on genotype or allele frequency extracted from corresponding article.

Recently, polymorphisms related with growth factors were assessed as potential risk markers of GC (Table 2). At 5′ UTR in epidermal growth factor (EGF) gene, 61G carrier was associated with reduced GC risk in the Asian studies from Japan and China.[56–58] Ile655Val variant of HER2, a member of the EGF receptor family, showed a significant association with GC.[59] *TGFB1*-509T and *TGFBR2*-875A were reported determining high levels of transforming growth factor β1 (TGF-β1) and TGF-β receptor 2 (TGF-βR2), respectively. Decreased risks of GC were observed for these two alleles in one study from China.[60] Li ZQ *et al*[64] studied polymorphisms of insulin-like growth factors (IGF)-related genes. No association was found between GC risk and SNPs of insulin (INS), IGF-II, insulin-like growth factor binding protein 1 (IGFBP1) and IGF-1 receptor (IGF1R) genes. However, a significant association was observed for *IGFBP3 -202A*>C in a British population[65] and for Gly32Ala in a Chinese population.[64] Pepsinogen C (PGC) insertion/deletion variant between exons 7 and 8 was significantly associated with GC risk in studies carried out among the Chinese and Portuguese populations in reverse directions.[67,68]

Discussion

This systematic review addressed the association of cell proliferation-related genetic polymorphisms with GC reported up to 15 September 2008. Twenty-three polymorphisms significantly related to GC in at least one published study were identified, which suggests that polymorphisms in genes implicated in cell proliferation could be candidate biomarkers of GC risk.

Cell cycle and apoptosis regulators, which are directly involved in the initiation of cellular malignant proliferation, have long been preferred targets as cancer risk markers.[75] Our analysis regarding polymorphisms in *TP53* are consistent with and extend findings from a recent meta-analysis focusing on the Arg73Pro polymorphism.[76] Our meta-analysis, which included two additional studies on this polymorphism,[19,21] confirmed associations to vary by population and histological type of GC. Significant heterogeneity was observed among all the included 14 studies on *TP53* 72Pro, with no evidence of an overall association with GC risk. When stratified by ethnicity, however, studies included in subgroup analyses displayed better homogeneity, with an indication of an increased risk



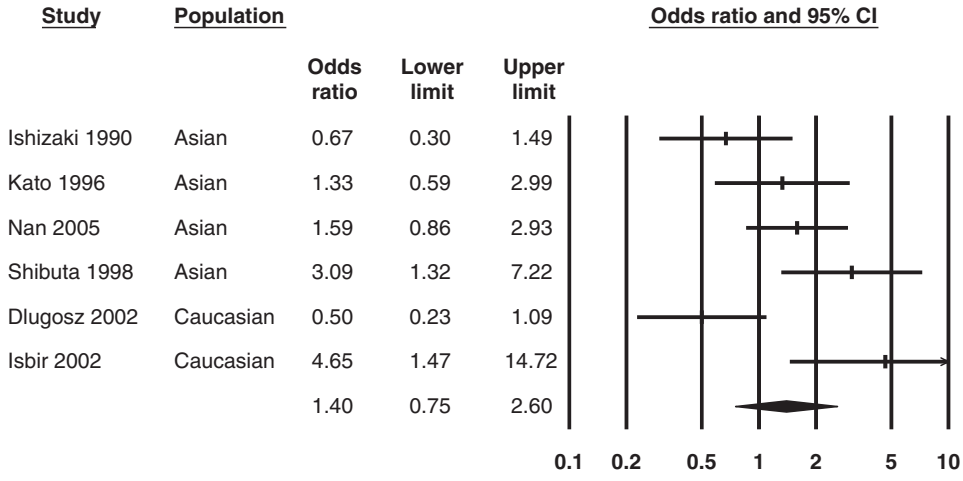
Subgroup analysis		Odds ratio (95% CI)	No. of studies	No. of cases/controls	Heterogeneity	
					I^2 (%)	P
Total	Asian	1.21 (1.03-1.42)	10	1478/2013	0	0.90
	Caucasian	0.76 (0.51-1.12)	4	370/718	51.95	0.10
	All subjects	1.08 (0.91-1.27)	14	1848/2731	28.88	0.15
Diffuse GC	Asian	1.44 (1.04-1.99)	4	258/434	0.97	0.39
	Caucasian	0.74 (0.48-1.16)	2	68/402	0	0.34
	All subjects	1.13 (0.77-1.66)	6	326/836	46.58	0.10
Intestinal GC	Asian	1.07 (0.64-1.80)	4	266/434	51.43	0.10
	Caucasian	0.56 (0.36-0.89)	2	71/402	0	0.51
	All subjects	0.84 (0.54-1.31)	6	337/836	58.85	0.03

Figure 2 Meta-analysis of *TP53* 72Pro and gastric cancer susceptibility.

among the Arg allele carriers in Asians and a tentatively reduced risk among Caucasians. Such inverse associations might be explained by differing environmental factors, which act jointly with either apoptotic or DNA repair machinery, respectively. Environmental risk factors might also determine the mutational spectrum of *TP53*, which was also shown to contribute to the functional consequences of the Pro72Arg polymorphism.[77] Alternatively, a different degree of linkage disequilibrium in different ethnicities of this variant with another functional variant might underlie the findings. One candidate polymorphism could be the 16-bp duplication in intron 3 that has previously been associated with reduced *TP53* mRNA.[78]

Heterogeneous results were found for the other two most widely studied polymorphisms in cell cycle-related genes, *L-myc Eco*RI polymorphism[39–42] and *p21* Arg31-Ser,[18,19,21,37] even in the same ethnicity. Such an inconsistency may be partly explained by study design and the interaction with non-genetic risk factors, such as *H. pylori* infection and dietary factors, which strongly vary between populations. So, besides stratification by ethnicity and different type of GC, larger population-based studies with careful ascertainment of 'lifestyle' and 'environmental' factors are essential to fully understand the role of host genetic susceptibility.

A consistently increased risk was observed for PPAR-γ 12Ala carriers in the Chinese, Japanese and Indian populations.[51–53] PPAR-γ is a member of the nuclear hormone receptor family that plays an important role in cell differentiation and regulation of metabolism. A potential interplay between PPAR-γ Pro12Ala polymorphism and *H. pylori* infection was observed in the



Subgroup analysis		Odds ratio (95% CI)	No. of studies	No. of cases/controls	Heterogeneity	
					I^2 (%)	P
Total	Asian	1.44 (0.81-2.55)	4	295/508	55.57	0.08
	Caucasian	1.46 0.16-13.01)	2	125/148	89.89	<0.01
	All subjects	1.40 (0.75-2.60)	6	420/656	71.49	<0.01
Diffuse GC	Asian	1.74 (0.75-4.05)	2	52/188	8.42	0.30
	Caucasian	0.57 (0.23-1.38)	1	53/65		
	All subjects	1.16 (0.47-2.87)	3	105/253	54.62	0.11
Intestinal GC	Asian	1.93 (0.90-4.12)	2	62/188	0	0.39
	Caucasian	0.44 (0.18-1.06)	1	47/65		
	All subjects	1.15 (0.39-3.43)	3	109/253	71.28	0.03

Figure 3 Meta-analysis of L-*myc* S allele and gastric cancer susceptibility.

development of GC.[51,53] It was also suggested that this polymorphism may be associated with gastric mucosal atrophy in *H. pylori*-infected patients, thereby increasing the risk of GC.[52] Further studies on different ethnic groups are needed to confirm the observed association and to clarify the role of PPAR-γ during gastric carcinogenesis.

Polymorphisms determining higher level of growth factors and related receptors, which are important to tissue repair, were associated with reduced risk of GC. Such associations were observed for *EGF* 5′ UTR 61G>A,[56,58] *TGFB1* -509C>T,[60] *TGFBR2* -875G>A,[60] and *IGFBP3* -202A>C[65] and Gly32Ala.[66] PGC was reported to not only act as a digestive enzyme, but might also be a growth factor during the healing of gastric lesions.[79] Genetic polymorphisms in PGC gene determining lower expression were also supposed to contribute to gastric ulcer and GC by failing to prevent disease development.[68,80]

Although this review indicates that cell proliferation-related genetic polymorphisms could be candidate biomarkers in GC risk, their overall effect seems to be modest and results were often inconsistent. Our analyses suggest that the inconsistencies may be explained, in part, by differences between the study populations and potentially different effects on different types of GC. In addition, different covariates were considered and controlled in different studies as presented in the Supplementary Tables. Considering *H. pylori* infection is suggested to be a (close to) necessary condition for development of noncardia gastric cancer,[81,82] the role of genetic polymorphisms may primarily be restricted to some (minor) modulation of the risk in the presence of *H. pylori* infection. In consideration of the potential misclassification of *H. pylori* status due to disease-related clearance of infection,[83] reports on gene–*H. pylori* interaction should be interpreted with caution.

There are some limitations to this systematic review that need careful consideration. First, because of the limited information supplied by included studies and the small sample sizes, relevant stratifications (eg, by ethnicity or type of GC) could not be made for many studies. Second, some of the included studies did not mention whether polymorphisms in controls were in Hardy–Weinberg equilibrium. However, no significant deviation from Hardy–Weinberg equilibrium was observed for all included studies based on our own calculations (data not shown), except the study by Xie *et al*,[37] which presented allele frequencies only. Third, owing to the heterogeneity in

length and detail of presentation of the included studies, no consistent formal rating of quality of studies was possible. Fourth, observed associations in the meta-analyses were generally weak and may partly reflect false positive results due to multiple testing.

In conclusion, this systematic review suggested that cell proliferation-related genetic polymorphisms could be candidate biomarkers of GC risk, but current evidence for the use for risk stratification is still very limited. Stratifications by ethnicity and GC type seem to be crucial in future studies aiming to clarify the effect of genetic polymorphisms on GC risk.

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