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ORIGINAL ARTICLE

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

Jie Tian*, Guanchu Liu*, Chunjian Zuo, Caiyang Liu, Wanlun He, Huanwen Chen

Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

**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 worldwide[1]. Although advances in diagnoses and treatment may reduce mortality and morbidity, the 5-year survival rate remains poor[2]. In 2016, 26,370 patients had GC, and 10,730 patients died from GC in the United States[3]. 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 disorder[4]. 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 diseases[5], and extend our understanding of associations between genetic variations and cancer risk[6]. 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

*These authors contributed equally to this work.
Correspondence to: Huanwen Chen
E-mail: cyfyyxxwkchw@126.com
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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 assessed[16].

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 $5 \times 10^{-8}$. 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-analyses[25]. 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 ($0.2 \leq$ 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 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.

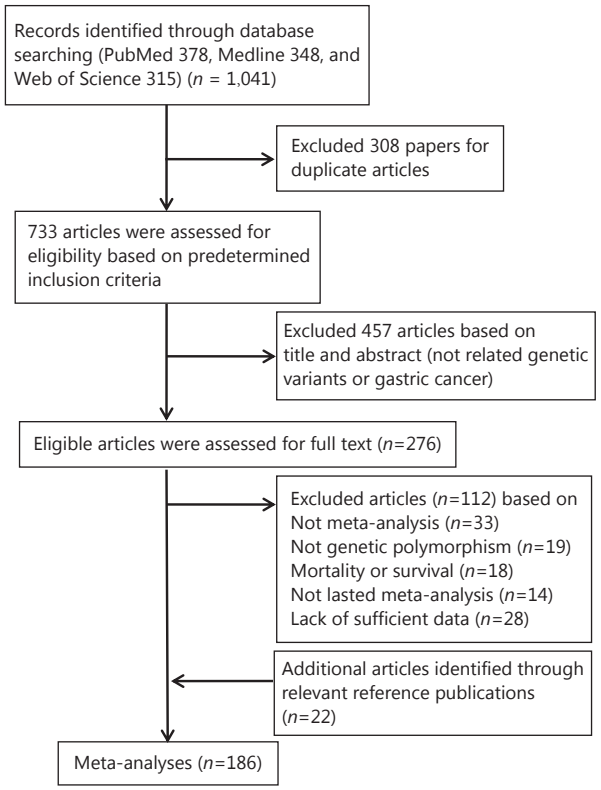


**Figure 1** Flow diagram of search strategy and study selection

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 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 |
| | | | Asian | 1.41 (1.09–1.83) | Na | Na | Na | Na | Na | Na | | | | | |
| 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 (1588) | 0.3756[d] | XCA | 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 (0–840) | 0.1841[d] | XAA | Na | | | Na |
| | | | Asian | 1.27 (1.05–1.52) | Na | Na | 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 (rs16999593) | 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 (342–684) | 0.1142[d] | XCX | 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 |
| | | | Asian | 1.23 (1.04–1.46) | 0.106/0.028 | 61.48 | 6 | 4048 (2494/2977) | 5471 | 0.6711 | ACA | Weak | 0.988 | 0.948 | Weak |
| | | | Caucasian | 0.91 (0.71–1.15) | Na | Na | Na | Na | Na | Na | | | | | |
| ERCC2 (rs1052559) | GC (2012)[30] | Recessive | Asian | 2.41 (1.69–3.43) | 0.989/0.701 | 0 | 5 | 3246 (1267/1979) | 143 | 0.1266 | BAA | Moderate | 0.002 | 0.055 | Moderate |
| ERCC2 (rs1799793) | GC (2012)[30] | Recessive | Diverse | 1.48 (1.12–1.97) | 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 | FPRP 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 | | | | | |
| 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 (rs22347677) | 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 | | | | | |

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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] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Caucasian | 1.15 (0.87–1.52) | Na | Na | Na | Na | Na | Na | | | | | |
| IL-4 (rs2243250) | GC (2017)[40] | T *vs* C | 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-8 (251A/T) | GC (2015)[41] | A *vs* T | 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 |
| | | | 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 |
| IL-17A (rs2275913) | GC (2018)[42] | 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 |
| | | A *vs* G | Asian | 1.25 (1.15–1.37) | Na | Na | Na | Na | Na | Na | | | | | |
| | | Recessive | Caucasian | 2.19 (1.40–3.44) | Na | Na | Na | Na | Na | Na | | | | | |
| IL-17F (rs763780) | GC (2016)[43] | 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 |
| MMP1 (rs1799750) | GC (2015)[44] | 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 |
| MDM2 (rs2278744) | GC (2014)[45] | 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 |
| MMP7 (rs11568818) | GC (2014)[46] | 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 |
| MMP9 (-1562C>T) | GC (2017)[47] | 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 | |
| MiR-608 (rs4919510) | GC (2017)[48] | 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 | |
| MTHFR (rs1801133) | GC (2016)[49] | 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 |
| NAD (p)H (rs1800566) | GC (2014)[50] | 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 |
| P53 (rs1042522) | GC (2012)[51] | 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 | FPRP 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 | | | | | |
| 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 | |
| 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 |
| BRCA1 (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 | |

Continued

Continued

| 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] | 0c | 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 | |
| GSTM1 (null/present) | GC (2017)[66] | null *vs* present | Diverse | 0.788 (0.725–0.857) | 0.000[c]/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 |
| | | | Asian | 0.651 (0.506–0.838) | Na | Na | Na | Na | Na | Na | | | | | |
| 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) | No/<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: 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 creteria and FPRP. [c] The information is calculated according to the data provided in the article since the article did not present (such as $I^2$, 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 *APE1* (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 | LOC 105379076 | 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* Ser326Cys[85], *IL-1B* rs1143627[86], *miR-146a* rs2910164[90], and *TGF-β1* rs1800469[58]. 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 carcinogenesis[94-96]. 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 activity[97]. 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 carcinoma[98]. 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 process[101]. A polymorphism (rs751402) is found in the promoter region of *ERCC5* and controls its expression and function during transcription in healthy human cells[102]. 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 death[105]. 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 1[105], 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 as 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.


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# Conflicts of interest statement

No potential conflicts of interest are disclosed.

# References


1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65: 87-108.
2. Xu LM, Wu W, Cheng GL, Qian MJ, Hu KW, Yin GJ, et al. Enhancement of proliferation and invasion of gastric cancer cell by KDM5C *via* decrease in p53 expression. Technol Cancer Res Treat. 2017; 16: 141-9.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66: 7-30.
4. Woo HD, Lee J, Choi IJ, Kim CG, Lee JY, Kwon O, et al. Dietary flavonoids and gastric cancer risk in a Korean population. Nutrients. 2014; 6: 4961-73.
5. Chang J, Wei LX, Miao XP, Yu DK, Tan W, Zhang XM, et al. Two novel variants on 13q22.1 are associated with risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2015; 24: 1774-80.
6. Chung CC, Chanock SJ. Current status of genome-wide association studies in cancer. Hum Genet. 2011; 130: 59-78.
7. Hardy J, Singleton A. Genomewide association studies and human disease. New Engl J Med. 2009; 360: 1759-68.
8. Bush WS, Moore JH. Genome-wide association studies. PLoS Comput Biol. 2012; 8: e1002822.
9. Glass GV. Primary, secondary, and meta-analysis of research. Educ Res. 1976; 5: 3-8.
10. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet. 1998; 351: 123-7.
11. Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. JAMA. 2008; 299: 2423-36.
12. Abnet CC, Freedman ND, Hu N, Wang ZM, Yu K, Shu XO, et al. A shared susceptibility locus in *PLCE1* at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nat Genet. 2010; 42: 764-7.
13. Jin GF, Ma HX, Wu C, Dai JC, Zhang RY, Shi YY, et al. Genetic variants at 6p21.1 and 7p15.3 are associated with risk of multiple cancers in Han Chinese. Am J Hum Genet. 2012; 91: 928-34.
14. Hu N, Wang ZM, Song X, Wei LX, Kim BS, Freedman ND, et al.

Genome-wide association study of gastric adenocarcinoma in Asia: a comparison of associations between cardia and non-cardia tumours. Gut. 2016; 65: 1611-8.

15. Wang ZM, Dai JC, Hu N, Miao XP, Abnet CC, Yang M, et al. Identification of new susceptibility loci for gastric non-cardia adenocarcinoma: pooled results from two Chinese genome-wide association studies. Gut. 2017; 66: 581-7.
16. Ioannidis JPA, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001; 29: 306-9.
17. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954; 10: 101-29.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629-34.
19. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst. 2004; 96: 434-42.
20. Jiang Y, Zhang J, Wu Y, Wang J, Li L. Association between ALDH2 rs671 G>A polymorphism and gastric cancer susceptibility in Eastern Asia. Oncotarget. 2017; 8: 102401-12.
21. Dai ZJ, Shao YP, Kang HF, Tang W, Xu D, Zhao Y, et al. Relationship between apurinic endonuclease 1 Asp148Glu polymorphism and gastrointestinal cancer risk: an updated meta-analysis. World J Gastroenterol. 2015; 21: 5081-9.
22. Hu D, Lin XD, Zhang HJ, Zheng XW, Niu WQ. APEX nuclease (multifunctional DNA repair enzyme) 1 gene Asp148Glu polymorphism and cancer risk: a meta-analysis involving 58 articles and 48903 participants. PLoS One. 2013; 8: e83527.
23. Liu Y, Li L, Qi HY, Gao Y, Liu S, Xu CA. Survivin -31G>C polymorphism and gastrointestinal tract cancer risk: a meta-analysis. PLoS One. 2013; 8: e54081.
24. Li F, Liu YL, Fu T, Tong WD, Zhang AP. Associations of three common polymorphisms in CD95 and CD95L promoter regions with gastric cancer risk. Tumor Biol. 2013; 34: 2293-8.
25. Yan WF, Sun PC, Nie CF, Wu G. Cyclooxygenase-2 polymorphisms were associated with the risk of gastric cancer: evidence from a meta-analysis based on case-control studies. Tumor Biol. 2013; 34: 3323-30.
26. Zhang XW, Li J, Jiang YX, Chen YX. Association between COX-2 -1195G>A polymorphism and gastrointestinal cancer risk: a meta-analysis. World J Gastroenterol. 2017; 23: 2234-45.
27. Li H, Liu JW, Sun LP, Yuan Y. A meta-analysis of the association between *DNMT1* Polymorphisms and cancer risk. Biomed Res Int. 2017; 2017: 3971259.
28. Li HJ, Li W, Liu SS, Zong SQ, Wang WB, Ren JL, et al. *DNMT1*, *DNMT3A* and *DNMT3B* polymorphisms associated with gastric cancer risk: a systematic review and meta-analysis. EBioMedicine. 2016; 13: 125-31.
29. Wu SJ, Jiang SY, Wu J, Xiong GL. Association between EGF +61 A>G polymorphism and gastric cancer risk: a meta-analysis. J Huazhong Univ Sci Technol Med Sci. 2015; 35: 327-32.
30. Xue HP, Lu Y, Lin B, Chen JX, Tang F, Huang G. The effect of XPD/ERCC2 polymorphisms on gastric cancer risk among different ethnicities: a systematic review and meta-analysis. PLoS One. 2012; 7: e43431.
31. Zhou HX, Shi TY, Zhang WW, Li QW, Zhu JH, He J, et al. *XPG* gene rs751402 C>T polymorphism and cancer risk: evidence from 22 publications. Oncotarget. 2017; 8: 53613-22.
32. Namazi A, Forat-Yazdi M, Jafari MA, Foroughi E, Farahnak S, Nasiri R, et al. Association between polymorphisms of ERCC5 gene and susceptibility to gastric cancer: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2017; 18: 2611-7.
33. Tian J, Pan F, Li J, Ma Y, Cen H, Pan HF, et al. Association between the FAS/FASL polymorphisms and gastric cancer risk: a meta-analysis. Asian Pac J Cancer Prev. 2012; 13: 945-51.
34. Bao LD, Niu JX, Song H, Wang Y, Ma RL, Ren XH, et al. Association between the GSTP1 codon 105 polymorphism and gastric cancer risk: an updated meta-analysis. Asian Pac J Cancer Prev. 2012; 13: 3687-93.
35. Meng YB, Cai XY, Lu WQ, Yang LH, Gan TQ, Drummen GPC. Meta-analysis of the association of glutathione *S*-transferase T1 null/presence gene polymorphism with the risk of gastric carcinoma. Mol Biol Rep. 2014; 41: 639-49.
36. Li S, Zheng Y, Tian T, Wang M, Liu XH, Liu K, et al. Pooling-analysis on hMLH1 polymorphisms and cancer risk: evidence based on 31,484 cancer cases and 45,494 cancer-free controls. Oncotarget. 2017; 8: 93063-78.
37. Zhang J, Liu X, You LH, Zhou RZ. Significant association between long non-coding RNA HOTAIR polymorphisms and cancer susceptibility: a meta-analysis. Onco Targets Ther. 2016; 9: 3335-43.
38. Ge YT, Jiang RZ, Zhang M, Wang H, Zhang L, Tang J, et al. Analyzing 37,900 samples shows significant association between HOTAIR polymorphisms and cancer susceptibility: a meta-analysis. Int J Biol Markers. 2017; 32: 231-42.
39. Park MJ, Hyun MH, Yang JP, Yoon JM, Park S. Effects of the interleukin-1β-511 C/T gene polymorphism on the risk of gastric cancer in the context of the relationship between race and *H. pylori* infection: a meta-analysis of 20,000 subjects. Mol Biol Rep. 2015; 42: 119-34.
40. Jia YX, Xie XC, Shi XH, Li SW. Associations of common IL-4 gene polymorphisms with cancer risk: a meta-analysis. Mol Med Rep. 2017; 16: 1927-45.
41. Zhang YF, Zeng XL, Lu HW, Li YM, Ji H. Association between Interleukin-8-251A/T polymorphism and gastric cancer susceptibility: a meta-analysis based on 5286 cases and 8000 controls. Int J Clin Exp Med. 2015; 8: 22393-402.
42. Hu LX, Kong FL, Pan YY. Association between IL-17A G197A polymorphism and gastric cancer risk: an updated meta-analysis based on 6,624 cases and 7,631 controls. Onco Targets Ther.

2018; 11: 703-10.

43. Dai ZM, Zhang TS, Lin S, Zhang WG, Liu J, Cao XM, et al. Role of IL-17A rs2275913 and IL-17F rs763780 polymorphisms in risk of cancer development: an updated meta-analysis. Sci Rep. 2016; 6: 20439.
44. Peng QS, Xu Y. Association between promoter polymorphisms of matrix metalloproteinase-1 and risk of gastric cancer. Onco Targets Ther. 2015; 8: 2519-26.
45. Chen WF, Wu QL, Ren HB. Meta-analysis of associations between MDM2 SNP309 polymorphism and gastric cancer risk. Biomed Rep. 2014; 2: 105-11.
46. Yang TF, Guo L, Wang Q. Meta-analysis of associations between four polymorphisms in the matrix metalloproteinases gene and gastric cancer risk. Asian Pac J Cancer Prev. 2014; 15: 1263-7.
47. Peng ZH, Jia JH, Gong WJ, Gao XH, Ma PR, Jin ZC, et al. The association of matrix metalloproteinase-9 promoter polymorphisms with gastric cancer risk: a meta-analysis. Oncotarget. 2017; 8: 99024-32.
48. Wu SS, Yuan WY, Shen Y, Lu X, Li Y, Tian T, et al. The miR-608 rs4919510 polymorphism may modify cancer susceptibility based on type. Tumour Biol. 2017;.
49. Xu W, Cheng YL, Zhu HR. Evaluation of an association of blood homocysteine levels with gastric cancer risk from 27 case-control studies. Medicine (Baltimore). 2016; 95: e3700.
50. Hu WG, Hu JJ, Cai W, Zheng MH, Zang L, Wang ZT, et al. The NAD(P)H: quinine oxidoreductase 1 (NQO1) gene 609 C>T polymorphism is associated with gastric cancer risk: evidence from a case-control study and a meta-analysis. Asian Pac J Cancer Prev. 2014; 15: 2363-7.
51. Tang WR, Zhou XH, Nie SJ, Yang Z, Zhu H, Wu XM, et al. Association of p53 Arg72Pro polymorphism with gastric cancer: a meta-analysis. Biomarkers. 2012; 17: 597-603.
52. Hu Y, Zhou M, Li K, Zhang K, Kong XQ, Zheng YM, et al. Two DNA repair gene polymorphisms on the risk of gastrointestinal cancers: a meta-analysis. Tumor Biol. 2014; 35: 1715-25.
53. Liu XY, Zhang XW, Wang ZC, Chang JJ, Wu Z, Zhang Z, et al. Genetic polymorphism of the phospholipase C epsilon 1 gene and risk of gastric cancer. Chin Med J (Engl). 2014; 127: 2511-7.
54. Wang YF, Chen Y, Jiang HP, Tang WF, Kang MQ, Liu TY, et al. *Peroxisome proliferator-activated receptor gamma* (*PPARG*) rs1801282 C>G polymorphism is associated with cancer susceptibility in Asians: an updated meta-analysis. Int J Clin Exp Med. 2015; 8: 12661-73.
55. Cai J, Ye Q, Luo S, Zhuang Z, He K, Zhuo ZJ, et al. *CASP8* -652 6N insertion/deletion polymorphism and overall cancer risk: evidence from 49 studies. Oncotarget. 2017; 8: 56780-90.
56. Wang M, Wang XJ, Ma YF, Ma XB, Dai ZM, Lv Y, et al. *PSCA* rs2294008 C>T polymorphism contributes to gastric and bladder cancer risk. Ther Clin Risk Manage. 2015; 11: 237-45.
57. Qin ZQ, Tang JY, Li X, Yu YJ, Zhang CJ, Han P, et al. Association between PSCA gene polymorphisms and the risk of cancer: an updated meta-analysis and trial sequential analysis. Oncotarget. 2017; 8: 51766-78.
58. Gu YY, Wang H, Wang S. TGF-β1 C-509T and T869C polymorphisms and cancer risk: a meta analysis. Int J Clin Exp Med. 2015; 8: 17932-40.
59. Zhou Q, Wang CC, Wang XF, Wu XY, Zhu ZG, Liu BY, et al. Association between TLR4 (+896A/G and +1196C/T) polymorphisms and gastric cancer risk: an updated meta-analysis. PLoS One. 2014; 9: e109605.
60. Yang JP, Hyun MH, Yoon JM, Park MJ, Kim D, Park S. Association between TNF-α-308 G/A gene polymorphism and gastric cancer risk: a systematic review and meta-analysis. Cytokine. 2014; 70: 104-14.
61. Wang P, Wang JE, Yu MX, Li ZQ. Tumor necrosis factor-α T-857C (rs1799724) polymorphism and risk of cancers: a meta-analysis. Dis Markers. 2016; 2016: 4580323.
62. Yu JY, Li L, Ma H, Liu K, Cheng XR, Li YL, et al. Tumor necrosis factor-α 238 G/A polymorphism and gastric cancer risk: a meta-analysis. Tumor Biol. 2013; 34: 3859-63.
63. Chen B, Zhou Y, Yang P, Wu XT. Polymorphisms of *XRCC1* and gastric cancer susceptibility: a meta-analysis. Mol Biol Rep. 2012; 39: 1305-13.
64. Xu GP, Zhao Q, Wang D, Xie WY, Zhang LJ, Zhou H, et al. The association between BRCA1 gene polymorphism and cancer risk: a meta-analysis. Oncotarget. 2018; 9: 8681-94.
65. Cai JR, Ye QJ, Luo SL, Zhuang Z, He K, Zhuo ZJ, et al. *CASP8* -652 6N insertion/deletion polymorphism and overall cancer risk: evidence from 49 studies. Oncotarget. 2017; 8: 56780-90.
66. Ribeiro RX, Nascimento CILL, Silva AMTC. Genotype association *GSTM1* null and gastric cancer: evidence-based meta-analysis. Arq Gastroenterol. 2017; 54: 101-8.
67. Yu ZB, Liu Q, Huang C, Wu MH, Li GY. The interleukin 10 -819C/T polymorphism and cancer risk: a HuGE review and meta-analysis of 73 studies including 15,942 cases and 22,336 controls. OMICS. 2013; 17: 200-14.
68. Xue HP, Wang YC, Lin B, An JF, Chen L, Chen JX, et al. A meta-analysis of interleukin-10 -592 promoter polymorphism associated with gastric cancer risk. PLoS One. 2012; 7: e39868.
69. Pan F, Tian J, Pan YY, Zhang Y. Association of IL-10-1082 promoter polymorphism with susceptibility to gastric cancer: evidence from 22 case-control studies. Mol Biol Rep. 2012; 39: 7143-54.
70. Li H, Diao SL, Li JS, Ma BX, Yuan SH. An updated meta-analysis of 23 case-control studies on the association between miR-34b/c polymorphism and cancer risk. Oncotarget. 2017; 8: 28888-96.
71. Li XY, Qu LX, Zhong Y, Zhao YJ, Chen HY, Daru L. Association between promoters polymorphisms of matrix metalloproteinases and risk of digestive cancers: a meta-analysis. J Cancer Res Clin Oncol. 2013; 139: 1433-47.
72. Ye Y, Yang C, Xu L, Fang DL. MUC1 rs4072037 polymorphism is associated with decreased risk of gastric cancer: a meta-analysis.

Int J Biol Markers. 2017; 32: 284-90.

73. Yang Y, Xiong YQ, Li J, Wu CP, Jiang JT. Association of TIMP-2-418G/C and TIMP-2-303G/A with gastric cancer: a meta-analysis. Onco Targets Ther. 2016; 9: 6801-8.
74. Cheng SD, Wang LY, Wang L, Wang ZT. Association of XRCC3 gene rs861539 polymorphism with gastric cancer risk: evidence from a case-control study and a meta-analysis. Int J Clin Exp Pathol. 2015; 8: 1911-9.
75. Shi JZ, Li WZ, Ding XP. Assessment of the association between ZBTB20 rs9841504 polymorphism and gastric and esophageal cancer susceptibility: a meta-analysis. Int J Biol Markers. 2017; 32: 96-101.
76. Shi YY, Hu ZB, Wu C, Dai JC, Li HZ, Dong J, et al. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet. 2011; 43: 1215-8.
77. Wei MT, Chen N, He YZ, Wang JR, Yang Y, Guo XJ, et al. Angiotensin-converting enzyme insertion/deletion polymorphism and gastric cancer: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2015; 39: 136-44.
78. Zhang YF, Zeng XL, Lu HW, Ji H, Zhao EF, Li YM. Association between cyclin D1 (CCND1) G870A polymorphism and gastric cancer risk: a meta-analysis. Oncotarget. 2016; 7: 66109-18.
79. Wang J, Guo XF, Yu SJ, Song J, Zhang JX, Cao Z, et al. Association between *CD14* gene polymorphisms and cancer risk: a meta-analysis. PLoS One. 2014; 9: e100122.
80. Chen B, Zhou Y, Yang P, Liu L, Qin XP, Wu XT. *CDH1* -160C>A gene polymorphism is an ethnicity-dependent risk factor for gastric cancer. Cytokine. 2011; 55: 266-73.
81. Jiang BC, Zhu K, Shao H, Bao CH, Ou JL, Sun W. Lack of association between the *CDH1* polymorphism and gastric cancer susceptibility: a meta-analysis. Sci Rep. 2015; 5: 7891.
82. Xue HP, Lu Y, Xue ZY, Lin B, Chen JX, Tang F, et al. The effect of CYP1A1 and CYP1A2 polymorphisms on gastric cancer risk among different ethnicities: a systematic review and meta-analysis. Tumor Biol. 2014; 35: 4741-56.
83. Zhang MX, Liu K, Wang FG, Wen XW, Song XL. Association between CYP2E1 polymorphisms and risk of gastric cancer: an updated meta-analysis of 32 case-control studies. Mol Clin Oncol. 2016; 4: 1031-8.
84. Chen BF, Wang JD, Gu XL, Zhang JL, Zhang JK, Feng XH. The *DNMT3B* -579G>T polymorphism is significantly associated with the risk of gastric cancer but not lung cancer in Chinese population. Technol Cancer Res Treat. 2017; 16: 1259-65. (in Chinese)
85. Zhang DD, Guo XX, Hu JL, Zeng GQ, Huang MM, Qi DD, et al. Association between hOGG1 polymorphism rs1052133 and gastric cancer. Oncotarget. 2017; 8: 34321-29.
86. Ying HY, Yu BW, Yang Z, Yang SS, Bo LH, Shan XY, et al. *Interleukin*-1B 31 C>T polymorphism combined with *Helicobacter pylori*-modified gastric cancer susceptibility: evidence from 37 studies. J Cell Mol Med. 2016; 20: 526-36.
87. Yin YW, Sun QQ, Hu AM, Wang Q, Liu HL, Hou ZZ, et al. Associations between interleukin-6 gene -174?C/G and -572?C/G polymorphisms and the risk of gastric cancer: a meta-analysis J Surg Oncol. 2012; 106: 987-93.
88. Li XF, Shen M, Cai JW, Zeng YQ, Li M, Yang GL, et al. Association of interleukin-17 gene polymorphisms and *Helicobacter pylori* infection with gastric cancer susceptibility: a cumulative and comprehensive meta-analysis. Int J Clin Exp Med. 2015; 8: 17623-33.
89. Chen MX, Fang WP, Wu XK, Bian SC, Chen GD, Lu LQ, et al. Distinct effects of rs895819 on risk of different cancers: an update meta-analysis. Oncotarget. 2017; 8: 75336-49.
90. Hao X, Xia LZ, Qu RY, Yang XL, Jiang M, Zhou BS. Association between miR-146a rs2910164 polymorphism and specific cancer susceptibility: an updated meta-analysis. Fam Cancer. 2018; 17: 459-68.
91. Ni Q, Ji AL, Yin JF, Wang XJ, Liu XN. Effects of two common polymorphisms rs2910164 in miR-146a and rs11614913 in miR-196a2 on gastric cancer susceptibility. Gastroenterol Res Pract. 2015; 2015: 764163.
92. Xia LZ, Liu Y, Xu XZ, Jiang PC, Ma G, Bu XF, et al. Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and gastric cancer susceptibility. World J Gastroenterol. 2014; 20: 11429-38.
93. Liu H, Wang SC, Huang C. *VEGFA*+936C/T and -634G/C polymorphisms and gastric cancer risk: a meta-analysis. Asian Pac J Cancer Prev. 2011; 12: 1979-83.
94. Li MX, Wilson III DM. Human apurinic/apyrimidinic endonuclease 1. Antioxid Redox Signal. 2014; 20: 678-707.
95. Tell G, Damante G, Caldwell D, Kelley MR. The intracellular localization of APE1/Ref-1: more than a passive phenomenon? Antioxid Redox Signal. 2005; 7: 367-84.
96. Tell G, Fantini D, Quadrifoglio F. Understanding different functions of mammalian AP endonuclease (APE1) as a promising tool for cancer treatment. Cell Mol Life Sci. 2010; 67: 3589-608.
97. Dai ZJ, Wang XJ, Kang AJ, Ma XB, Min WL, Lin S, et al. Association between APE1 single nucleotide polymorphism (rs1760944) and cancer risk: a meta-analysis based on 6,419 cancer cases and 6,781 case-free controls. J Cancer. 2014; 5: 253-9.
98. Turek-Plewa J, Jagodziński PP. The role of mammalian DNA methyltransferases in the regulation of gene expression. Cell Mol Biol Lett. 2005; 10: 631-47.
99. Zhang BG, Hu L, Zang MD, Wang HX, Zhao W, Li JF, et al. *Helicobacter pylori* CagA induces tumor suppressor gene hypermethylation by upregulating DNMT1 *via* AKT-NFκB pathway in gastric cancer development. Oncotarget. 2016; 7: 9788-800.
100. Zhang Q, Wang HY, Woetmann A, Raghunath PN, Odum N, Wasik MA. STAT3 induces transcription of the DNA methyltransferase 1 gene (*DNMT1*) in malignant T lymphocytes.

Blood. 2006; 108: 1058-64.

101. Clarkson SG. The XPG story. Biochimie. 2003; 85: 1113-21.

102. Blomquist TM, Crawford EL, Willey JC. *Cis*-acting genetic variation at an E2F1/YY1 response site and putative p53 site is associated with altered allele-specific expression of ERCC5 (XPG) transcript in normal human bronchial epithelium. Carcinogenesis. 2010; 31: 1242-50.

103. Grenet J, Teitz T, Wei T, Valentine V, Kidd VJ. Structure and chromosome localization of the human *CASP8* gene. Gene. 1999; 226: 225-32.

104. Ho PK, Hawkins CJ. Mammalian initiator apoptotic caspases. FEBS J. 2005; 272: 5436-53.

105. Sun T, Gao Y, Tan W, Ma SF, Shi YK, Yao JR, et al. A six-nucleotide insertion-deletion polymorphism in the CASP8 promoter is associated with susceptibility to multiple cancers. Nat Genet. 2007; 39: 605-13.

106. Hayes JD, Strange RC. Glutathione S-transferase polymorphisms and their biological consequences. Pharmacology. 2000; 61: 154-66.

107. Strange RC, Spiteri MA, Ramachandran S, Fryer AA. Glutathione-S-transferase family of enzymes. Mutat Res. 2001; 482: 21-6.

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# 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.[a]The 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/<0.000001 | 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） | 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.[a]The information is calculated according to the data provided in the article since the article did not present (such as $I^2$, OR, publication bias and heterogeneity)[b]The 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 |

[a]The 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.[a]The information is calculated according to the data provided in the article since the article did not present(such as $I^2$, OR, publication bias and heterogeneity)