



ORIGINAL ARTICLE

Genetic polymorphisms and gastric cancer risk: a comprehensive review synopsis from meta-analysis and genome-wide association studies

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ABSTRACT

Objective: In the past few decades, more than 500 reports have been published on the relationship between single nucleotide polymorphisms (SNPs) on candidate genes and gastric cancer (GC) risk. Previous findings have been disputed and are controversial. Therefore, we performed this article to summarize and assess the credibility and strength of genetic polymorphisms on the risk of GC.

Methods: We used Web of Science, PubMed, and Medline to identify meta-analyses published before July 30th, 2018 that assessed associations between variants on candidate genes and the risk of GC. Cumulative epidemiological evidence of statistical associations was assessed combining Venice criteria and a false-positive report probability (FPRP) test.

Results: Sixty-one variants demonstrated a significant association with GC risk, whereas 29 demonstrated no association. Nine variants on nine genes were rated as presenting strong cumulative epidemiological evidence for a nominally significant association with GC risk, including *APE1* (rs1760944), *DNMT1* (rs16999593), *ERCC5* (rs751402), *GSTT1* (null/presence), *MDM2* (rs2278744), *PPARG* (rs1801282), *TLR4* (rs4986790), *IL-17F* (rs763780), and *CASP8* (rs3834129). Eleven SNPs were rated as moderate, and 33 SNPs were rated as weak. We also used the FPRP test to identify 13 noteworthy SNPs in five genome-wide association studies.

Conclusions: Sixty-one variants are significantly associated with GC risk, and 29 variants are not associated with GC risk; however, five variants on five genes presented strong evidence for an association upgraded from moderate. Further study of these variants may be needed in the future. Our study also provides referenced information for the genetic predisposition to GC.

KEYWORDS

Gastric cancer; genetic variants; susceptibility; meta-analysis; genome-wide association study

Introduction

Gastric cancer (GC) is a malignant carcinoma of the digestive tract and has become the third highest cause of carcinoma-associated deaths worldwide¹. Although advances in diagnoses and treatment may reduce mortality and morbidity, the 5-year survival rate remains poor². In 2016, 26,370 patients had GC, and 10,730 patients died from GC in the United States³. Because the carcinogenic mechanism of GC is not fully understood, GC has affected public health and has become a common concern. As with other complex diseases, the development of GC is a complicated, multistep,

multifactorial process, with various potential risk factors, including tobacco use, diet, alcohol consumption, *Helicobacter pylori* (HP) infection, obesity, and a history of stomach disorder⁴. In addition, the development of GC may be related to genetic susceptibility factors^{5-8,12-14}. Single nucleotide polymorphisms (SNPs), a common type of genetic mutation, may accelerate the development of GC. Genome-wide association studies (GWAS) may be able to identify sequence variations in the human genome, screen SNPs related to human diseases⁵, and extend our understanding of associations between genetic variations and cancer risk⁶. To date, two-stage GWAS (discovery and replication) have discovered millions of SNPs and identified relationships between candidate-gene SNPs and disease susceptibility^{7,8}. There are two limitations associated with the study of candidate genes: small sample size and low statistical power. A more precise and true association can be observed via a meta-analysis using previously available results^{9,10}. In

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Received August 25, 2018; accepted October 30, 2018.

Available at www.cancerbiomed.org

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2008, Dong et al.¹¹ performed a meta-analysis and reported that six variants were significantly associated with the risk of GC. Subsequently, more GC-related genes or loci have been discovered in research on genetic variants and identified in GWAS. In 2010, Abnet et al.¹² identified two identified GC-related loci (3q13.31 and 5p13.1). In 2011, Jin et al.¹³ found a locus (6p21.1) associated with GC in a GWAS. Later, Hu et al.¹⁴ identified a new locus (1q22) associated with GC, and Wang et al.¹⁵ found two novel loci (5q14.3 and 8q24.3) associated with GC. Recently, the results of most meta-analyses for same variant have been inconsistent, suggesting the possibility of false positive associations. Although meta-analyses involving large numbers of patients may reflect true associations between genetic variants and GC risk, the credibility and strength of these associations need to be further assessed¹⁶.

Therefore, a comprehensive review associated with genetic susceptibility to GC is needed. Our study assesses the credibility and strength of significant associations between candidate-gene SNPs and GC risk and provides comprehensive information for further investigation.

Methods

Literature search

Web of Science, PubMed, and Medline were searched to identify relevant meta-analyses published on before July 30th, 2018 using the following terms: (“gastric”) and (“cancer” or “carcinoma” or “adenocarcinoma” or “tumor” or “malignant” or “malignancy” or “neoplasm” or “neoplasia” or “oncology”) and (“genetic” or “gene” or “polymorphism” or “SNP” or “single nucleotide polymorphism” or “genetic variant”) and (“meta-analysis”). Additionally, we examined all relevant references to identify potential meta-analyses that could offer relevant data.

Criteria for selection

We used the following criteria to screen meta-analyses : (i) publications were in English, (ii) cancer type was GC, (iii) patients with GC were pathologically or histologically confirmed, (iv) the sample size was not fewer than 1,000, and (v) the studies were on GC incidence (rather than mortality or survival rate). Meta-analyses of GWAS were obtained from PubMed. We used the following criteria for GWAS-related articles: (i) publications were in English; (ii) cancer type was GC, which includes all GC subtypes; (iii) patients with GC were pathologically or histologically confirmed; (iv)

the studies were on GC incidence (rather than mortality or survival rate); and (v) the studies included two phases (discovery and replication).

Data extraction

Two authors (J.T. and G.L.) worked together to extract all data. Any disagreement was resolved by further discussion. The publication details collected included: first author, publication year, gene name, genetic variant, odds ratio (OR), and 95% confidence intervals (CIs) under the additive model, number of studies, number of subjects (cases and controls), ethnicity of participants, I-square (I^2), heterogeneity (Q test)¹⁷, and publication bias (Egger's test)¹⁸. For GWAS, the following inclusion criteria were reported for SNPs: (i) the results contained two stages (discovery and replication), (ii) the OR and 95% CI could be collected, and (iii) the P value was less than the cutoff of 5×10^{-8} . The publication details collected for each eligible qualified SNP included: PubMed identifier (PMID) number, first author, publication year, gene name, genetic variant, ethnicity of participants, number of subjects (cases and controls), minor allele frequency (MAF), OR and 95% CI, and P -value.

The eligible studies reported two major ethnicities: Asian and Caucasian. Twenty meta-analyses reported a single ethnicity; however, several others reported “diverse populations” indicative of two or more ethnicities. Some studies grouped their results by ethnicity, providing data on subgroup analyses. If the same genetic variant was reported in more than one study, we selected the most recently published study with the greatest number and most integrated participants. Current gene names were used to identify the different variants. A P -value of 0.05 or less was considered significant. Many studies utilized different genetic models; we selected the additive model (**Supplementary Table S1**) as our unified model to extract data and mitigate selection bias. As we were unable to use certain SNPs ($n = 20$) in the additive model, dominant, recessive, and homozygous models were also used where necessary.

Evaluation of cumulative evidence

We employed the Venice criteria to assess the epidemiological credibility of significant associations identified by the meta-analyses²⁵. Credibility was rated as strong, moderate, or weak (grade A, B, or C, respectively) according to three factors: amount of evidence, replication of association, and protection from bias. Evidence was evaluated by summing the number of alleles or genotypes

among cases and controls and divided into three groups: greater than 1000, 100–1000, and less than 100, representing grades A, B, and C, respectively. Certain test allele numbers or genotype amounts could not be extracted; in these cases, we searched the MAF from the NCBI SNP database (dbSNP) to calculate the amounts. Association replication was calculated using heterogeneity statistics assigning one of three grades: grade A ($I^2 < 25\%$), grade B ($25\% < I^2 < 50\%$), or grade C ($I^2 > 50\%$). Bias was evaluated using the P -value for publication bias; grade A indicated no observed publication bias ($P > 0.05$), grade B indicated bias accompanied by a lack of information for identification of evidence, and grade C indicated that bias was statistically evident ($P < 0.05$). The magnitude of association was related to protection from bias; a summary OR less than 1.15 was graded as a C for an association, unless several studies had identified that the association was replicated prospectively with an absence of publication bias. Cumulative epidemiological evidence of significant associations was assigned one of three levels: strong (A was assigned to all three grades), weak (C was assigned to any grade), or moderate (all other combinations).

We performed a false positive report probability (FPRP) assay with a prior probability of 0.001 and an FPRP cut-off value of 0.2 to uncover potential false positive results among significant associations, and to evaluate whether these associations should be omitted, as suggested by Wacholder et al.¹⁹. Statistical power and FPRP values were calculated by the Excel spreadsheet offered on website (<http://jncicancerspectrum.oupjournals.org/jnci/content/vol96/issue6>). If the calculated FPRP value was below the prespecified noteworthiness value of 0.2, we would consider the association noteworthy, indicating that the association might be true. FPRP evidence was categorized according to three levels: strong (FPRP < 0.05), moderate ($0.2 \leq \text{FPRP} \leq 0.05$), or weak (FPRP > 0.2). An FPRP less than 0.05 triggered an upgrading of cumulative evidence from moderate to strong or from weak to moderate. Conversely, an FPRP greater than 0.2 triggered a downgrading of cumulative evidence from strong to moderate or from moderate to weak.

Results

Characteristics of the articles included in our study

Our search yielded 1,041 articles (Figure 1). Of these, 308 articles were excluded as duplicates, 457 articles were excluded as irrelevant (not related to genetic variants or GC) after screening the titles and abstracts; the remaining 276

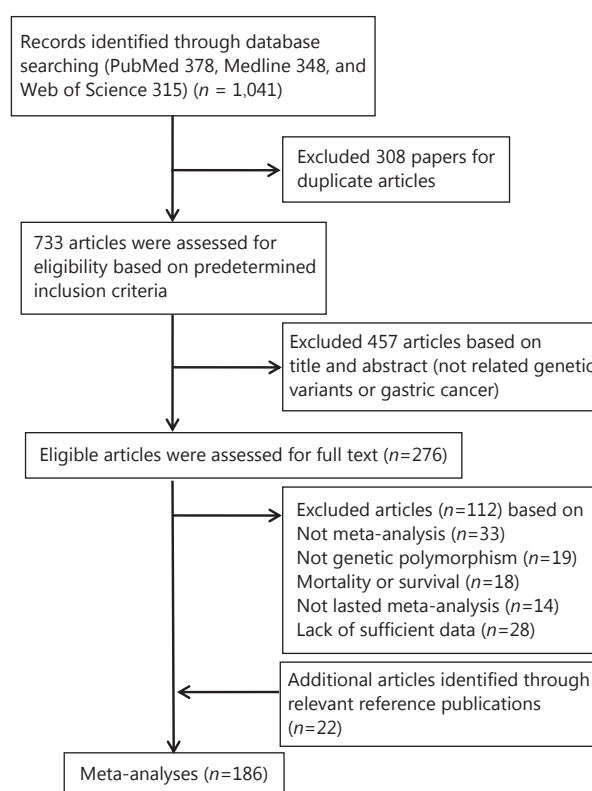


Figure 1 Flow diagram of search strategy and study selection

eligible articles were assessed for full-text review. We further excluded 33 non-meta-analyses, 19 non-genetic polymorphisms, 18 mortality or survival studies, 14 studies without an overall meta-analysis, and 28 studies with insufficient data. Twenty-two studies were screened from the reference publication. Subsequently, 186 meta-analyses were eligible for review; these identified 61 variants associated with the risk of GC. In addition, 18 variants (29.5%) were discovered in 2017.

PubMed was used to identify GWAS related to GC etiology, resulting in a total of five GWAS. All 13 SNPs identified were located within eight genes.

Significant associations in meta-analyses and GWAS

Among the main meta-analyses, cumulative epidemiological evidence was graded for 61 significant associations (Table 1). We assessed these associations using Venice criteria. With regards to the amount of evidence, 41 SNPs were Grade A, 13 Grade B, and 0 Grade C. Based on replication of association, 19 were Grade A, 13 were Grade B, and 28 were Grade C. Regarding protection from bias, 52 were Grade A, 7 Grade B,

Table 1 Statistically significant variants from meta-analysis, false-positive report probabilities (FPRP), and cumulative epidemiological evidence

Gene (variant)	Cancer type (year) ^{ref}	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Sample size (cases/control)	Number of test allele or genotype (calculated value according to MAF)	Maf	Venice criteria ^a	Venice grade	Power OR of 1.5	FPRP values at prior probability of 0.001 at power at OR of 1.5	Cumulative epidemiological evidence ^b
ALDH2 (rs671)	GC (2017) ²⁰	A vs G	Asian	1.17 (1.01–1.36)	No/0.325	0	2	2982 (1153/1829)	1618	0.2674	AAA	Strong	0.999	0.976	Moderate
APE1 (rs1760944)	GC (2017) ²¹	G vs T	Diverse	1.77 (1.40–2.24)	>0.05/0.29	19	4	2113 (802/1311)	1779	0.3863	AAA	Strong	0.084	0.023	Strong
APEX1 (rs1130409)	GC (2015) ²²	Asp vs Glu	Diverse	1.42 (1.09–1.84)	0.16/0.016	71	4	2114 (803/1311)	Na	0.3756 ^d	XCA	Na	Na	Na	Na
BIRC5 (rs9904341)	GC (2013) ²³	Recessive	Diverse	1.75 (1.07–2.86)	0.948/0.053	61.2 ^c	4	1147 (583/564)	293	0.4752	BCA	Weak	0.269	0.990	Weak
CD95 (rs2234767)	GC (2013) ²⁴	Recessive	Diverse	1.27 (1.05–1.53)	No/0.495	0	8	4563 (Na/Na)	Na	0.1841 ^d	XAA	Na	Na	Na	Na
COX-2 (rs20417)	GC (2013) ²⁵	Dominant	Diverse	1.58 (1.06–2.35)	0.05/0.000	85.4	10	7096 (2198/4898)	1157	0.0779	ACA	Weak	0.399	0.984	Weak
COX-2 (rs689466)	GC (2017) ²⁶	Dominant	Diverse	1.24 (1.06–1.45)	0.690/0.000	68.8	11	7723 (2500/5223)	6123	0.516	ACA	Weak	0.991	0.876	Weak
DNMT1 (rs1699593)	GC (2017) ²⁷	Dominant	Asian	1.36 (1.15–1.60)	0.982/0.720	0	3	2647 (999/1675)	2558	0.8194	AAA	Strong	0.881	0.191	Strong
DNMT3A (rs1550117)	GC (2016) ²⁸	Dominant	Asian	1.20 (1.01–1.42)	Na/0.04	69	3	2996 (1104/1892)	Na	0.1142 ^d	XCX	Na	Na	Na	Na
EGF (rs4444903)	GC (2015) ²⁹	G vs A	Diverse	1.18 (1.00–1.39)	0.106/0.009	66.61	7	5194 (1992/3202)	6524	0.6071	ACA	Weak	0.988	0.979	Weak
ERCC2 (rs1052559)	GC (2012) ³⁰	Recessive	Asian	2.41 (1.69–3.43)	0.106/0.028	61.48	6	4048 (2494/2977)	5471	0.6711	ACA	Weak	0.988	0.948	Weak
ERCC2 (rs1799793)	GC (2012) ³⁰	Recessive	Caucasian	0.91 (0.71–1.15)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
					0.989/0.701	0	5	3246 (1267/1979)	143	0.1266	BAA	Moderate	0.002	0.055	Moderate
					0.045/0.272	19.2	9	5144 (1715/3429)	416	0.2528	BAC	Weak	0.537	0.931	Weak

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Gene (variant)	Cancer type (year) ^{Ref}	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Sample size (cases/control)	Number of test allele or genotype (calculated value according to MAF)	MAF	Venice criteria ^a	Venice grade	Power OR of 1.5	FRP values at prior probability of 0.001 at power OR of 1.5	Cumulative epidemiological evidence ^b
			Asian	1.77 (1.19–2.63)	0.045/0.470	0	6	2529 (1256/1703)	113	0.1292	BAC	Weak	0.206	0.958	Weak
			Caucasian	1.31 (0.86–1.99)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
ERCC5 (rs751402)	GC (2017) ³¹	Dominant	Asian	1.17 (1.07–1.26)	0.249/0.437	0.1	10	9814 (4664/5150)	8568	0.6587	AAA	Strong	1.000	0.032	Strong
ERCC5 (rs873601)	GC (2017) ³²	A vs G	Asian	1.087 (1.021–1.159)	0.29/0.336	12.26	5	7645 (3727/3918)	7407	0.4743	AAC ^e	Weak	1.000	0.915	Weak
ERCC5 (rs2296147)	GC (2017) ³²	C vs T	Asian	1.268 (1.049–1.532)	0.355/<0.001	82.83	5	7589 (3699/3890)	3205	0.2121	ACA	Weak	0.959	0.935	Weak
FAS (rs2234767)	GC (2012) ³³	AA vs GG	Diverse	1.313 (1.045–1.650)	0.743/0.347	10.8	6	3420 (1413/2007)	400	0.3179	BAA	Moderate	0.873	0.957	Weak
			Asian	1.309 (1.041–1.646)	0.743/0.240	27.3	5	3068 (1299/1769)	398	0.3488	BBA	Moderate	0.878	0.96	Weak
FASL (rs763110)	GC (2012) ³³	CC vs TT	Diverse	1.352 (1.043–1.752)	0.536/0.461	0	6	3617 (1513/2104)	1713	0.6274	AAA	Strong	0.784	0.966	Moderate
			Asian	1.420 (1.081–1.865)	0.536/0.524	0	5	3165 (1399/1766)	1686	0.7095	AAA	Strong	0.653	0.947	Moderate
GSTP1 (Ile105Val)	GC (2012) ³⁴	GG vs AA	Asian	2.013 (1.197–3.387)	0.776/0.000	71.8	10	5605 (1664/3941)	335	0.1926	BCA	Weak	0.134	0.984	Weak
GSTT1 (null/presence)	GC (2014) ³⁵	Null vs presence	Diverse	1.21 (1.11–1.32)	0.475/0.0005	44	42	24294 (9029/15265)	9285	0.1787	ABA	Moderate	1.000	0.017	Strong
hMLH1 (rs1800734)	GC (2017) ³⁶	A vs G	Asian	1.14 (1.02–1.28)	No/0.585c	0 ^c	4	2578 (1250/1328)	2992	0.5644	AAC ^e	Weak	1.000	0.964	Weak
HOTAIR (rs4759314)	GC (2016) ³⁷	G vs A	Diverse	1.29 (1.10–1.51)	0.350/Na ^c	43.5	4	5590 (2290/3298)	646	0.052	BBA	Moderate	0.97	0.611	Weak
HOTAIR (rs920778)	GC (2017) ³⁸	T vs C	Diverse	1.372 (1.206–1.560)	No/0.05	68.8 ^c	3	2716 (907/1809)	1377	0.2338	ACA	Weak	0.913	0.002	Moderate
IL-1B (511C>T)	GC (2015) ³⁹	Recessive	Diverse	1.15 (1.03–1.29)	>0.1/<0.00001	58	45	20258 (9066/11192)	4005	0.4200	ACA	Weak	1.000	0.945	Weak
			Asian	1.14 (1.01–1.29)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na

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Gene (variant)	Cancer type (year) ^{ref}	Comparison	Ethnicity	OR (95% CI)	Publication Bias/heterogeneity	I ² (%)	No. of studies	Sample size (cases/control)	Number of test allele or genotype (calculated value according to MAF)	MAF	Venice criteria ^a	Venice grade	Power OR of 1.5	FPRP values at prior probability of 0.001 at power of 1.5	Cumulative epidemiological evidence ^b
IL-4 (rs2243250)	GC (2017) ⁴⁰	T vs C	Caucasian	1.15 (0.87–1.52)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
IL-8 (251A/T)	GC (2015) ⁴¹	A vs T	Diverse	1.15 (1.01–1.32)	No/0.28	21	7	3887 (1475/2412)	2894	0.3178	AAA	Strong	1.000	0.979	Moderate
IL-17A (rs2275913)	GC (2018) ⁴²	A vs G	Diverse	1.16 (1.05–1.27)	>0.05/<0.000001	66	26	13286 (5286/8000)	10933	0.4038	ACA	Weak	1.000	0.569	Weak
IL-17F (rs763780)	GC (2016) ⁴³	A vs G	Asian	1.23 (1.10–1.37)	>0.05/0.0005	61	17	8585 (3818/4767)	6620	0.3651	ACA	Weak	1.000	0.143	Weak
MMP1 (rs1799750)	GC (2015) ⁴⁴	A vs G	Diverse	1.24 (1.14–1.36)	No/0.000	67	16	14255 (6624/7631)	11647	0.3836	ACA	Weak	1.000	0.005	Moderate
MDM2 (rs2278744)	GC (2014) ⁴⁵	A vs G	Asian	1.25 (1.15–1.37)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
MMP7 (rs11568818)	GC (2014) ⁴⁶	Recessive	Caucasian	2.19 (1.40–3.44)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
MMP9 (-1562C>T)	GC (2017) ⁴⁷	C vs T	Asian	1.37 (1.25–1.51)	No/0.17	31	9	7346 (3244/4102)	2187	0.1273	ABA	Moderate	0.966	0.000	Strong
MIR-608 (rs4919510)	GC (2017) ⁴⁸	2G vs 1G	Asian	1.05 (1.01–1.06)	0.964/0.101	45.7	6	2920 (1377/1543)	3952	0.664	ABC ^e	Weak	1.000	0.000	Moderate
MTHFR (rs1801133)	GC (2016) ⁴⁹	G vs T	Asian	1.35 (1.24–1.47)	No/0.21	30	7	5400 (2199/3201)	5438	0.4848	ABA	Moderate	0.992	0.000	Strong
NAD (pH) (rs1800566)	GC (2014) ⁵⁰	Recessive	Diverse	1.768 (1.153–2.712)	0.345c/0.54	0	5	2175 (701/1474)	606	0.1547	BAA	Moderate	0.226	0.976	Weak
P53 (rs1042522)	GC (2012) ⁵¹	C vs T	Diverse	1.150 (1.014–1.304)	>0.1/0.231	23.9	9	3555 (1345/2210)	Na (1102)	0.1552d	XAA	Na	Na	Na	Na
		GG vs CC	Diverse	1.27 (1.00–1.62)	No/0.20	37.9	2	2604 (1261/1343)	Na (0–947)	0.3638d	XBA	Na	Na	Na	Na
		T vs C	Diverse	1.158 (1.055–1.271)	0.045/0	71.3	27	18206 (7566/10640)	8935	0.2454d	ACC	Weak	1.000	0.668	Weak
		T vs C	Diverse	1.38 (1.10–1.73)	0.22/<0.001	79.8	8	4037 (1662/2375)	3104	0.3672	ACA	Weak	0.765	0.872	Weak
		Dominant	Asian	1.18 (1.049–1.328)	>0.05/0.183	26.7	12	9726 (4582/5144)	7991	0.6001	ABA	Moderate	1.000	0.858	Weak

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Gene (variant)	Cancer type (year) ^{Ref}	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Sample size (cases/control)	Number of test allele or genotype (calculated value according to MAF)	MAF	Venice criteria ^a	Venice grade	Power OR of 1.5	FPR values at prior probability of 0.001 at power OR of 1.5	Cumulative epidemiological evidence ^b
PARP-1 (rs1136410)	GC (2014) ⁵²	C vs T	Asian	1.29 (1.11–1.49)	No/0.08	52	5	3889 (1429/2460)	2949	0.3599	ACA	Weak	0.98	0.353	Weak
PLCE1 (rs2274223)	GC (2014) ⁵³	G vs A	Diverse	1.21 (1.08–1.36)	No/<0.00001	88.1	11	37245 (13676/23569)	Na (22236)	0.2985d	ACA	Weak	1.000	0.581	Weak
			Asian	1.27 (1.11–1.45)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
PPARG (rs1801282)	GC (2015) ⁵⁴	G vs C	Diverse	2.26 (1.69–3.02)	0.202/0.909	0	5	1418 (546/872)	241	0.0728	BAA	Moderate	0.003	0.012	Strong
PRKAA1 (rs13361707)	GC (2018) ⁵⁵	C vs T	Diverse	1.34 (1.24–1.44)	0.574/<0.01	76.4	15	33026 (14615/18143)	33026	0.4703	ACA	Weak	0.999	0.000	Moderate
PSCA (rs2294008)	GC (2015) ⁵⁶	T vs C	Diverse	1.26 (1.10–1.45)	No/<0.00001	94	17	43848 (14974/28874)	35616	0.3855	ACA	Weak	1.000	0.002	Moderate
PSCA (rs2976392)	GC (2017) ⁵⁷	A vs G	Diverse	1.24 (1.08–1.41)	0.842/0.000	86.3	13	17077 (9059/8018)	13202	0.3583	ACA	Weak	0.998	0.508	Weak
TGF-β1 (rs1800470)	GC (2015) ⁵⁸	C vs T	Diverse	1.38 (1.11–1.73)	No/<0.01	87	11	5703 (2730/2973)	5435	0.4601	ACA	Weak	0.765	0.872	Weak
TLR4 (rs4986790)	GC (2014) ⁵⁹	G vs A	Diverse	1.64 (1.37–1.95)	0.322/0.065	42.6	11	5321 (1888/3433)	391	0.0501	BBA	Moderate	0.156	0.000	Strong
TLR4 (rs4986791)	GC (2014) ⁵⁹	T vs C	Diverse	1.36 (1.08–1.72)	0.365/0.219	25.3	9	4128 (1304/2824)	373	0.0439	BBA	Moderate	0.793	0.928	Weak
TNF-α (rs1800629)	GC (2014) ⁶⁰	A vs G	Diverse	1.18 (1.07–1.30)	No/0.015	39	32	19128 (7009/12119)	5095	0.1027	ABA	Moderate	1.000	0.447	Weak
TNF-α (rs1799724)	GC (2016) ⁶¹	T vs C	Diverse	1.12 (1.01–1.25)	0.06/0.46	0	9	5089 (1870/3219)	1828	0.1741	AAC	Weak	1.000	0.977	Weak
TNF-α (rs361525)	GC (2013) ⁶²	A vs G	Diverse	1.32 (1.02–1.72)	No/0.002	59.2	15	7795 (Na/Na)	Na (949)	0.0609d	XCA	Na	Na	Na	Na
XRCC1 (rs1799782)	GC (2012) ⁶³	Recessive	Diverse	1.31 (1.04–1.65)	0.40/0.101c	40c	9	5652 (2124/3528)	242	0.1977	BBA	Moderate	0.875	0.961	Weak
BRCAL (rs799917)	GC (2018) ⁶⁴	T vs C	Asian	0.76 (0.65–0.88)	0.934/Na	Na	1	1460 (660/800)	1066	0.3944	AXA	Na	Na	Na	Na

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Gene (variant)	Cancer type (year) ^{Ref}	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Sample size (cases/control)	Number of test allele or genotype (calculated value according to MAF)	MAF	Venice criteria ^a	Venice grade	Power OR of 1.5	FPRP values at prior probability of 0.001 at power OR of 1.5	Cumulative epidemiological evidence ^b
CASP8 (rs3834129)	GC (2017) ⁶⁵	Del vs Ins	Diverse	0.73 (0.62–0.86) (c)	0.727/0.000 ^c	0 ^c	3	1701 (616/1085)	1083	0.3645	AAA	Strong	0.861	0.163	Strong
DNMT3B (rs1569686)	GC (2016) ²⁸	Dominant	Asian	0.74 (0.61–0.90)	Na/0.000	81	5	3014 (1225/1789)	Na (832–1664)	0.2762d	XCX	Na	Na	Na	Na
GSTM1 (null/present)	GC (2017) ⁶⁶	null vs present	Diverse	0.788 (0.725–0.857)	0.000/0.000	54.6 ^c	70	28549 (11208/17341)	13890	0.2519	ACC	Weak	1.000	0.000	Moderate
IL-10 (rs1800871)	GC (2013) ⁶⁷	T vs C	Asian	0.88 (0.79–0.99)	0.70/0.18	28	10	5021 (1968/3053)	Na (4365)	0.4347d	ABA	Moderate	1.000	0.971	Weak
IL-10 (-592A/C)	GC (2012) ⁶⁸	Recessive	Asian	0.81 (0.68–0.97)	0.914/0.163	31.8	9	4008 (1526/2482)	1652	0.6364	ABA	Moderate	0.983	0.957	Weak
IL-10 (1082G>A)	GC (2012) ⁶⁹	A vs G	Diverse	0.489 (0.335–0.713)	0.961/0.000	94.9	22	10254 (4289/5965)	15860	0.7609	ACA	Weak	0.054	0.789	Weak
MIR-34 (rs895719)	GC (2012) ⁷⁰	C vs T	Asian	0.758 (0.643–0.893)	0.677/0.843	0	2	1382 (616/691)	887	0.3669	BAA	Moderate	0.938	0.496	Weak
MMP2 (rs243865)	GC (2013) ⁷¹	Dominant	Diverse	0.68 (0.47–0.99)	0.072/<0.00001	84	8	5154 (1792/3353)	1298	0.1506	ACA	Weak	0.541	0.988	Weak
MUC1 (rs4072037)	GC (2017) ⁷²	G vs A	Diverse	0.85 (0.74–0.97)	Na/<0.001	84	18	27381 (12373/15008)	7778	0.1482	ACA	Weak	1.000	0.941	Weak
TIMP-2 (300G/A)	GC (2016) ⁷³	A vs G	Diverse	0.80 (0.68–0.93)	>0.05/0.934	0	4	1883 (948/935)	860	0.245	BAA	Moderate	0.991	0.787	Weak
XRCC3 (rs861539)	GC (2015) ⁷⁴	Thr vs Met	Asian	0.62 (0.40–0.96)	0.055/0.000	86.5	4	3249 (1470/1779)	1718	0.2456	ACA	Weak	0.372	0.989	Weak
ZBTB20 (rs9841504)	GC (2017) ⁷⁵	G vs C	Diverse	0.840 (0.787–0.897)	>0.505/0.000	90.1 ^c	6	15694 (7810/7884)	4661	0.1544	ACA	Weak	1.000	0.000	Moderate
			Asian	0.840 (0.787–0.898)	>0.505/0.000	87.6 ^c	5	15440 (7679/7761)	4576	0.154	ACA	Weak	1.000	0.000	Moderate
			Caucasian	0.365 (0.140–0.949)	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na

Na: Not available, No: significant publication bias/heterogeneity was not found, Present: significant publication bias was found; Diverse: two or more ethnicities were reported in the meta-analysis. ^a Venice criteria grades are evidence of amount, replication of the association, and protection from bias. ^b Cumulative epidemiological evidence as graded by combination of results from Venice criteria and FPRP. ^c The information is calculated according to the data provided in the article since the article did not present (such as I², OR, publication bias and heterogeneity). ^d The MAF is obtained from dbSNP database. ^e The grade of C is given because the OR value is less than 1.15 and the association is not replicated by GWAS or GWAS meta-analysis

and 0 Grade C. Evidence for association with GC risk was thereby considered strong for seven SNPs, moderate for 17 SNPs, and weak for 29 SNPs based on Venice criteria.

We then evaluated the probability of a true association with GC risk for the nominally significant variants by calculating their FPRP values. Associations with GC risk showed an FPRP value of less than 0.05 for 12 variants (*GSTT1* null/presence, *MDM2* rs2278744, *PPARG* rs1801282, *TLR4* rs4986790, *IL-17F* rs763780, *HOTAIR* rs920778, *IL-17A* rs2275913, *PRKAA1* rs13361707, *PSCA* rs2294008, *MMP1* rs1799750, *ZBTB20* rs9841504, and *GSTM1* null/present), 0.05–0.2 for 27 variants, and greater than 0.2 for the remaining 14 variants. Finally, nine variants on nine genes were rated as demonstrating strong cumulative epidemiological evidence of association with GC risk after combining Venice criteria and FPRP results, including *APEI*

(rs1760944), *DNMT1* (rs16999593), *ERCC5* (rs751402), *GSTT1* (null/presence), *MDM2* (rs2278744), *PPARG* (rs1801282), *TLR4* (rs4986790), *IL-17F* (rs763780), and *CASP8* (rs3834129). A moderate association with risk was found for 11 variants, and weak association for 33 variants. Eight variants in our study could not be graded because of significant differences between calculated and true amounts. Calculated amounts of less than 3,000 were not included for assessment in MAFs obtained from the dbSNP.

In five GWAS, 13 variants were significantly associated with GC risk (**Table 2**)^{12-15,76}. Eight variants were significantly associated with an increased risk of GC. The opposite associations were found in five variants, all of which were regarded as significant following the FPRP assay. Venice criteria were not applicable to GWAS.

Table 2 Statistically significant variants from GWAS

PMID	Gene	Variant	Ethnicity	Year	OR (95% CI)	MAF ^a	P ^b	Sample size (cases/control)	Power OR of 1.5	FPRP values at prior probability of 0.001 at power OR of 1.5	References
26701879	ASH1L	rs80142782	Asian	2017	0.62 (0.56–0.69)	Na	1.71E-19	15191 (5572/9619)	0.120	0.000	15
26701879	MUC1	rs4072037	Asian	2017	0.74 (0.69–0.79)	Na	6.28E-17	15191 (5572/9619)	0.996	0.000	15
26701879	LOC105379076	rs7712641	Asian	2017	0.84 (0.80–0.88)	Na	1.21E-11	15191 (5572/9619)	1.000	0.000	15
26701879	PSCA	rs2294008	Asian	2017	1.20 (1.15–1.28)	Na	5.95E-11	15191 (5572/9619)	1.000	0.000	15
26129866	PRKAA1	rs10074991	Asian	2016	0.80 (0.77–0.83)	Na	4.83E-26	20014 (9758/10256)	1.000	0.000	14
23103227	LRFN2	rs2494938	Asian	2012	1.18 (1.12–1.25)	0.26/0.23	4.91E-09	17721 (4332/13399)	1.000	0.000	13
22037551	ZBTB20	rs9841504	Asian	2011	0.76 (0.69–0.83)	0.11/0.15	1.70E-09	10176 (4294/5882)	0.998	0.000	76
22037551	PRKAA1	rs13361707	Asian	2011	1.41 (1.32–1.49)	0.57/0.48	7.60E-29	10176 (4294/5882)	0.915	0.000	76
20729852	PLCE1	rs2274223	Asian	2010	1.31 (1.19–1.43)	0.209/0.259	8.40E-09	5542 (3302/2240)	0.999	0.000	12
20729852	PLCE1	rs3765524	Asian	2010	1.31 (1.20–1.44)	0.207–0.259	5.32E-09	5542 (3302/2240)	0.997	0.000	12
20729852	PLCE1	rs3781264	Asian	2010	1.36 (1.23–1.50))	0.152/0.199	3.76E-09	5542 (3302/2240)	0.975	0.000	12
20729852	PLCE1	rs11187842	Asian	2010	1.34 (1.21–1.49)	0.147/0.190	2.53E-08	5542 (3302/2240)	0.981	0.000	12
20729852	PLCE1	rs753724	Asian	2010	1.34 (1.21–1.49)	0.147/0.190	1.74E-08	5542 (3302/2240)	0.981	0.000	12

Na: Not available. ^a Minor allele frequency (MAF) in case/control. ^b The P values are all less than 5.00E-08.

Non-significant associations in meta-analyses

We performed power analyses to determine the stability of associations. Based on our meta-analysis results, 29 variants were not significantly associated with GC risk^{24,25,27,32,33,58,63,77-93}. Four variants with sample sizes greater than 10,000 were not significantly associated with GC; further investigations into these variants may not be necessary, including *hOGG1* Ser326Cys⁸⁵, *IL-1B* rs1143627⁸⁶, *miR-146a* rs2910164⁹⁰, and *TGF-β1* rs1800469⁵⁸. Certain variants presented relatively small sample sizes; as such, the evidence for non-association (**Supplementary Table S2**) was considered unstable.

Inconsistency among meta-analyses

Controversial results were obtained for 23 variants (**Supplementary Table S3**). Overall, 16 variants were found to be significantly associated with GC, as follows: *BIRC5* rs9904341, *EGF* rs4444903, *ERCC5* rs2296147, *IL-4* rs2243250, *IL-8* 251T/A, *IL-17F* rs763780, *MMP7* rs11568818, *MMP1* rs1799750, *MMP9* -1562C > T, *TGF-β1* rs1800470, *TNF-α* rs361525, *DNMT3B* rs1569686, *GSTM1* null/active, *IL-10* -592C > A, *IL-10* 1082G > A, and *MMP2* rs243865. Seven variants were found to be non-significant: *CDH1* rs16260, *CDH1* +54T > C, *hOGG1* Ser726Cys, *IL-1B* rs1143627, *miR-146a* rs2910164, *miR-196a2* rs11614913, and *TGF-β1* rs1800469.

Discussion

In this study, we collated epidemiological evidence demonstrating significant associations between genetic variants and GC risk. We extracted related useful information from meta-analyses and GWAS to support a comprehensive assessment for further evaluation. Using FPRP tests and Venice criteria, we evaluated the credibility of this cumulative epidemiological evidence of nominally significant associations. Nine variants on nine genes were rated as demonstrating strong evidence of association with GC risk, including *APE1* rs1760944, *DNMT1* rs16999593, *ERCC5* rs751402, *GSTT1* null/presence, *MDM2* rs2278744, *PPARG* rs1801282, *TLR4* rs4986790, *IL-17F* rs763780, and *CASP8* rs3834129. Eleven variants presented moderate evidence of association with GC risk, and 33 variants presented weak evidence.

Apurinic/apyrimidinic endonuclease 1 (*APE1*), located on chromosome 14q11.2, participates in DNA base excision repair and has been associated with human carcino-

genesis⁹⁴⁻⁹⁶. Our analysis provides strong evidence for an association between the G allele of the *APE1* polymorphism and GC risk *via* an additive model, with a 1.77-fold increased risk of GC in a diverse population with a total sample size of 2,113. This variant promotes the development of cancer by impeding DNA repair activity⁹⁷. In our subgroup analysis, the mutant G allele also increased the risk of GC compared with the wild-type T allele. However, this study was performed exclusively on the Asian population. One reason that concentrated on single (Asian) population could be the small sample size of this meta-analysis, which made subgroup analyses challenging. Therefore, further investigations into this variant are necessary.

DNMT1, located on human chromosome 19p13.2, encodes a protein comprising 1,632 amino acids, which may be associated with the development of carcinoma⁹⁸. Some studies have suggested that DNA methylation contributes to the progression of GC and that over-expression of *DNMT1* may be associated with GC risk. The AKT-NFκB and STAT3 signaling pathways have been implicated in the over-expression of *DNMT1*, which may cause aberrant DNA methylation on tumor suppressor genes, thereby promoting the progression of GC^{99,100}. There was strong evidence for an association between SNP rs16999593 and GC risk in a sample of 2,647 Asians; this polymorphism occurs on the C allele of *DNMT1* (OR = 1.36, 95% CI = 1.15–1.60). This variant results in a histidine to arginine substitution at position 97 (His97Arg) of the translated sequence, which may disrupt the function of *DNMT1*, thus increasing susceptibility to GC. This study sample was limited to Asian populations, and involved a large proportion of Chinese patients. Further studies should investigate this polymorphism in other ethnic groups.

ERCC5, also known as *XPG*, is an endonuclease that may prevent carcinogenesis by excising damaged DNA during the DNA repair process¹⁰¹. A polymorphism (rs751402) is found in the promoter region of *ERCC5* and controls its expression and function during transcription in healthy human cells¹⁰². The present study showed that this SNP in a dominant model was strongly associated with increased risk of GC; rs751402, which contains a C to T transition, may alter the transcription domain-associated repair capacity of *ERCC5* that could account for its correlation with GC cancer risk in Asians ($n = 9,814$). However, all studies were performed on a single ethnic group (Asian), and we recommend expanding studies on this polymorphism to other populations.

Human *CASP8*, located on chromosome 2q33–q34, participates in cell cycle regulation^{103,104}. This SNP (rs3834129), located in the promoter region of *CASP8*¹⁰⁵,

leads to reduced expression of this gene. Impaired *CASP8* expression can decrease T lymphocyte-induced cell death¹⁰⁵. In the additive model, this SNP was strongly associated with GC, with a 1.14-fold decreased risk of GC in the sample population ($n = 1,701$). The variant inhibits *CASP8* transcription by inactivating the binding site of transcription factor stimulatory protein 1¹⁰⁵, potentially altering immune surveillance and decreasing the risk of GC. Although this SNP was only evaluated in case-control studies (not in GWAS), its association with GC risk in the meta-analysis was well established, with an overall schema of AAA. We assigned this SNP a rating of strong evidence because of an FPRP value of less than 0.05. This polymorphism could present a novel target for gene therapy of GC and lead to new drug developments against GC.

Five variants were upgraded from moderate to strong because of an FPRP value less than 0.05, including *GSTT1* null/presence, *MDM2* rs2278744, *PPARG* rs1801282, *TLR4* rs4986790, and *IL-17F* rs763780. Homozygous deletion (null genotype) of *GSTT1* (null/presence) leads to GST enzymatic inactivation and was associated with GC progression in a population of over 20,000^{35,106,107}. Based on these inconsistent results, we assigned strong evidence for the association of this SNP with GC risk, even though this SNP was not evaluated by GWAS. Total samples for the four remaining SNPs were less than 8,000, with 5,400 for *MDM2* rs2278744, 1,418 (546/872) for *PPARG* rs1801282, 5,321 for *TLR4* rs4986790, and 7,346 for *IL-17F* rs763780. According to the results of the FPRP and Venice criteria evaluations, evidence for an association with GC for these four SNPs was not statistically convincing. These results are potentially due to the use of Venice criteria, which accounts for potential bias such as genotyping errors, phenotype misclassifications, and population stratification. Some of the SNPs were difficult to assess using a meta-analysis. It is possible that the results would be more convincing if different weights were assigned to the different categories included in the Venice criteria.

Three SNPs, *ALDH2* rs671, *FASL* rs763110, and *IL-4* rs2243250, were rated as being moderately associated with GC risk; all were downgraded from strong to moderate based on an FPRP greater than 0.2. The FPRP method considers the *P* value, prior probability, and statistical power of the test; as we calculated FPRP at a prior probability of 0.001 and used the statistical power to detect an odds ratio of 1.5 for alleles with an elevated risk in FPRP calculations, some otherwise significant associations may have been excluded. Previous studies using different prior probabilities have classified their results as more noteworthy. Further investigations on these three variants may be necessary to analyze their associations

in greater depth.

Seven variants (*HOTAIR* rs920778, *IL-17A* rs2275913, *PRKAA1* rs13361707, *PSCA* rs2294008, *MMP1* rs1799750, *ZBTB20* rs9841504, and *GSTM1* null/present) were rated as being moderately associated with GC risk, after being upgraded from weak to moderate based on their FPRP values (< 0.05). Among these variants, rs13361707 on *PRKAA1*, rs2294008 on *PSCA*, and rs9841504 on *ZBTB20* were evaluated by meta-analysis and GWAS. A high degree of heterogeneity may explain how all three variants were graded “ACA” overall; these variants were designated as having moderate associations with GC. Two SNPs (rs13361707 and rs2294008) increased GC risk by 1.34- and 1.26-fold in the overall study population, respectively. No statistical data were presented for ethnicity subgroups; which could explain the heterogeneity in the data. We recommend subdividing populations by ethnicity to identify potential differences in the association between these two variants and GC. The variant rs9841504 variant was associated with a 1.26-fold decreased risk of GC in the overall population based on a total sample size of 15,694; this sample included a large number of Asian individuals but relatively few individuals of other ethnicities. We found stronger evidence to support an association for this variant in the Asian population based on the large sample size, but not in the smaller mixed-ethnicity group. While ethnicity may be one factor affecting heterogeneity, other factors such as methodology, GC subtypes, and environmental factors may also account for variation in the data. Further investigations of this and two further variants (*MMP1* rs1799750 and *HOTAIR* rs920778) are necessary, due to a lack of power in the smaller sample sizes.

Twenty-nine variants were not significantly associated with GC risk, including eight variants on five genes and two miRNAs in a sample of approximately 4,000 patients, at approximately 95% power to detect an OR of 1.15 in an additive model for a variant with MAF of 20%. Most of the MAFs of those eight variants exceeded 0.2, despite sample sizes greater than 4,000. We can therefore conclude, that these eight variants are unlikely to be associated with GC (**Supplementary Table S4**). It is probable that further investigations evaluating these eight variants will not yield meaningful results with regards to GC.

Of the remaining variants, 23 presented inconsistent associations with GC risk, 16 variants were nominally associated with GC risk, and seven variants were conclusively not associated with GC risk. Many studies analyzing the same SNP from this group yielded inconsistent results, due to variation in sample size, selection of association models, and

ethnicity. If the same genetic variant was reported in more than one article and the results were not consistent, we selected the most recently published meta-analysis to obtain the highest number or most integrated participants. When selecting association models, the additive one was the model of choice; others were employed only when the additive model was unusable. We extracted information from subgroup analyses based on ethnicity and found that some results for the same variant differed by ethnicity, which may have contributed to inconsistency in the results (**Supplementary Table S5**). Of note, we found that all GWAS and most of the meta-analyses included in our review were performed in Asian populations. Approximately 40% of all patients with GC worldwide are Asians, with a high proportion found in China. Studies in western populations performed with smaller sample sizes may exist but were not included in our study because of low statistical power. Additional studies on other ethnicities with larger sample groups are strongly recommended for the future.

Certain limitations apply to this report. Although we performed a comprehensive literature search, it is possible that some articles may have been missed. Variability in sample size was found among different studies; smaller sizes may have affected the credibility of the data. We evaluated data extracted from a single source, which may have introduced a critical bias. Finally, we only evaluated the susceptibility to, and incidences of association between genetic variants and GC risk; the involvement of genetic polymorphisms as they contribute to tumor progression, metastasis, and drug resistance in GC were not assessed due to a lack of data or information. Despite these limitations, we believe that our study, which provides an updated summary and evaluation of existing literature on the genetic predisposition to GC, will be of value in informing future genetic studies.

This paper evaluated the cumulative epidemiological evidence of significant associations between genetic variants and GC risk by combining Venice criteria and a FPRP assay. Nine SNPs presented strong evidence for an association with GC, of which five variants on five genes were upgraded from moderate to strong evidence based on their FPRP values, and should be further assessed in future studies. If these nine variants are confirmed to be associated with GC risk, they may explain the partial effect of the genetic variant on GC risk. In summary, our study summarizes current literature on the genetic architecture of GC susceptibility, and provides useful data for designing future studies aiming to assess genetic factors for GC risk.

Acknowledgements

Part of the suggestion for the discussion on statistics and proofreading of English grammar were provided by Dr. Shengping Hou (The First Affiliated Hospital of Chongqing Medical University, Chongqing Eye Institute, Chongqing Key Laboratory of Ophthalmology, Chongqing, China).

Conflicts of interest statement

No potential conflicts of interest are disclosed.

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Cite this article as: Tian J, Liu G, Zuo C, Liu C, He W, Chen H. Genetic polymorphisms and gastric cancer risk: a comprehensive review synopsis from meta-analysis and genome-wide association studies. *Cancer Biol Med*. 2019; 16: 361-76. doi: 10.20892/j.issn.2095-3941.2018.0290

Supplementary materials

Table S1 The complete data structure of genetic polymorphism study

Genotype amount			
Genotype type	AA	AB	BB
Case group	a_n	b_n	c_n
Control group	d_n	e_n	f_n

AA: Wild homozygous AB: Heterozygous mutant BB: Mutant homozygous n: indicating the N_{th} study. For a SNP, two alleles, A and B, could be presented. Specifically, A was considered as wild type, meanwhile, B was considered mutant type. Therefore, there may be three genotypes, AA, AB, BB, respectively, in population. Suppose there were three genotypes of the subjects, we could assign a, b, c to AA, AB, BB in case group, and d, e, f to AA, AB, BB in control group, respectively. The table above could offer additional explanation. In meta-analysis for SNPs, polygenic model was used to decrease probabilities of type I error. The following genetic models may be used in our study: 1) Additive model (i.e. B vs. A); 2) Dominant model (BB+BA vs. AA); 3) Recessive model (BB vs. BA+AA); 4) Homozygous model (BB vs. AA). Specifically, the additive model was used first, and the rest models were also used when additive model was not usable.

Table S2 Non-significant association in meta-analysis

PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Cases/control	Maf
25154002	ACE1 (rs4646994)	GC	2015	DD+DI vs II	Diverse	1.06 (0.92–1.21)	0.791/0.317	15.1	6	4262 (1311/2951)	0.3746
27623072	CCND1 (rs603965)	GC	2016	A vs G	Diverse	1.07 (0.88–1.30)	>0.05/<0.0001	77	9	3986 (1813/2173)	0.512
24978812	CD14 (rs2569190)	GC	2014	Dominant	Diverse	0.99 (0.77–1.26)	0.144/0.005	63	12	5304 (2968/2336)	0.4991
23681795	CD95L (rs763110)	GC	2013	Dominant	Diverse	1.02 (0.83–1.25)	No/Na	Na	8	4563 (Na/Na)	0.4696 ^a
23681795	CD95 (rs1800682)	GC	2013	Dominant	Diverse	1.00 (0.87–1.15)	Na/Na	Na	8	3970 (Na/Na)	0.4543 ^a
21570316	CDH1 (-616 G>C)	GC	2011	Recessive	Diverse	1.27 (0.86–1.88)	Na/Na	Na	3	1962 (565/1397)	0.2466
25599647	CDH1 (rs16260)	GC	2015	AA vs CC	Diverse	1.19 (0.89–1.58)	0.323/0.001	55	22	9679 (4218/9679)	0.2545
21570316	CDH1 (+54 T>C)	GC	2011	Recessive	Diverse	1.00 (0.75–1.34)	Na/Na	Na	5	2280 (996/1284)	0.2667
23775011	COX-2 (-587 G>A)	GC	2013	A vs G	Diverse	0.56 (0.19–1.70)	Na/<0.01	Na	3	3585 (885/2700)	0.0313
24443269	CYP1A1 (rs4646903)	GC	2014	Dominant	Diverse	0.950 (0.800–1.128)	0.017/0.163	30.7	10	3460 (923/2537)	0.2237
24443269	CYP1A1 (rs1048943)	GC	2014	Dominant	Diverse	0.936 (0.786–1.114)	0.113/0.876	0	8	4773 (1754/3019)	0.1577
27284439	CYP2E1 (RsaI/PstI)	GC	2016	C2 vs C1	Diverse	1.02 (0.86–1.19)	No/<0.0001	61.4	26	9237 (3727/5510)	0.1529
27284439	CYP2E1 (DraI)	GC	2016	C vs D	Diverse	1.05 (0.91–1.20)	No/0.784	0	6	2595 (1225/1370)	0.1861
29332452	DNMT3B (rs2424913)	GC	2017	T vs C	Asian	1.25 (0.89–1.76)	Na/0.81	0	5	3040 (1320/1720)	0.9706
28473984	DNMT1 (rs2228611)	GC	2017	Dominant	Asian	1.02 (0.83–1.26)	0.505/0.618	0	3	1469 (652/817)	0.7173

Continued

Continued

PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Cases/control	Maf
29072052	ERCC5 (rs2094258)	GC	2017	T vs C	Asian	1.076 (0.926–1.251)	0.234/<0.001	76.21	7	7989 (3812/4177)	0.3973
29072052	ERCC5 (rs1047768)	GC	2017	C vs T	Asian	0.95 (0.880–1.025)	0.301/0.074	50.13	6	6477 (3064/3413)	0.3415
22631677	FAS (rs1800682)	GC	2012	G vs A	Diverse	1.025 (0.913–1.151)	0.856/0.735	0	5	2523 (1065/1458)	0.416
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs G	Diverse	1.02 (0.92–1.12)	0.344/0.046	40.6	15	10046 (4024/6022)	0.6283
26805397	IL-1B (rs1143627)	GC	2016	Dominant	Diverse	1.02 (0.91–1.15)	0.398/0.001	48.3	37	15088 (6108/8980)	0.4724 ^a
22711691	IL-6 (rs1800795)	GC	2011	C vs G	Diverse	1.09 (0.76–1.53)	0.70/<0.00001	83	9	3598 (1249/2349)	0.3372
26770352	IL-17A (rs3748067)	GC	2015	T vs C	Asian	1.30 (0.84–2.03)	0.23/Na	92	5	4583 (2160/2423)	0.4144
29088869	MiR-27a (rs895819)	GC	2017	Dominant	Diverse	0.97 (0.72–1.31)	0.085/<0.001	91.2	8	8798 (4016/4782)	0.3638 ^a
29127520	miR-146a (rs2910164)	GC	2017	C vs G	Diverse	0.984 (0.903–1.072)	>0.05/0.005	57.3	13	12773 (5831/6942)	0.5632
25983750	miR-196a2 (rs11614913)	GC	2015	C vs T	Diverse	1.25 (0.97–1.60)	present/Na	Na	9	9410 (3992/5418)	0.4862
25170232	MTHFR (rs1801131)	GC	2014	C vs A	Diverse	0.97 (0.83–1.14)	No/0.03	Na	13	5686 (2007/3679)	0.2134
26770387	TGF-β1 (rs1800469)	GC	2015	T vs C	Diverse	0.95 (0.86–1.03)	No/<0.01	82	31	28474 (12940/15530)	0.4097
22292637	VEGF (+936C>T)	GC	2011	T vs C	Diverse	1.08 (0.90–1.27)	Na/0.49	Na	9	5101 (2281/2820)	0.1739
21604176	XRCC1 (rs25487)	GC	2012	Recessive	Diverse	1.04 (0.89–1.21)	0.93/Na	Na	16	9279 (3216/6063)	0.3051

Na: Not available, No: significant publication bias/heterogeneity was not found, Diverse: two or more ethnicities were reported in the meta-analysis.^aThe MAF is obtained from dbSNP database

Table S3 Inconsistency among meta-analysis

Gene/ PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/ heterogeneity	I ² (%)	No. of studies	Cases/ control	Number of test allele or genotype (calculated value according to MAF)	Maf
BIRC5-31G/C												
21611748	BIRC5 (rs9904341)	GC	2012	CC vs. GG	Diverse	2.88 (0.55–15.00)	0.525/Na	Na	3	707 (363/344)	Na (0–275)	0.3886 ^b
23405077	BIRC5 (rs9904341)	GC	2013	CC vs. GG+GC	Diverse	1.75 (1.07–2.86)	0.948/0.053	Na ^a	4	1147 (583/564)	293	0.4752
24077840	BIRC5 (rs9904341)	GC	2014	CC vs. GG	Diverse	2.21 (1.06–4.64)	0.317/0.013	72.4	4	1275 (451/824)	Na (0–495)	0.3886 ^b
CDH1												
21214416	CDH1 (rs16260)	GC	2011	AA+AC vs. CC	Diverse	1.03 (0.86–1.22)	0.114/0.005	Na ^a	15	6196 (2509/3687)	2909	0.2719
				AA+AC vs. CC	Asian	0.84 (0.72–0.99)	0.114/0.185	Na ^a	7	2671 (1220/1451)	1049	0.2191
				AA+AC vs. CC	European	1.26 (0.98–1.61)	0.114/0.022	Na ^a	8	3525 (1289/2236)	1860	0.3061
21570316	CDH1 (rs16260)	GC	2011	AA vs. AC+CC	Diverse	1.50 (1.03–2.19)	0.54/Na	Na ^a	17	8337 (3511/4826)	586	0.2582
21612411	CDH1 (rs16260)	GC	2011	AA vs. AC+CC	Diverse	1.16 (0.83–1.63)	0.606/0.004	Na ^a	14	6421 (3723/2698)	488	0.2732
24870781	CDH1 (rs16260)	GC	2014	AA+AC vs. CC	Diverse	1.11 (0.95–1.30)	No/0.026	48.3	13	6412 (2722/3690)	Na (1510–3021)	0.2356 ^b
25599647	CDH1 (rs16260)	GC	2015	AA vs. CC	Diverse	1.19 (0.89–1.58)	0.323/0.001	55	22	9679 (4218/9679)	672	0.2545
CDH1												
21570316	CDH1 (+54 T>C)	GC	2011	CC vs. CT+TT	Diverse	1.00 (0.75–1.34)	Na/Na	Na ^a	5	2280 (996/1284)	248	0.2667
24870781	CDH1 +54 T>C	GC	2014	CC+CT vs. TT	Diverse	0.57 (0.44–0.75)	No/0.097	57.1	3	1373 (643/730)	Na (434–868)	0.1546 ^b
DNMT3B												
27356727	DNMT3B (rs1569686)	GC	2016	G vs. T	Diverse	0.75 (0.30–1.88)	>0.05/0.00	91	2	1928 (706/1222)	356	0.0953
27789275	DNMT3B (rs1569686)	GC	2016	Dominant	Asian	0.74 (0.61–0.90)	Na/0.000	81	5	3014 (1225/1789)	Na (832–1664)	0.2762 ^b
29332452	DNMT3B (rs1569686)	GC	2017	T vs. G	Asian	1.69 (1.36–2.10)	Na/0.48	0	3	1891 (769/1122)	3342	0.8614
EGF												
20033794	EGF G61A (rs4444903)	GC	2010	A vs. G	Asian	0.80 (0.71–0.92)	0.033/0.389	Na ^a	3	2359 (1019/1340)	1370	0.3104
20207214	EGF 61A>G (rs4444903)	GC	2010	Dominant	Asian	1.40 (1.03–1.90)	0.108/0.86	0	3	2359 (1019/1340)	2159	0.6896
23403233	EGF 61A>G (rs4444903)	GC	2013	G vs. A	Diverse	1.16 (0.96–1.39)	0.476/0.065	58.5	4	3505 (1181/3505)	4401	0.5936
25729328	EGF 61A>G (rs4444903)	GC	2014	Dominant	Diverse	1.256 (1.025–1.539)	0.738/0.468	0	6	4309 (1547/2762)	Na (1701–3402)	0.3948 ^b
				Dominant	Asian	1.473 (1.134–1.914)	0.738/0.928	0	5	3115 (1340/1775)	Na (1230–2460)	0.3948 ^b

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Gene/ PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/ heterogeneity	I ² (%)	No. of studies	Cases/ control	Number of test allele or genotype (calculated value according to MAF)	Maf
				Dominant	Caucasian	0.98 (0.71–1.35)	Na	Na	Na	Na	Na	Na
26072068	EGF 61A>G (rs4444903)	GC	2015	G vs. A	Diverse	1.18 (1.00–1.39)	0.106/0.009	66.61	7	5194 (1992/3202)	6524	0.6071
					Asian	1.23 (1.04–1.46)	0.106/0.028	61.48	6	4048 (2494/2977)	5471	0.6711
					Caucasian	0.91 (0.71–1.15)	Na	Na	Na	Na	Na	Na
ERCC5												
29072052	ERCC5 (rs2296147)	GC	2017	C vs. T	Asian	1.268 (1.049–1.532)	0.355/<0.001	82.83	5	7589 (3699/3890)	3205	0.2121
28416771	ERCC5 (rs2296147)	GC	2017	C vs. T	Asian	0.99 (0.91–1.07)	0.129/0.197	Na ^a	5	7589 (3699/3890)	3205	0.2121
GSTM1												
21167396	GSTM1 (null/active)	GC	2010	null vs. active	Diverse	1.26 (1.14–1.39)	Na ^a / <0.0001	53	49	20976 (7746/13230)	10977	0.2536
					Asian	1.38 (1.22–1.57)	Na	Na	Na	Na	Na	Na
					Caucasian	1.08 (0.93–1.26)	Na	Na	Na	Na	Na	Na
28327825	GSTM1 (null/ present)	GC	2017	null vs. present	Diverse	0.788 (0.725–0.857)	Na ^a / <0.0001	Na ^a	70	28549 (11208/ 17341)	13890	0.2519
hOGG1												
22294108	hOGG1 (Ser326Cys)	GC	2012	Dominant	Diverse	0.91 (0.81–1.03)	0.005/0.24	22	11	6165 (2180/3985)	3435	0.3536
22343785	hOGG1 (Ser326Cys)	GC	2012	Recessive	Diverse	1.31 (1.03–1.67)	0.665/0.160	Na ^a	9	3624 (1180/2444)	363	0.2885
					Asian	1.43 (1.06–1.92)	Na	Na	Na	Na	Na	Na
					Caucasian	1.10 (0.72–1.68)	Na	Na	Na	Na	Na	Na
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs. G	Diverse	1.02 (0.92–1.12)	0.344/0.046	40.6	15	10046 (4024/6022)	12568	0.6283
IL1B												
21653279	IL-1B (rs1143627)	GC	2011	Recessive	Diverse	0.88 (0.80–0.97)	No/0.158	21.9	25	11211 (4392/6819)	Na (0–5296)	0.4724 ^b
26805397	IL-1B (rs1143627)	GC	2016	Dominant	Diverse	1.02 (0.91–1.15)	0.398/0.001	48.3	37	15088 (6108/8980)	Na (7134–14267)	0.4724 ^b
IL-4												
23576103	IL-4 (rs2243250)	GC	2013	T vs. C	Diverse	1.00 (0.84–1.19)	0.884/Na ^a	Na ^a	8	4226 (1813/2413)	3284	0.3174
24072495	IL-4 (rs2243250)	GC	2014	T vs. C	Diverse	0.94 (0.83–1.06)	No/0.49	Na ^a	7	4252 (2454/1798)	3390	0.4780
					Asian	1.07 (0.90–1.27)	Na	Na	Na	Na	Na	Na

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Gene/ PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/ heterogeneity	I ² (%)	No. of studies	Cases/ control	Number of test allele or genotype (calculated value according to MAF)	Maf
					Caucasian	0.83 (0.70–0.98)	No/0.93	0	3	2592 (1700/892)	863	0.1889
27143935	IL-4 (rs2243250)	GC	2016	T vs. C	Diverse	1.05 (0.95–1.17)	0.57/0.51	0	11	5617 (2247/3370)	5245	0.4470
28656227	IL-4 (rs2243250)	GC	2017	T vs. C	Diverse	1.15 (1.01–1.32)	No/0.28	21	7	3887 (1475/2412)	2894	0.3178
IL-8												
19777350	IL-8 (251T/A)	GC	2010	AA vs. TT	Diverse	1.363 (1.199–1.527)	>0.1/<0.001	Na ^a	10	5700 (2195/3505)	909	0.3247
					Asian	1.593 (1.013–2.173)	Na	Na	Na	Na	Na	Na
20363644	IL-8 (251A/T)	GC	2010	TT+TA vs. AA	Diverse	0.88 (0.69–1.12)	0.23/<0.01	Na ^a	12	6905 (3012/3893)	5832	0.6115
21681427	IL-8 (251T/A)	GC	2012	AA+TA vs. TT	Diverse	1.17 (1.01–1.36)	>0.05/<0.0001	65	18	10722 (4274/6498)	6957	0.4025
					Asian	1.27 (1.08–1.48)	>0.05/<0.0001	53	13	6860 (3036/3824)	4190	0.3597
22279522	IL-8 (251A/T)	GC	2012	AA vs. TT	Diverse	1.32 (1.05–1.66)	0.031/0.000	66.7	18	10717 (4163/6554)	1813	0.4049
					Asian	1.52 (1.16–2.00)	0.031/0.001	63.9	13	7033 (3153/3880)	1036	0.3643
26885219	IL-8 (251A/T)	GC	2015	A vs. T	Diverse	1.16 (1.05–1.27)	>0.05/<0.00000 1	66	26	13286 (5286/8000)	10933	0.4038
					Asian	1.23 (1.10–1.37)	>0.05/0.0005	61	17	8585 (3818/4767)	6620	0.3651
IL-10												
20087693	IL-10 (-592C>A)	GC	2011	CC+CA vs. AA	Diverse	1.16 (0.92–1.46)	0.63/Na ^a	Na ^a	12	6521 (2285/4236)	5302	0.6289
					Asian	1.31 (1.08–1.59)	0.63/Na ^a	Na ^a	5	2100 (864/1236)	1303	0.4134
					Caucasian	0.93 (0.56–1.55)	Na	Na	Na	Na	Na	Na
22859944	IL-10 (-592A/C)	GC	2012	Recessive	Diverse	0.88 (0.74–1.05)	0.914/0.020	46	17	8729 (2999/5730)	2108	0.4333
					Asian	0.81 (0.68–0.97)	0.914/0.163	31.8	9	4008 (1526/2482)	1652	0.6364
					Caucasian	1.03 (0.64–1.65)	Na	Na	Na	Na	Na	Na
IL-10												
23311038	IL-10 (1082G>A)	GC	2012	A vs. G	Diverse	0.489 (0.335–0.713)	0.961/0.000	94.9	22	10254 (4289/5965)	15860	0.7609
					Asian	0.651 (0.506–0.838)	Na	Na	Na	Na	Na	Na
					Caucasian	0.365 (0.140–0.949)	Na	Na	Na	Na	Na	Na

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Gene/ PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/ heterogeneity	I ² (%)	No. of studies	Cases/ control	Number of test allele or genotype (calculated value according to MAF)	Maf
22335769	IL-10 (1082A/G)	GC	2012	Dominant	Diverse	1.41 (1.13–1.76)	0.249/0.000	72.9	20	10062 (3631/6431)	4278	0.2862
					Asian	1.81 (1.44–2.27)	Na	Na	Na	Na	Na	Na
					Caucasian	1.01 (0.77–1.33)	Na	Na	Na	Na	Na	Na
IL-17F												
24913709	IL-17F (rs763780)	GC	2014	C vs. T	Asian	1.29 (1.13–1.47)	0.018/0.320	12.3	3	3360 (1500/1860)	1084	0.1371
24965422	IL-17F (rs763780)	GC	2014	C vs. T	Asian	1.29 (1.14–1.46)	0.102/Na	0	4	4122 (1760/2362)	1269	0.1319
25338988	IL-17F (rs763780)	GC	2014	Dominant	Asian	1.30 (1.12–1.50)	Na ^a /0.4	0	4	4122 (1760/2362)	1269	0.1319
25500254	IL-17F (rs763780)	GC	2015	C vs. T	Asian	1.30 (1.15–1.47)	0.860/0.528	0	5	4376 (1784/2592)	Na (818)	0.0935 ^b
26770352	IL-17F (rs763780)	GC	2015	C vs. T	Asian	1.08 (0.81–1.44)	0.83/Na ^a	86.3	8	6693 (2917/3776)	4944	0.337
26843459	IL-17F (rs763780)	GC	2016	C vs. T	Asian	1.37 (1.25–1.51)	No/0.17	31	9	7346 (3244/4102)	2187	0.1273
miR-146a												
21947843	miR-146a (rs2910164)	GC	2012	Dominant	Asian	1.15 (0.88–1.50)	No/0.325	73	3	4077 (1439/2638)	2498	0.3945
24528016	miR-146a (rs2910164)	GC	2014	C vs. G	Asian	0.87 (0.81–0.93)	No/Na ^a	47.6	4	6346 (3003/3343)	6543	0.5316
25326754	miR-146a (rs2910164)	GC	2014	C vs. G	Diverse	1.028 (0.914–1.155)	0.355/0.000	72.5	9	11243 (4507/6736)	10440	0.4463
25983750	miR-146a (rs2910164)	GC	2015	Dominant	Diverse	0.88 (0.80–0.97)	0.481/0.12	36	9	11312 (4468/6844)	8695	0.5595
26337564	miR-146a (rs2910164)	GC	2015	C vs. G	Diverse	0.975 (0.874–1.088)	No/0.001	69	10	11864 (5020/6844)	12902	0.5595
29127520	miR-146a (rs2910164)	GC	2017	C vs. G	Diverse	0.984 (0.903–1.072)	>0.05/0.005	57.3	13	12773 (5831/6942)	14129	0.5632
miR-196a2												
23160898	miR-196a2 (rs11614913)	GC	2013	CC vs. TT	Asian	2.19 (1.23–3.91)	Na/0.07	68.5	2	1709 (782/927)	Na (568–1137)	0.3327
25983750	miR-196a2 (rs11614913)	GC	2015	C vs. T	Diverse	1.25 (0.97–1.60)	present/Na ^a	Na ^a	9	9410 (3992/5418)	9305	0.4862
MMP2												
23644699	MMP2 (rs243865)	GC	2013	Dominant	Diverse	0.68 (0.47–0.99)	0.072/<0.00001	84	8	5154 (1792/3353)	1298	0.1506
24606450	MMP2 (rs243865)	GC	2014	T vs. C	Diverse	1.042 (0.496–2.186)	Na ^a /0.107	40.7	8	5770 (1926/3844)	1468	0.1316
MMP7												
23644699	MMP7 (rs11568818)	GC	2013	Dominant	Diverse	1.49 (1.17–1.91)	0.368/0.6	0	5	1999 (757/1242)	547	0.1369

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Gene/ PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/ heterogeneity	I ² (%)	No. of studies	Cases/ control	Number of test allele or genotype (calculated value according to MAF)	Maf
23893803	MMP7 (rs11568818)	GC	2013	A vs. G	Diverse	0.91 (0.78–1.06)	Na/0.006	76	4	1891 (686/1205)	371	0.1025
24606450	MMP7 (rs11568818)	GC	2014	Recessive	Diverse	1.768 (1.153–2.712)	Na ^a /0.54	0	5	2175 (701/1474)	606	0.1547
23725125	MMP7 (rs11568818)	GC	2013	Recessive	Diverse	1.13 (1.01–1.26)	Na/0.711	Na	6	2893 (1039/1854)	Na (1036–2072)	0.3582 ^b
MMP1												
23893803	MMP1 (rs1799750)	GC	2013	2G vs. 1G	Asian	1.03 (0.94–1.12)	Na/0.118	53.2	3	1412 (644/768)	2070	0.7356
24606450	MMP1 (rs1799750)	GC	2014	2G vs. 1G	Asian	0.927 (0.480–1.791)	Na ^a /0.134	55.5	2	914 (398/516)	533	0.2926
26392779	MMP1 (rs1799750)	GC	2015	2G vs. 1G	Asian	1.05 (1.01–1.06)	0.964/0.101	45.7	6	2920 (1377/1543)	3952	0.664
MMP9												
24606450	MMP9 (-1562C>T)	GC	2014	T vs. C	Diverse	1.615 (0.872–2.991)	Na ^a /0.847	0	4	2116 (636/1480)	693	0.1632
29228747	MMP9 (-1562C>T)	GC	2017	C vs. T	Diverse	1.150 (1.014–1.304)	>0.1/0.231	23.9	9	3555 (1345/2210)	Na (1102)	0.1552 ^b
TGF-β1												
24254308	TGF-β1 (rs1800469)	GC	2014	Recessive	Diverse	1.23 (1.09–1.38)	No/0.13	35.7	10	6522 (2990/3532)	1623	0.4561
26770387	TGF-β1 (rs1800469)	GC	2015	T vs. C	Diverse	0.95 (0.86–1.03)	No/<0.01	82	31	28474 (12940/ 15530)	22729	0.4097
TGF-β1												
24254308	TGF-β1 (rs1800470)	GC	2014	C vs. T	Diverse	1.11 (0.90–1.35)	No/Na ^a	Na ^a	6	4884 (2260/2624)	4676	0.4703
26770387	TGF-β1 (rs1800470)	GC	2015	C vs. T	Diverse	1.38 (1.11–1.73)	No/<0.01	87	11	5703 (2730/2973)	5435	0.4601
TNF-α												
22748850	TNF-α (rs909253)	GC	2012	Dominant	Diverse	1.11 (0.93–1.36)	Na ^a /0.001	Na ^a	16	8189 (2758/5341)	6498	0.5831
23900678	TNF-α (rs361525)	GC	2013	A vs. G	Diverse	1.32 (1.02–1.72)	No/0.002	59.2	15	7795 (Na/Na ^c)	Na (949)	0.0609 ^b

Na: Not available, No: significant publication bias/heterogeneity was not found, Diverse: two or more ethnicities were reported in the meta-analysis.^aThe information is calculated according to the data provided in the article since the article did not present (such as I², OR, publication bias and heterogeneity)^bThe MAF is obtained from dbSNP database

Table S4 The value of power under different model for a variant with different MAF

Gene/PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	No. of studies	The sample size is more than 4000	MAF	Power (%)	The value of power (%) if the MAF is 0.2	The value of power (%) if the MAF is 0.1
ACE1 (insertion/deletion)												
25154002	ACE1 (rs4646994)	GC	2015	DD+DI vs. II	Diverse	1.06 (0.92–1.21)	6	4262 (1311/2951)	0.3746	85.63	85.68	70.67
CCND1 (G870A)												
27623072	CCND1 (rs603965)	GC	2016	A vs. G	Diverse	1.07 (0.88–1.30)	9	3986 (1813/2173)	0.512	99.28	95.01	77.79
CD14 159C/T												
24978812	CD14 (rs2569190)	GC	2014	Dominant	Diverse	0.99 (0.77–1.26)	12	5304 (2968/2336)	0.4991	78.82	85.68	70.67
CD95												
23681795	CD95L (rs763110)	GC	2013	Dominant	Diverse	1.02 (0.83–1.25)	8	4563 (Na/Na)	0.4696 ^a	78.96	85.68	70.67
CYP1A1												
24443269	CYP1A1 (rs1048943)	GC	2014	Dominant	Diverse	0.936 (0.786–1.114)	8	4773 (1754/3019)	0.1577	82.03	85.68	70.67
CYP2E1												
27284439	CYP2E1 (RsaI/PstI)	GC	2016	C2 vs. C1	Diverse	1.02 (0.86–1.19)	26	9237 (3727/5510)	0.1529	90.25	95.01	77.79
ERCC5												
29072052	ERCC5 (rs2094258)	GC	2017	T vs. C	Asian	1.076 (0.926–1.251)	7	7989 (3812/4177)	0.3973	99.16	95.01	77.79
ERCC5												
29072052	ERCC5 (rs1047768)	GC	2017	C vs. T	Asian	0.95 (0.880–1.025)	6	6477 (3064/3413)	0.3415	98.84	95.01	77.79
IL-17A												
26770352	IL-17A (rs3748067)	GC	2015	T vs. C	Asian	1.30 (0.84–2.03)	5	4583 (2160/2423)	0.4144	99.21	95.01	77.79
MIR-27a												

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Gene/PMID	Gene (variant)	Cancertype	Year	Comparison	Ethnicity	OR (95% CI)	No. of studies	The sample size is more than 4000	Maf	Power (%)	The value of power (%) if the MAF is 0.2	The value of power (%) if the MAF is 0.1
29088869	MIR-27a (rs895819)	GC	2017	Dominant	Diverse	0.97 (0.72–1.31)	8	8798 (4016/4782)	0.3638a	86.08	85.68	70.67
MTHFR												
25170232	MTHFR (rs1801131)	GC	2014	C vs. A	Diverse	0.97 (0.83–1.14)	13	5686 (2007/3679)	0.2134	95.82	95.01	77.79
VEGF												
22292637	VEGF (+936C>T)	GC	2011	T vs. C	Diverse	1.08 (0.90–1.27)	9	5101 (2281/2820)	0.1739	92.84	95.01	77.79
XRCC1												
21604176	XRCC1 (rs25487)	GC	2012	Recessive	Diverse	1.04 (0.89–1.21)	16	9279 (3216/6063)	0.3051	46.33	24.4	9.86
CDH1												
25599647	CDH1 (rs16260)	GC	2015	AA vs. CC	Diverse	1.19 (0.89–1.58)	22	9679 (4218/9679)	0.2545	97.45	95.01	77.79
hOGG1												
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs. G	Diverse	1.02 (0.92–1.12)	15	10046 (4024/6022)	0.6283	98.83	95.01	77.79
IL1B												
26805397	IL-1B (rs1143627)	GC	2016	Dominant	Diverse	1.02 (0.91–1.15)	37	15088 (6108/8980)	0.4724a	78.69	85.68	70.67
miR-146a												
29127520	miR-146a (rs2910164)	GC	2017	C vs. G	Diverse	0.984 (0.903–1.072)	13	12773 (5831/6942)	0.5632	99.17	95.01	77.79
miR-146a												
25983750	miR-196a2 (rs11614913)	GC	2015	C vs. T	Diverse	1.25 (0.97–1.60)	9	9410 (3992/5418)	0.4862	99.29	95.01	77.79
TGF-β1												
26770387	TGF-β1 (rs1800469)	GC	2015	T vs. C	Diverse	0.95 (0.86–1.03)	31	28474 (12940/15530)	0.4097	99.20	95.01	77.79

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Gene/PMID	Gene (variant)	Cancertype	Year	Comparison	Ethnicity	OR (95% CI)	No. of studies	The sample size is more than 4000	Maf	Power (%)	The value of power (%) if the MAF is 0.2	The value of power (%) if the MAF is 0.1
CD95												
23681795	CD95 (rs1800682)	GC	2013	Dominant	Diverse	1.00 (0.87–1.15)	8	3970 (Na/Na)	0.4543a	80.09	85.43	70.35
CDH1												
21570316	CDH1 (-616 G>C)	GC	2011	CC vs. CG+GG	Diverse	1.27 (0.86–1.88)	3	1962 (565/1397)	0.2466	19.02	14.36	7.36
COX-2												
23775011	COX-2 (-587 G>A)	GC	2013	A vs. G	Diverse	0.56 (0.19–1.70)	3	3585 (885/2700)	0.0313	32.49	92.7	73.23
CYP1A1												
24443269	CYP1A1 (rs4646903)	GC	2014	Dominant	Diverse	0.950 (0.800–1.128)	10	3460 (923/2537)	0.2237	81.64	80.36	64.38
CYP2E1												
27284439	CYP2E1 (DraI)	GC	2016	C vs. D	Diverse	1.05 (0.91–1.20)	6	2595 (1225/1370)	0.1861	80.81	82.8	59.34
DNMT3B												
29332452	DNMT3B (rs2424913)	GC	2017	T vs. C	Asian	1.25 (0.89–1.76)	5	3040 (1320/1720)	0.9706	24.24	88.18	66.12
DNMT1												
28473984	DNMT1 (rs2228611)	GC	2017	Dominant	Asian	1.02 (0.83–1.26)	3	1469 (652/817)	0.7173	16.94	44.99	32.93
FAS												
22631677	FAS (rs1800682)	GC	2012	G vs. A	Diverse	1.025 (0.913–1.151)	5	2523 (1065/1458)	0.416	93.5	81.7	58.1
IL-6												
22711691	IL-6 (rs1800795)	GC	2011	C vs. G	Diverse	1.09 (0.76–1.53)	9	3598 (1249/2349)	0.3372	97.94	92.79	73.39
CDH1												
21570316	CDH1 (+54 T>C)	GC	2011	CC vs. CT+TT	Diverse	1.00 (0.75–1.34)	5	2280 (996/1284)	0.2667	23.93	15.92	7.75

aThe MAF is obtained from dbSNP database

Table S5 Subgroup analysis by ethnicity from inconsistent results of meta-analyses

PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Cases/control
BIRC5 -31G/C										
24077840	BIRC5 (rs9904341)	GC	2014	CC vs. GG	Asian	2.36 (0.28–20.27)	0.392/<0.001	83.8	2	603 (316/287)
24077840	BIRC5 (rs9904341)	GC	2014	CC vs. GG	European	2.33 (1.22–4.47)	Na/Na	Na	1	568 (88/480)
24077840	BIRC5 (rs9904341)	GC	2014	CC vs. GG	Mixed	1.18 (0.38–3.67)	Na/Na	Na	1	104 (47/57)
CDH1										
25599647	CDH1 (rs16260)	GC	2015	AA vs. CC	Asian	0.92 (0.61–1.38)	0.323/0.008	Na	14	5724 (2697/3027)
25599647	CDH1 (rs16260)	GC	2015	AA vs. CC	Caucasian	1.25 (0.97–1.61)	0.323/0.106	Na	8	3729 (1424/2305)
CDH1										
21570316	CDH1 (+54 T>C)	GC	2011	CC vs. CT+TT	Asian	0.78 (0.52–1.16)	Na/Na	Na	3	2219 (220/226)
21570316	CDH1 (+54 T>C)	GC	2011	CC vs. CT+TT	Caucasian	1.35 (0.87–2.08)	Na/Na	Na	2	446 (220/226)
EGF										
26072068	EGF 61A>G (rs4444903)	GC	2015	G vs. A	Asian	1.23 (1.04–1.46)	0.106/0.028	61.48	6	3976 (1758/2218)
26072068	EGF 61A>G (rs4444903)	GC	2015	G vs. A	Caucasian	0.91 (0.71–1.15)	Na	Na	1	1155 (207/948)
GSTM1										
28327825	GSTM1 (null/present)	GC	2017	null vs. present	Asian	0.736 (0.670–0.809)	Na/<0.0001	Na	50	Na
28327825	GSTM1 (null/present)	GC	2017	null vs. present	America	0.866 (0.549–1.364)	Na/<0.0292	Na	5	Na
28327825	GSTM1 (null/present)	GC	2017	null vs. present	Eurasia	0.671 (0.456–0.988)	Na/<0.6637	Na	3	Na
28327825	GSTM1 (null/present)	GC	2017	null vs. present	Europe	1.033 (0.873–1.222)	Na/<0.0189	Na	12	Na
hOGG1										
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs. G	Asian	0.98 (0.88–1.09)	No/0.121	38.8	8	6472 (2792/3680)
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs. G	Caucasian	1.08 (0.79–1.48)	No/0.052	61.2	4	2467 (820/1647)
28415729	hOGG1 (Ser326Cys)	GC	2017	C vs. G	Others	1.07 (0.84–1.37)	No/0.265	24.3	4	1107 (412/695)
IL1B										
26805397	IL-1B (rs1143627)	GC	2016	Dominant	Asian	0.99 (0.85–1.15)	0.398/0.005	51.2	20	8518 (3694/4824)
26805397	IL-1B (rs1143627)	GC	2016	Dominant	Caucasian	1.08 (0.90–1.30)	0.398/0.036	41.8	17	6570 (2414/4156)
IL-4										
28656227	IL-4 (rs2243250)	GC	2017	C vs. T	Asian	1.07 (0.88–1.31)	0.837/0.089	58.6	3	1607 (669/938)

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PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Cases/control
28656227	IL-4 (rs2243250)	GC	2017	C vs. T	Caucasian	0.98 (0.82–1.17)	0.837/0.0707	61.1	3	2358 (686/1622)
28656227	IL-4 (rs2243250)	GC	2017	C vs. T	Mixed	0.71 (0.47–1.06)	0.837/Na	Na	1	331 (122/209)
IL-8										
26885219	IL-8 (251A/T)	GC	2015	A vs. T	Asian	1.23 (1.10–1.37)	>0.05/0.0005	61	17	8585 (3818/4767)
26885219	IL-8 (251A/T)	GC	2015	A vs. T	European	1.01 (0.87–1.17)	>0.05/0.03	54	9	4701 (1468/2233)
IL-10										
22859944	IL-10 (-592A/C)	GC	2012	Recessive	Asian	0.81 (0.68–0.97)	0.914/0.163	31.8	9	4008 (1526/2482)
22859944	IL-10 (-592A/C)	GC	2012	Recessive	Caucasian	1.03 (0.64–1.65)	0.914/0.029	59.8	6	3872 (1240/2632)
					Latinos	1.10 (0.53–2.26)	0.914/0.107	61.5	2	849 (233/616)
IL-10										
23311038	IL-10 (1082G>A)	GC	2012	A vs. G	Asian	0.651 (0.506–0.838)	Na	Na	Na	Na
23311038	IL-10 (1082G>A)	GC	2012	A vs. G	Caucasian	0.365 (0.140–0.949)	Na	Na	Na	Na
miR-146a										
29127520	miR-146a (rs2910164)	GC	2017	C vs. G	Asian	0.94 (0.81–1.09)	0.719/<0.0001	85.4	9	10146 (5056/5090)
29127520	miR-146a (rs2910164)	GC	2017	C vs. G	Caucasian	0.85 (0.72–1.01)	0.719/0.864	0	4	2627 (775/1852)
miR-196a2										
25983750	miR-196a2 (rs11614913)	GC	2015	C vs. T	Asian	1.08 (0.91–1.28)	0.015/<0.0001	83.6	7	8054 (3466/4588)
25983750	miR-196a2 (rs11614913)	GC	2015	C vs. T	Caucasian	2.15 (0.43–10.66)	0.015/<0.0001	98.7	2	1356 (526/830)
MMP2										
23644699	MMP2 (rs243865)	GC	2013	Dominant	Asian	0.62 (0.40–0.97)	0.124/<0.0001	87.8	6	4713 (1578/3126)
23644699	MMP2 (rs243865)	GC	2013	Dominant	European	0.92 (0.61–1.40)	0.124/0.802	0	2	441 (214/227)
MMP7										
24606450	MMP7 (rs11568818)	GC	2014	Recessive	Asian	2.13 (1.30–3.50)	Na/0.807	0	4	1764 (632/1132)
24606450	MMP7 (rs11568818)	GC	2014	Recessive	European	1.00 (0.42–2.44)	Na/0.000	0	1	248 (79/169)
MMP9										
29228747	MMP9 (-1562C>T)	GC	2017	C vs. T	Asian	1.170 (1.003–1.364)	0.706/0.234	24.5	8	3307 (1266/2041)
29228747	MMP9 (-1562C>T)	GC	2017	C vs. T	European	0.84 (0.49–1.45)	0.706/Na	Na	1	248 (79/169)

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PMID	Gene (variant)	Cancer type	Year	Comparison	Ethnicity	OR (95% CI)	Publication bias/heterogeneity	I ² (%)	No. of studies	Cases/control
TGF-β1										
26770387	TGF-β1 (rs1800470)	GC	2015	C vs. T	Asian	1.18 (0.90–1.54)	No/0.23	89	6	4245 (2060/2185)
26770387	TGF-β1 (rs1800470)	GC	2015	C vs. T	Caucasian	1.70 (1.46–1.98)	No/<0.01	16	5	1458 (670/788)
TNF-α										
23900678	TNF-α (rs361525)	GC	2013	A vs. G	Asian	1.59 (1.29–1.97)	No/<0.001	45.1	10	3825 (Na/Na)
23900678	TNF-α (rs361525)	GC	2013	A vs. G	Caucasian	0.93 (0.74–1.15)	No/0.488	39.9	5	3970 (Na/Na)

Na: Not available, No: significant publication bias/heterogeneity was not found, Diverse: two or more ethnicities were reported in the meta-analysis.^aThe information is calculated according to the data provided in the article since the article did not present (such as I², OR, publication bias and heterogeneity)