Cumulative evidence for associations between matrix metalloproteinase-1, -3 and -8 variants and cancer risk

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Abstract. Matrix metalloproteinase (MMP) gene polymorphisms have been implicated in cancer susceptibility; however, the results from previous studies have been inconsistent across populations and tumor types. The present study aimed to systematically evaluate the associations between MMP-1, MMP-3 and MMP-8 polymorphisms and cancer risk through a comprehensive meta-analysis. A total of 36,368 cancer cases and 40,246 controls from eligible studies were included. Pooled odds ratios and 95% confidence intervals were calculated to assess the associations between selected MMP polymorphisms and cancer risk. Venice criteria and false-positive report probability were applied to evaluate the cumulative evidence. Subgroup analyses according to ethnicity, genetic model and cancer type were conducted. Functional annotation was also integrated to explore potential biological mechanisms. In total, three polymorphisms (MMP-3 rs35068180, MMP-3 rs3025058 and MMP-1 rs1799750) were found to be significantly associated with the risk of seven types of cancer. Of these, strong evidence was assigned to two single nucleotide polymorphisms for three cancer risks (four associations), including MMP-3 rs3025058 with esophageal cancer in all populations under the dominant model, MMP-1 rs1799750 with glioblastoma in all populations under the recessive model and MMP-1 rs1799750 with renal cancer in all populations under both the recessive and allelic models. A total of six associations showed moderate evidence, while 14 were classified as weak. Notably, the effect sizes and statistical significance varied by ethnicity, genetic model and cancer type, suggesting context-dependent and population-specific effects. Functional annotation indicated that key variants may affect gene expression and tumor biology via regulation of promoter or enhancer activity. No significant association was observed between MMP-8 polymorphisms and cancer risk. The findings provide new insights into the complexity of gene-environment interactions underlying cancer susceptibility. This comprehensive meta-analysis highlights the complex, context-dependent associations of MMP-1, MMP-3 and MMP-8 polymorphisms with cancer risk. The results of the present study underscore the need for large, multi-ethnic studies and integrated genomic, functional and environmental analyses to clarify the roles of MMP variants in cancer development and to identify high-risk populations for precision prevention.

Introduction

Cancer remains one of the leading causes of mortality worldwide, with an estimated 20 million new cases and 9.7 million cancer-related mortalities globally in 2022 (1,2). The incidence and mortality rates vary across different types of cancer, among which breast, lung, colorectal, prostate and gastric cancer are the most common malignancies (3-5). Lung cancer continues to be the primary cause of cancer-related mortality, accounting for ~18.7% of all cancer-associated mortalities globally (1). Genetic factors play a key role in the occurrence and progression of cancer. In recent years, numerous genetic polymorphisms have been shown to be associated with susceptibility to various types of cancer (6,7).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases that can degrade the extracellular matrix (ECM), playing notable roles in tumor growth, invasion and metastasis (8,9). MMPs, particularly MMP-1, MMP-3 and MMP-8, are closely involved in several key processes of tumorigenesis, including apoptosis, angiogenesis and immune evasion (10-12). MMP-1 is widely expressed, participates in the degradation of type I, II and III collagen, and promotes tumor cell proliferation and metastasis by remodeling the tumor microenvironment (13). As an MMP, MMP-3 can hydrolyze various ECM components, such as laminin and collagen, thereby facilitating tumor cell migration and invasion (14-17). MMP-8, functioning as a collagenase, may affect the carcinogenic process by altering the balance of the tumor microenvironment (18,19).

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Abbreviations: ECM, extracellular matrix; FPRP, false-positive report probability; HWE, Hardy-Weinberg equilibrium; MMP, matrix metalloproteinase; SNP, single nucleotide polymorphism

Key words: MMP, genetic polymorphism, cancer, meta-analysis, SNP

Although numerous studies have investigated the association between MMP polymorphisms and cancer susceptibility, the results have shown considerable heterogeneity. For example, the MMP-1-1607 polymorphism (rs1799750), a 1G/2G insertion/deletion variant, has been associated with an increased risk of bladder, colorectal and esophageal cancer, but with a reduced risk of prostate cancer in certain populations (20-22). Similarly, inconsistent findings have also been reported for MMP-3 and MMP-8 polymorphisms. A systematic review summarized that the MMP-8 rs11225395 polymorphism was associated with reduced risks of breast and bladder cancer, but increased risks of melanoma and ovarian cancer, while rs2155052 was associated with decreased lung cancer risk (18). By contrast, an updated meta-analysis found no significant association between the MMP-3-1171 5A/6A polymorphism and lung cancer risk (23). These differences in study outcomes may be attributed to variations in study design, population characteristics and the genetic models employed.

Given these inconsistencies, the present study conducted a systematic review and meta-analysis to evaluate the relationships between MMP-1, MMP-3 and MMP-8 polymorphisms and cancer risk. The primary aim of the present study was to clarify whether these polymorphisms are universally associated with cancer susceptibility across different populations and cancer types, and to assess the functional significance of these genetic variants by utilizing publicly available genomic data, thereby providing a comprehensive understanding of their roles in cancer risk.

Materials and methods

Study selection. A systematic review and meta-analysis were conducted following the guidelines of the Human Genome Epidemiology Network for systematic reviews of genetic association studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (24-26). Studies were eligible for inclusion if they met the following criteria: i) Case-control or cohort studies investigating the association between MMP-1, MMP-3 and MMP-8 polymorphisms and cancer risk; ii) provision of the necessary genotype data or a method to calculate the odds ratio (OR) and 95% confidence interval (CI); and iii) publication in English. Studies were excluded if they: i) Lacked sufficient data; ii) were review articles, meta-analyses, editorials, case reports or treatment guidelines; and iii) were conducted on animal models or cell lines.

Search strategy. PubMed (https://pubmed.ncbi.nlm.nih.gov), Medline (via the National Library of Medicine; https://www.nlm.nih.gov/medline) and Web of Science (https://webofscience.clarivate.com) were used to conduct the literature search from database inception up to November 1, 2024. The following key words were used: 'Tumor or neoplasm or cancer or tumor or malignancy', 'polymorphism or genotype or mutation or variants or SNP or single nucleotide polymorphism' and 'metalloproteinases or collagenase or matrix metalloproteinase or MMP or gelatinase or matrilysin'. Although a broad MMP-family search was used to minimize missed studies reporting multiple MMP SNPs, only data on MMP-1/3/8 polymorphisms were eligible for inclusion and were extracted for analysis. Additionally, reference lists from the included studies were also examined for potentially relevant studies.

Data extraction. In total, two independent reviewers performed the data extraction from the eligible studies. The extracted data included the first author, year of publication, study design, cancer type, MMP polymorphisms, sample size and genotype distribution. Any discrepancies between the reviewers were resolved by discussion.

Statistical analysis. Meta-analysis was performed using STATA 12.0 software (StataCorp LP). A total of three genetic models (allelic, dominant and recessive) were applied in the analysis. Ethnicity-based subgroup analyses were performed when applicable. The heterogeneity among studies was assessed using the I^2 statistic and Cochran's Q test. Heterogeneity was categorized as low ($I^2 \leq 25\%$), moderate ($25\% < I^2 < 50\%$) or high ($I^2 \geq 50\%$). A random-effects model was used to pool effect estimates across studies, as heterogeneity was expected *a priori*. Heterogeneity was evaluated using Cochran's Q test and the I^2 statistic. Sensitivity analysis was performed to evaluate the robustness of the results by excluding studies one at a time and evaluating deviations from the Hardy-Weinberg equilibrium (HWE) in the control group. Publication bias was assessed using Egger's test and Begg's test. To account for the limited statistical power, a $P<0.10$ threshold was adopted as evidence of suggestive bias, following previous genetic association studies (21,27,28).

Cumulative evidence assessment. Epidemiological credibility of significant associations was assessed using the Venice criteria (29-31). The evidence for each polymorphism was graded based on three criteria: i) Replication of the association; ii) protection from bias; and iii) the amount of evidence. Each criteria was graded A, B or C. A strong association was defined by all A grades, moderate by a mix of A and B grades and weak by any C grade.

The false-positive report probability (FPRP) was calculated to assess the likelihood of a false-positive finding. The FPRP values were classified as strong (FPRP <0.05), moderate ($0.05 \leq$ FPRP ≤ 0.20) or weak (FPRP >0.20) (30).

Functional annotation. Functional annotation was performed to assess the potential regulatory effects of the polymorphisms on gene expression. The present study used the ENCODE project database tool HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) and the UCSC Genome browser (10-kb view; http://genome.ucsc.edu/) to evaluate the regions of promoter or enhancer activity, DNase I hypersensitivity, histone modification patterns and transcription factor binding sites (32,33). Additionally, the present study explored genome-wide cis-eQTL data from the Genotype-Tissue Expression project (GTEx Portal Release V10; dbGaP accession phs000424.v10.p2; https://gtexportal.org/home) and the Multiple Tissue Human Expression Resource project (MuTHER; ArrayExpress accession E-TABM-1140; http://www.muther.ac.uk/Data.html) to assess whether the identified single nucleotide polymorphisms (SNPs) influence gene expression across various tissues (34,35). Data from Phase 3 of the 1000 Genomes Project (https://www.

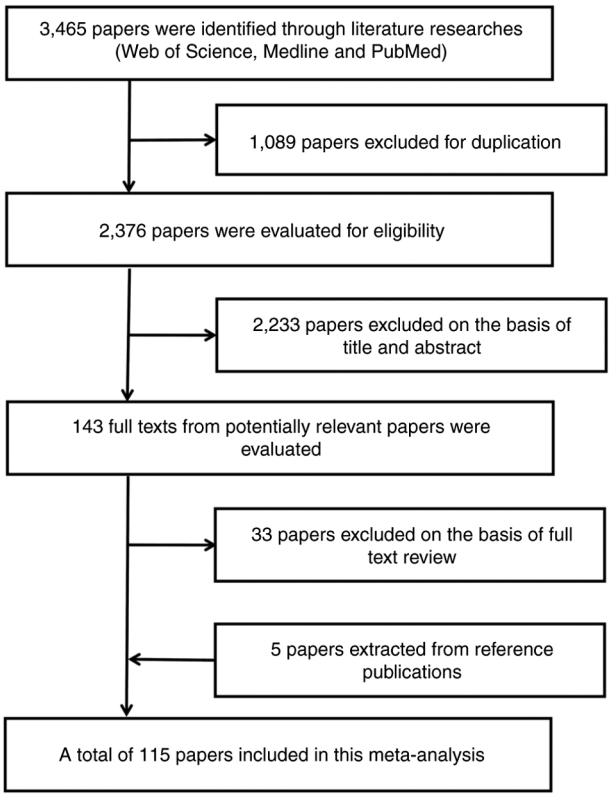

Figure 1. Flow diagram of search strategy and study selection.

internationalgenome.org/) (36) were accessed and analyzed using the LDlink web-based application (https://ldlink.nih.gov/) (37) to examine the genetic structure of the significant SNPs in different populations.

Results

Characteristics of eligible studies. As shown in Fig. 1, Web of Science, Medline and PubMed were used to identify associated studies, retrieving 3,465 articles. After removing 1,089 duplicates and excluding 2,233 articles based on titles and abstracts, 143 full-text articles were assessed for eligibility, of which 33 were excluded after full-text review. Additionally, 5 articles were added from examining references. Ultimately, 115 studies, with 36,368 cases and 40,246 controls, on the associations of MMP-1, MMP-3 and MMP-8 polymorphisms with cancer risk were included. The basic characteristics of these studies, including author, publication year, ethnicity, cancer type, gene type, genotyping data and sample size, are detailed in Table SI. These studies examined 43 variants and risk in 23 cancer types.

Main meta-analyses. This meta-analysis investigated the associations of MMP-1, MMP-3 and MMP-8 polymorphisms with tumor susceptibility. Table SII summarizes the results. Significant associations were found for three variants: Two in MMP-3 (rs35068180 and rs3025058) and one in MMP-1 (rs1799750). Specifically, as shown in Table I, MMP-1 rs1799750 showed significant associations with seven types of cancer; it was associated with bladder cancer risk in the overall population under the recessive model (OR, 1.739; 95% CI, 1.074-2.816; P=0.024) and colorectal cancer risk under all models in the overall population, and significant associations with colorectal cancer risk were observed under the allelic and dominant models in Asian populations and under the allelic and recessive models in Caucasian populations. This SNP was also associated with esophageal cancer risk under the dominant model (OR, 1.367; 95% CI, 1.043-1.67; P=0.024) and with gastric cancer risk in Asian individuals (allelic model: OR, 1.121; 95% CI, 1.005-1.251; P=0.041). Additionally, significant associations were found with glioblastoma in the overall population (allelic model: OR, 1.756; 95% CI, 1.439-2.144; P<0.001; dominant model: OR, 1.877;95% CI, 1.279-2.755; P=0.001; recessive model: OR, 2.036; 95% CI, 1.444-2.869; P<0.001) and nasopharyngeal cancer (allelic model: OR, 1.382; 95% CI, 1.097-1.741; P=0.006) in the overall populations, as well as in Asian individuals under the allelic and recessive models. MMP-1 rs1799750 was also linked to renal cancer risk in the overall population under the allelic (OR, 1.351; 95% CI, 1.149-1.590; P<0.001) and recessive (OR, 1.674; 95% CI, 1.351-2.073; P<0.001) models.

MMP-3 rs35068180 was significantly associated with colorectal cancer risk in Asian individuals under the dominant model (OR, 0.421; 95% CI, 0.255-0.694; P=0.001). MMP-3 rs3025058 showed significant associations with esophageal cancer risk in the overall population under the allelic model (OR, 1.379; 95% CI, 1.098-1.731; P=0.006), as well as under the dominant (OR, 1.563; 95% CI, 1.165-2.04; P=0.003) and recessive (OR, 1.566; 95% CI, 1.027-2.387; P=0.037) models.

However, MMP-1 rs1799750 showed no significant associations with breast cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma, oral cancer, lung cancer, prostate cancer or ovarian cancer. The MMP-8 rs11225395 variant was not significantly associated with bladder cancer risk in any population and MMP-3 rs35068180 had no significant associations with six other types of cancer.

Cumulative evidence of association. Cumulative epidemiological evidence was used to grade variations associated with cancer susceptibility, as shown in Table I. According to the Venice criteria, the evidence was evaluated across three categories: Amount of evidence (17 grade A, 7 grade B and 0 grade C), replication of association (9 grade A, 5 grade B and 10 grade C) and protection from bias (13 grade A, 0 grade B and 11 grade C). By integrating these three dimensions, the overall credibility was determined: Three associations (specifically SNP-cancer pairs) reached a 'strong' level of evidence, while five and 16 associations were classified as 'moderate' and 'weak', respectively.

The FPRP values were used to assess the likelihood of true associations. A total of seven associations had FPRP values <0.05 (colorectal cancer and MMP-1 rs1799750 under the allelic model in the overall population; esophageal cancer and MMP-1 rs1799750 under the dominant model in the overall population; esophageal cancer and MMP-3 rs3025058 under the dominant model in the overall population; glioblastoma and MMP-1 rs1799750 in the overall population under recessive and allelic models; renal cancer and MMP-1 rs1799750 under recessive and allelic models in the overall population), six had FPRP values between 0.05 and 0.20, and 11 had values >0.20. Combining the Venice criteria and FPRP results, the

Table I. Significant associations between variants in MMP-1, MMP-3 and MMP-8 with cancer risk.

						Number evaluation		Random-effects model meta-analysis for risk							
MMP	rs number	Alleles	Cancer type	Ethnicity	MAF[a]	N	Sample size (cases/ controls)	Genetic models	OR (95% CI)	P-value	I^2	P_Q[b]	Venice criteria[c]	FPRP[d]	Credibility of evidence[e]
MMP-1	rs1799750	2Gvs1G	Bladder	Overall	0.5215	4	2,146 (1,098/1,048)	Recessive	1.739 (1.074-2.816)	0.024	81.7	0.001	BCC	0.629	Weak
MMP-1	rs1799750	2Gvs1G	Colorectal	Overall	0.5882	9	3,628 (1,678/1,950)	Allelic	1.319 (1.116-1.560)	0.001	58.8	0.013	ACA	0.024	Moderate
MMP-1	rs1799750	2Gvs1G	Colorectal	Overall	0.5882	9	3,628 (1,678/1,950)	Dominant	1.400 (1.088-1.803)	0.009	28.0	0.196	ABC	0.198	Weak
MMP-1	rs1799750	2Gvs1G	Colorectal	Overall	0.5882	9	3,628 (1,678/1,950)	Recessive	1.429 (1.141-1.790)	0.002	54.6	0.024	ACA	0.051	Weak
MMP-1	rs1799750	2Gvs1G	Colorectal	Asian	0.7024	5	1,698 (789/909)	Allelic	1.398 (1.041-1.877)	0.026	71.2	0.008	ACA	0.419	Weak
MMP-1	rs1799750	2Gvs1G	Colorectal	Asian	0.7024	5	1,698 (789/909)	Dominant	1.684 (1.176-2.412)	0.004	0.0	0.447	AAA	0.243	Moderate
MMP-1	rs1799750	2Gvs1G	Colorectal	Caucasian	0.4780	3	1,714 (781/933)	Allelic	1.227 (1.001-1.504)	0.049	38.3	0.198	ABA	0.488	Weak
MMP-1	rs1799750	2Gvs1G	Colorectal	Caucasian	0.4780	3	1,714 (781/933)	Recessive	1.403 (1.090-1.807)	0.009	13.4	0.315	BAA	0.192	Moderate
MMP-3	rs35068180	6Avs5A	Colorectal	Asian	0.7977	4	1,123 (525/598)	Dominant	0.421 (0.255-0.694)	0.001	0.0	0.843	AAA	0.269	Moderate
MMP-1	rs1799750	2Gvs1G	Esophageal	Overall	0.55	4	2,197 (986/1,121)	Dominant	1.367 (1.043-1.67)	0.024	30.1	0.232	ABC	0.049	Moderate
MMP-3	rs3025058	5Avs6A	Esophageal	Overall	0.4538	3	1,620 (754/866)	Allelic	1.379 (1.098-1.731)	0.006	57.7	0.094	ACC	0.122	Weak
MMP-3	rs3025058	5Avs6A	Esophageal	Overall	0.4538	3	1,620 (754/866)	Dominant	1.563 (1.165-2.04)	0.003	34.6	0.217	ABA	0.048	Strong
MMP-3	rs3025058	5Avs6A	Esophageal	Overall	0.4538	3	1,620 (754/866)	Recessive	1.566 (1.027-2.387)	0.037	57.4	0.096	BCC	0.626	Weak
MMP-1	rs1799750	2Gvs1G	Gastric	Asian	0.6534	8	3,997 (1,741/2,256)	Allelic	1.121 (1.005-1.251)	0.041	18.8	0.281	AAC	0.440	Weak
MMP-1	rs1799750	2Gvs1G	Glioblastoma	Overall	0.6143	3	985 (412/573)	Allelic	1.756 (1.439-2.144)	<0.001	0.0	0.941	AAC	<0.001	Moderate
MMP-1	rs1799750	2Gvs1G	Glioblastoma	Overall	0.6143	3	985 (412/573)	Dominant	1.877 (1.279-2.755)	0.001	4.9	0.349	BAC	0.164	Weak

Table I. Continued.

MMP	rs number	Alleles	Cancer type	Ethnicity	MAF[a]	Number evaluation: N	Number evaluation: Sample size (cases/controls)	Random-effects model meta-analysis for risk: Genetic models	Random-effects model meta-analysis for risk: OR (95% CI)	Random-effects model meta-analysis for risk: P-value	Random-effects model meta-analysis for risk: I^2	Random-effects model meta-analysis for risk: P_Q[b]	Venice criteria[c]	FPRP[d]	Credibility of evidence[e]
MMP-1	rs1799750	2Gvs1G	Glioblastoma	Overall	0.6143	3	985 (412/573)	Recessive	2.036 (1.444-2.869)	<0.001	28.3	0.248	BBA	0.022	Strong
MMP-1	rs1799750	2Gvs1G	Nasopharyngeal	Overall	0.61	4	2,626 (1,262/1,364)	Allelic	1.382 (1.097-1.741)	0.006	64.9	0.036	ACC	0.132	Weak
MMP-1	rs1799750	2Gvs1G	Nasopharyngeal	Overall	0.61	4	2,626 (1,262/1,364)	Dominant	1.387 (1.049-1.835)	0.022	20.4	0.287	AAC	0.371	Weak
MMP-1	rs1799750	2Gvs1G	Nasopharyngeal	Overall	0.61	4	2,626 (1,262/1,364)	Recessive	1.505 (1.097-2.066)	0.011	64.3	0.038	ACC	0.307	Weak
MMP-1	rs1799750	2Gvs1G	Nasopharyngeal	Asian	0.6014	3	2,281 (1,088/1,193)	Allelic	1.390 (1.027-1.881)	0.033	74.4	0.02	ACA	0.475	Weak
MMP-1	rs1799750	2Gvs1G	Nasopharyngeal	Asian	0.6014	3	2,281 (1,088/1,193)	Recessive	1.611 (1.030-2.521)	0.037	76.1	0.015	BCA	0.645	Weak
MMP-1	rs1799750	2Gvs1G	Renal	Overall	0.5803	4	1,569 (697/872)	Allelic	1.351 (1.149-1.590)	<0.001	12.8	0.328	AAA	0.006	Strong
MMP-1	rs1799750	2Gvs1G	Renal	Overall	0.5803	4	1,569 (697/872)	Recessive	1.674 (1.351-2.073)	<0.001	0.0	0.58	BAA	<0.001	Strong

[a]Allelics: Minor allelic vs. major allelic. [b]P-value for the heterogeneity test based on the Q statistic. [c]Venice criteria grades are for the amount of evidence, replication of the association and protection from bias. [d]The prior probability of FPRP is 0.05 and the FPRP level of noteworthiness is 0.20. [e]Degree of epidemiological credibility based on the combination of results from the Venice guidelines and FPRP tests. MMP, matrix metalloproteinase; A, adenine; G, guanine; OR, odds ratio; CI, confidence interval; MAF, minor allelic frequency in control; FPRP, false-positive report probability.

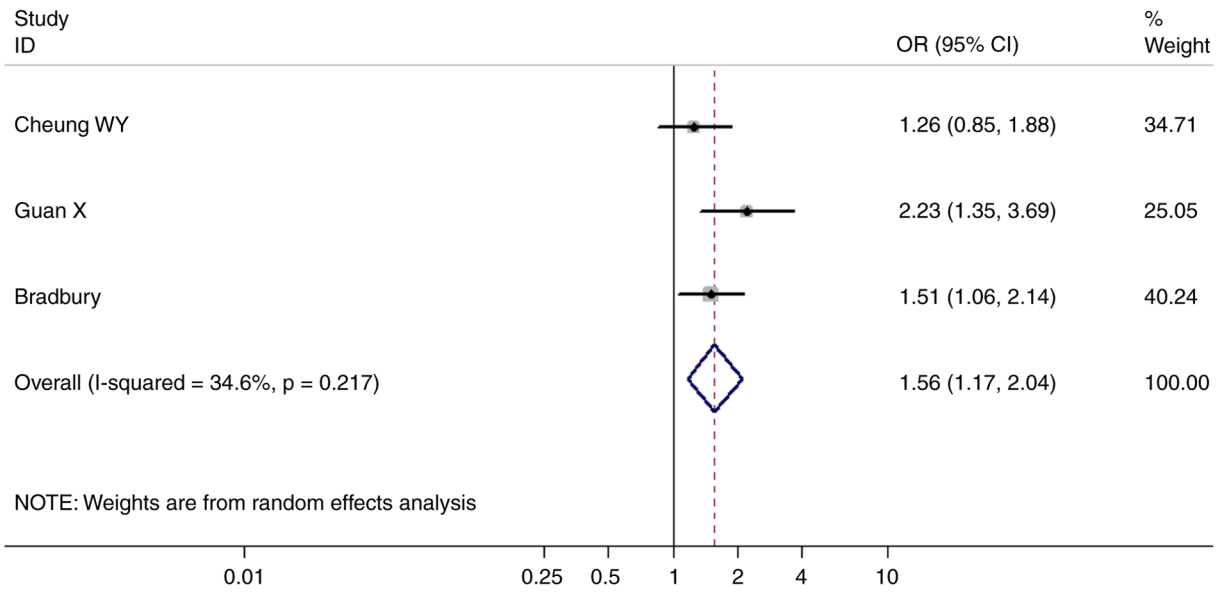

Figure 2. Association between matrix metalloproteinase-3 rs3025058 and the risk of esophageal cancer in the overall population under the dominant model. OR, odds ratio; CI, confidence interval.

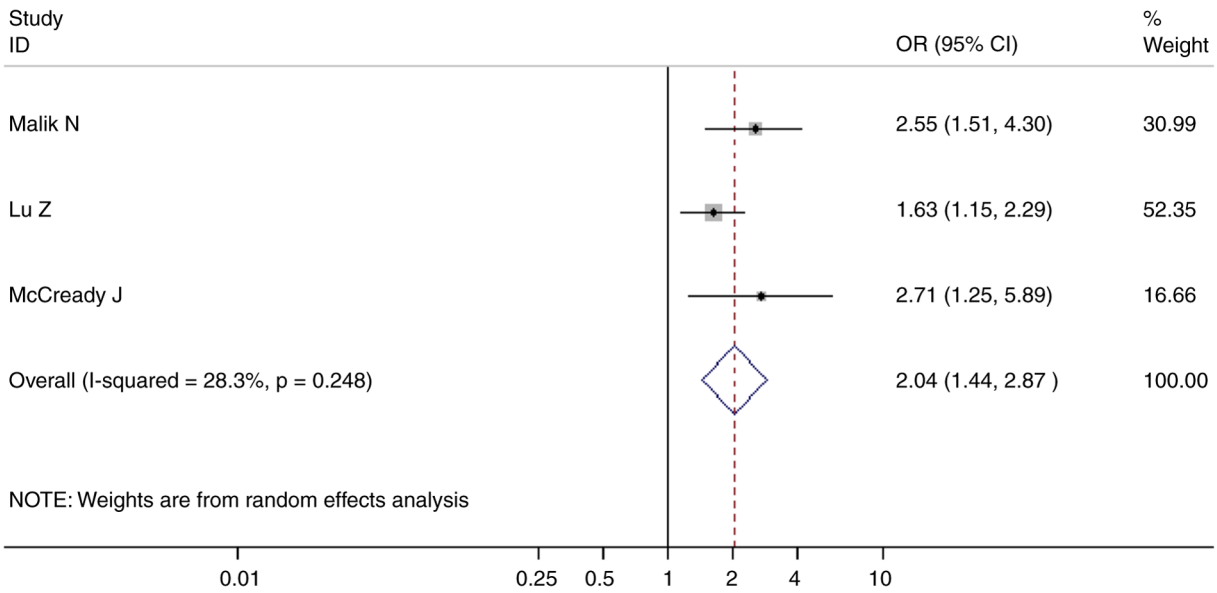

Figure 3. Association between matrix metalloproteinase-1 rs1799750 and the risk of glioblastoma cancer in the overall population under the recessive model. OR, odds ratio; CI, confidence interval.

present study identified four strong associations: MMP-3 rs3025058 was associated with esophageal cancer risk in the overall population under the dominant model (Fig. 2), MMP-1 rs1799750 was associated with glioblastoma risk in the overall population under the recessive model (Fig. 3), and MMP-1 rs1799750 was associated with renal cancer risk in the overall population under the allelic and recessive models (Figs. 4 and 5). In addition, six associations were graded as moderate and 14 were graded as weak.

Heterogeneity, bias and sensitivity analyses. Heterogeneity was systematically evaluated for all associations included in the current study, with the corresponding I^2 values provided for every entry in Table SII. Among the 24 significant associations identified (comprising 2 SNPs across 7 types of cancer), low heterogeneity ($I^2 \leq 25\%$) was observed for 9 associations (2 variants and 5 types of cancer), moderate heterogeneity ($25\% < I^2 < 50\%$) for 5 associations (2 variants and 3 types of cancer) and high heterogeneity ($I^2 \geq 50\%$) for 10 associations (2 variants and 4 types of cancer). No publication bias was found for the majority of gene-cancer associations ($P>0.10$), except for MMP-1 rs1799750 in gastric cancer in Asian individuals and nasopharyngeal cancer in the overall population under the allelic model ($P<0.10$). Sensitivity analysis showed that removing any individual study or those deviating from HWE did not significantly alter the summary ORs for the majority of associations. However, significance was lost for specific associations, including esophageal cancer

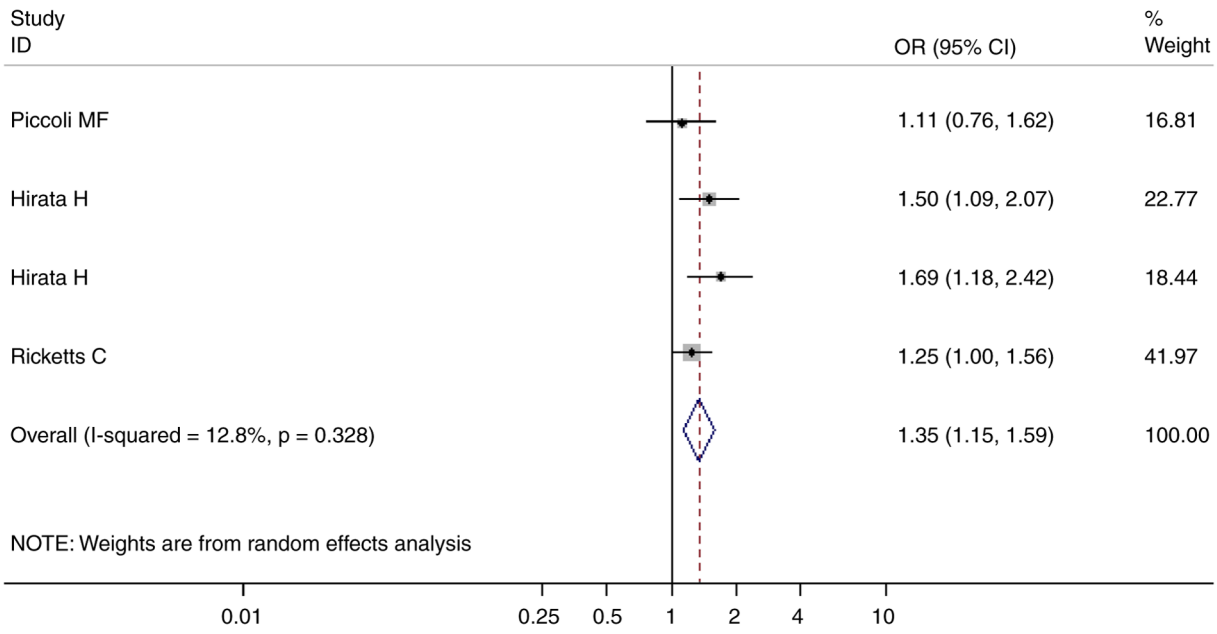

Figure 4. Association between matrix metalloproteinase-1 rs1799750 and the risk of renal cancer in the overall populations under the allele model. OR, odds ratio; CI, confidence interval.

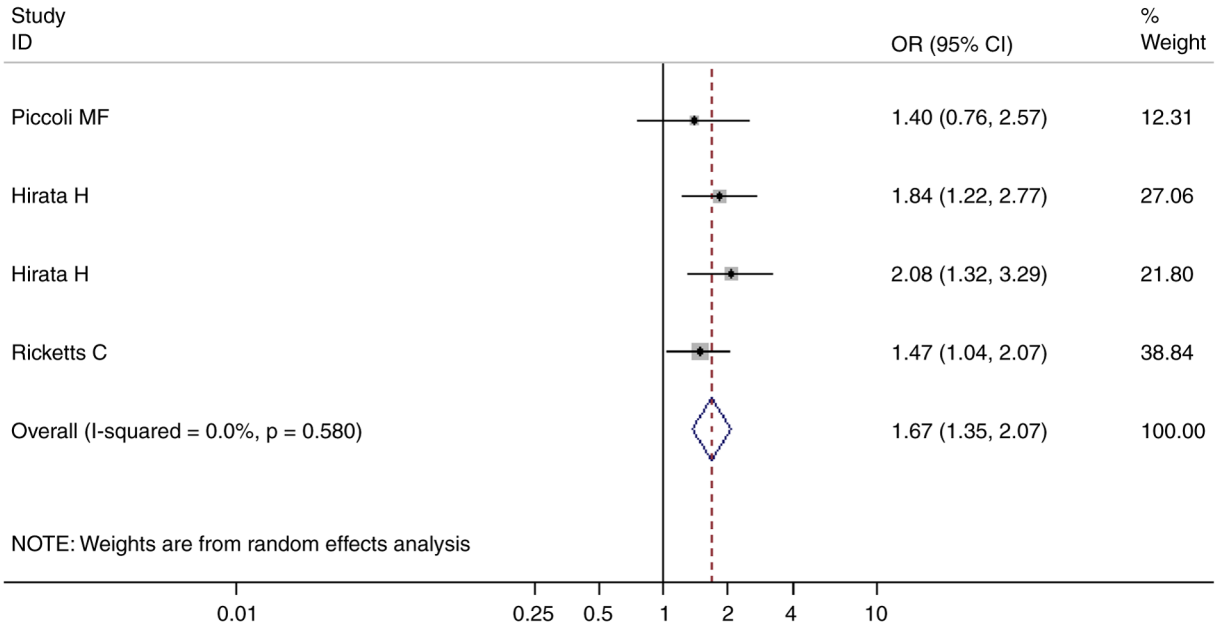

Figure 5. Association between matrix metalloproteinase-1 rs1799750 and the risk of renal cancer in the overall population under the recessive model. OR, odds ratio; CI, confidence interval.

and MMP-3 rs3025058 (recessive/allelic model), glioblastoma and MMP-1 rs1799750 (dominant model), and nasopharyngeal cancer and MMP-1 rs1799750 (dominant model), when studies deviating from HWE were excluded.

Functional annotation for variants with strong evidence. As shown in Table II, the present study used HaploReg v4.1 to assess the functional roles of variants with strong evidence (two SNPs associated with three types of cancer). rs1799750 is located in intronic regions and may be in a region with enhancer activity, DNase I hypersensitivity and regulatory motif alterations. Figs. S1 and S2 show linkage disequilibrium (LD) plots indicating distinct genetic structures across ancestries. Specifically, the density and boundaries of LD blocks, as well as the magnitude of allelic correlation (measured by r2), exhibited population-specific patterns among individuals of European (Northern and Western European ancestry), Asian (Han Chinese from Beijing and Japanese from Tokyo) and African (Yoruba from Nigeria) descent. The Genotype-Tissue Expression Project data indicate that rs1799750 is an eQTL for MMP-1, MMP-10 and WTAP pseudogene 1 (WTAPP1). Specifically, rs1799750 is associated with decreased MMP-1

Table II. Summary of functional annotations for two single nucleotide polymorphisms in three cancerous diseases with strong epidemiological credibility.

Variant	Gene	Position[a]	Annotation	Enhancer histone marks[b]	DNAse[c]	Proteins bound[d]	Motifs changed[e]
rs3025058	MMP-3	102845217	-	GI and skin	THYM	-	CIZ and Gfi1b
rs1799750	MMP-1	102799765	Intronic	5 tissues	5 tissues	CFOS and GATA2	21 altered motifs

[a]Chromosome position is based on NCBI Build 38. [b]Histone modification of H3K4me3 (tissue types: if >3, only the number is included). [c]Levels of DNase I hypersensitivity (tissue types: if >3, only the number is included). [d]Alteration in transcription factor binding (disruptions: if >3, only the number is included). [e]Alteration in regulatory motif (disruptions: if >3, only the number is included). MMP, matrix metalloproteinase; GI, gastrointestinal tract; THYM, thymus; CFOS, proto-oncogene c-Fos; GATA2, GATA binding protein 2; CIZ, CDKN1A interacting zinc finger protein 1; Gfilb, growth factor independent 1B transcriptional repressor.

expression in adipose, artery, breast, esophagus, heart, lung, tibial nerve and thyroid tissues; decreased MMP-10 expression in lung tissue; and decreased WTAPP1 expression in testis tissue (Table SIII).

Discussion

MMP-1, MMP-3 and MMP-8 polymorphisms have been associated with tumor susceptibility, but results have been inconsistent. The present meta-analysis, based on data from 36,368 patients and 40,246 controls, assessed the associations between these polymorphisms and tumor susceptibility. A total of three polymorphisms were significantly associated with cancer risk: MMP-3 rs35068180 and rs3025058, and MMP-1 rs1799750. Using the Venice criteria and FPRP test, the cumulative evidence showed four strong associations (MMP-3 rs3025058 with esophageal cancer in the overall population under the dominant model, MMP-1 rs1799750 with glioblastoma in the overall population under the recessive model, and MMP-1 rs1799750 with renal cancer in the overall population under both the recessive and allelic models), six moderate associations and 14 weak associations.

MMP-1 (NCBI Gene ID: 4312; https://www.ncbi.nlm.nih.gov/gene/) is expressed in tumor cells and predicts poor survival (for example, in colorectal, gastric, pancreatic, lung, breast, prostate, bladder and oral/head-and-neck cancer) (38). The MMP-1 rs1799750 (1G>2G) variant, located in the promoter region, enhances MMP-1 transcription by creating an Ets-binding site. The 2G allele is associated with active matrix degradation and tumor progression (39). Increasing evidence has linked MMP-1 rs1799750 (1G>2G) to several types of cancer, including bladder, colorectal and gastric cancer (40-42). The meta-analysis performed in the present study found that this SNP significantly increases glioblastoma risk by 2.036-fold in the overall population under the recessive model (985 samples), with the association upgraded to strong (FPRP<0.05). Studies suggest that members of the E26 transformation-specific family of transcription factors in glioma cells bind to the 2G promoter, possibly contributing to glioblastoma (43,44). Additionally, MMP-1 rs1799750 was shown to be associated with increased renal cell carcinoma risk under both allelic and recessive models (1,569 samples), with a 1.351-fold increased risk under the allelic model and a 1.674-fold increased risk under the recessive model. However, no subgroup analysis by ethnicity was possible, likely due to the small sample size. Further studies, particularly in different ethnicity groups, are warranted.

MMP-3 (Gene ID: 4314) located within the MMP cluster on chromosome 11q22.3, is expressed by epithelial cells, fibroblasts and macrophages, contributing to ECM remodeling. Through broad ECM-degrading activity and activation of other pro-MMPs, MMP-3 promotes tumor invasion and progression (10,45,46). The MMP-3 promoter contains a 5A/6A polymorphism at -1612, with the 5A allele showing twice the promoter activity of the 6A allele in *in vitro* assays, suggesting that transcription inhibitors may bind to the 6A allele (47). The present study found a strong association between MMP-3 rs3025058 and esophageal cancer risk under the dominant model (1,620 samples), with the 5A allele increasing risk by 1.563-fold (OR, 1.563; 95% CI, 1.165-2.04). This association was observed in European populations but is limited by the lack of data on Asian populations, which warrants further investigation.

In the present study, six associations with cancer risk were rated as moderate evidence. A total of three associations (colorectal cancer with MMP-1 rs1799750, esophageal cancer with MMP-1 rs1799750 and glioblastoma with MMP-1 rs1799750) were upgraded to strong evidence, graded 'ACA', 'ABC' and 'AAC', respectively, by the Venice criteria due to replication and small-study effects. With FPRP<0.05, these were considered medium-strength associations with tumor susceptibility. In total, two associations in Asian individuals (colorectal cancer with MMP-1 rs1799750 and MMP-3 rs35068180) were downgraded from strong to moderate (FPRP>0.2). The remaining associations (colorectal cancer with MMP-1 rs1799750) were not upgraded or downgraded ($0.05 \leq$ FPRP ≤ 0.20), with the relation rated 'BAA' by the Venice criteria due to the amount of evidence. Further analysis revealed that these moderate-evidence associations exhibited considerable complexity across different populations, cancer types and genetic models. A possible mechanism is that polymorphisms in genes such as MMP-1 and MMP-3 may influence transcription factor binding, promoter activity or linked functional variants, thereby affecting MMP expression

Table III. MMP variants show no relation to cancer risk in meta-analyses, with at least 2,000 cases and 2,000 controls in the additive model.

MMP	rs number	Alleles	Cancer type	Ethnicity	MAF	Number evaluation		Random-effects model meta-analysis for risk					Power (%)	Power (%) if the MAF is 0.2	Power (%) if the MAF is 0.1
						N	Sample size (cases/controls)	Genetic Models	OR (95% CI)	P-value	I^2	P_Q			
MMP-1	rs1799750	2Gvs1G	Breast	Overall	0.5564	6	6,127 (2,979/3,148)	Allelic	1.161 (0.937-1.439)	0.173	82.9	<0.001	96.5	87.5	65.2
MMP-1	rs1799750	2Gvs1G	Breast	Asian	0.5631	3	5,528 (2,764/2,764)	Allelic	1.235 (0.904-1.687)	0.186	93.1	<0.001	95.2	85.0	62.0
MMP-1	rs1799750	2Gvs1G	Lung	Overall	0.5316	11	13,060 (6,726/6,334)	Allelic	1.087 (0.992-1.191)	0.075	60.6	0.005	100.0	99.7	94.2
MMP-1	rs1799750	2Gvs1G	Lung	Caucasian	0.4878	7	9,651 (5,259/4,392)	Allelic	1.073 (0.963-1.195)	0.201	61.2	0.017	99.9	98.5	87.8
MMP-3	rs35068180	6Avs5A	Lung	Overall	0.5092	4	4,872 (2,800/2,072)	Allelic	0.898 (0.735-1.097)	0.291	63.7	0.041	95.8	85.5	62.6
MMP-3	rs35068180	6Avs5A	Lung	Caucasian	0.5126	3	4,780 (2,759/2,021)	Allelic	0.985 (0.907-1.070)	0.726	0.0	0.639	95.5	85.0	61.9

MMP, matrix metalloproteinase; A, adenine; G, guanine; OR, odds ratio; CI, confidence interval; MAF, minor allelic frequency in control; FPRP, false-positive report probability; P_Q, P-value for the heterogeneity test based on the Q statistic.

and activation in a tissue- and environment-dependent manner and contributing to cancer susceptibility (48,49). Tumor heterogeneity, diverse genetic backgrounds among populations, environmental factors, as well as differences in sample size and methodological design, may all contribute to the observed variability (50,51). Therefore, the differential effects of the same SNP in various populations and cancer types warrant further systematic investigation in future studies.

In the present study, 14 associations were classified as weak regarding tumor susceptibility. MMP-1 rs1799750 was significantly associated with several types of cancer (colorectal cancer, gastric cancer, nasopharyngeal carcinoma, bladder cancer, esophageal cancer and glioblastoma), although the association with colorectal cancer in Caucasian individuals under the allelic model was rated as weak (FPRP=0.488), despite moderate heterogeneity ('ABA' by Venice criteria). Sample size, environmental factors and methodology may explain variations across ethnicities. A total of two associations (gastric cancer with MMP-1 rs1799750 and glioblastoma with MMP-1 rs1799750) were also rated as weak, mainly due to low ORs and HWE deviations; thus, further studies are needed. MMP-3 rs3025058 (recessive/allelic models) showed a weak association with esophageal cancer, with Venice criteria ratings 'ACC' and 'BCC' due to limited study populations. No significant association was found between MMP-8 polymorphism and cancer risk, warranting larger sample sizes for confirmation.

Although the present study identified several statistically significant associations, the majority of effect sizes were modest, indicating that individual MMP variants (including rs1799750) are unlikely to provide sufficient predictive value as stand-alone clinical markers. For example, even for the strong association between MMP-1 rs1799750 and glioblastoma, the pooled effect (OR=2.036 under the recessive model) reflects relative risk rather than absolute risk and thus does not directly translate into high positive predictive value (PPV) in the general population. Instead, the most plausible translational pathway is risk stratification in high-risk settings, where germline variants may help refine risk when combined with other determinants. In future work, rs1799750 and other credible MMP loci could be incorporated into multi-locus genetic scores or polygenic risk models and further integrated with established environmental/clinical factors (for example, smoking, chronic inflammation, hormonal status or occupational exposures) to improve discrimination and calibration. Prospective, multi-ethnic cohort studies that include baseline incidence and exposure data will be required to estimate absolute risk, PPV and model performance (for example, area under the curve) and to determine whether adding MMP variants meaningfully enhances existing prevention or screening frameworks (52-56).

Overall, the present findings are broadly consistent with previous meta-analyses, although the strength and direction of some associations appear to vary across cancer types and populations (57-60). The present study adds notable value by incorporating a larger sample size, applying more rigorous Venice criteria and FPRP evaluation, and conducting more detailed subgroup analyses by ethnicity and tumor subtype. Notably, the present study identified context-dependent and ethnicity-specific associations that were previously unrecognized or only partially addressed. Previous studies have shown that MMP-1 rs1799750, MMP-3 rs3025058 and other MMP variants may influence cancer susceptibility, albeit with moderate effect sizes and considerable heterogeneity across populations and tumor types (48,61). The present study further refines these associations by applying rigorous Venice criteria and FPRP testing, supporting strong epidemiological credibility for only a small subset of associations (notably, MMP-1 rs1799750 with glioblastoma and renal cancer, as well as MMP-3 rs3025058 with esophageal cancer). Mechanistically, MMP-1 and MMP-3 variants may modulate gene expression by altering promoter or enhancer regions, thus affecting the degradation of ECM components, tumor cell invasion, angiogenesis and immune cell infiltration in the tumor microenvironment (45). Functional annotation from ENCODE and eQTL data performed in the present study suggests that rs1799750 and rs3025058 could influence transcription factor binding and gene expression across multiple tissues, further supporting their biological plausibility in tumorigenesis. However, the overall moderate or weak evidence for the majority of associations in the present meta-analysis also suggests that MMP variants alone are unlikely to be major determinants of cancer risk and may interact with environmental or lifestyle factors such as smoking, inflammation or hormonal status.

In the present study, associations varied across ethnicities, genetic models and tumor types. While the majority of studies focused on Asian populations, research on non-Asian populations is key. Different genetic models showed varying associations with tumors, and gaps in research on certain tumor types highlight the need for larger, more focused studies.

The present study revealed that four SNPs in three MMPs were not associated with seven types of cancer in any genetic model and/or ethnicity (Table III). Among these, two SNPs in two MMPs showed no association with the risk of two types of cancer in meta-analyses, including a minimum of 2,000 cases and 2,000 controls, which offers >85% power to detect an OR of 1.15 under the additive model for a variant with minor allelic frequency 0.20, Type 1 error 0.05. Therefore, further research on these SNPs with a similar sample size may not yield positive results.

Several limitations of the present study should be acknowledged. First, the meta-analysis included studies only published in English, potentially introducing language and publication bias. Second, the present analysis was primarily restricted to case-control studies, limiting causal inference. In addition, the selection of hospital-vs. population-based controls varied across studies, potentially introducing selection bias, and survival bias may exist if genotype affects both cancer incidence and prognosis. Third, subgroup analyses could not account for all possible confounders, such as age, sex, environmental exposures or comorbidities, due to limited available data. Furthermore, the observed heterogeneity ($I^2 \leq 81.7\%$) may reflect differences in population genetic structure, analytical models, clinical characteristics of included cases and genotyping platforms across studies. These factors are well-recognized sources of variability in genetic epidemiology and likely contributed to the inconsistent effect estimates. Another limitation is that some ethnicity-stratified analyses were based on a limited number of studies (for example, the association between MMP-1

rs1799750 and renal cancer), which restricts the robustness of population-specific conclusions and warrants caution when generalizing these findings across diverse ancestral groups. Additionally, the broad ethnicity classifications (such as Asian and Caucasian) of the present study may inadequately capture population substructure and admixture patterns within these groups, as different subpopulations may exhibit distinct allele frequencies and LD structures. Fourth, only a subset of functionally annotated SNPs was investigated and gene-gene or gene-environment interactions were not systematically evaluated. Moreover, since individual-level baseline risk and exposure data were unavailable in the included studies, the present study could not estimate absolute risk measures or predictive metrics such as PPV, negative PV or area under the curve for any single SNP. It is also possible that the analyzed SNPs may represent LD proxies rather than causal variants themselves and population-specific differences in LD patterns could contribute to observed heterogeneity. Technical heterogeneity across studies, including different genotyping platforms and quality control thresholds, represents a potential source of systematic bias. To address this and minimize bias, a strict sensitivity analysis based on HWE was performed. Since deviations from HWE often indicate genotyping errors, this analysis acted as a rigorous quality filter. The results demonstrated that the primary findings, specifically the strong associations between MMP-1 rs1799750 and glioblastoma and renal cancer, remained robust after this strict exclusion. This resilience suggests that the core conclusions of the present study are not driven by technical variations or platform-specific biases, whereas less robust associations (which lost significance) should be interpreted with caution. Additionally, the exclusive focus of the present study on common variants overlooks potentially important contributions from rare variants, which may exhibit larger effect sizes and account for additional heritability in cancer susceptibility. Fifth, the present study focused only on cancer susceptibility, without addressing prognosis, response to therapy or functional effects at the cellular level. Similarly, the present study treated broad cancer types as homogeneous entities without considering histological subtypes, molecular classifications or disease stages that may have distinct genetic architectures. Finally, temporal changes in diagnostic criteria and treatment protocols across the present study period spanning multiple decades may affect case definition consistency.

Future research should include larger, multi-ethnic cohorts, more comprehensive genotyping, and integrated analyses of environmental risk factors, lifestyle and somatic mutations. Experimental studies investigating the functional impact of MMP variants on protein expression, enzyme activity and tumor biology are also warranted. Furthermore, emerging genomic and transcriptomic data from single-cell and spatial profiling technologies may shed light on the context-dependent effects of MMP polymorphisms in different tumor microenvironments (62). The present study identified four strong associations between gene mutations and cancer risk (MMP-3 rs3025058 in esophageal cancer under the dominant model, MMP-1 rs1799750 in glioblastoma under the recessive model, and in renal cancer under both allelic and recessive models across the overall population) as well as six moderate associations and 14 weak associations. These findings may help to identify populations at increased risk of cancer and provide a comprehensive summary of current evidence regarding MMP polymorphisms and cancer risk, thereby offering valuable insights for future studies. Overall, the present comprehensive meta-analysis highlights the complex and context-dependent associations between MMP-1, MMP-3 and MMP-8 gene variants and cancer risk, emphasizing the importance of multi-dimensional approaches in genetic epidemiology and laying the groundwork for further exploration of the interplay between ECM remodeling, genetic susceptibility and cancer development.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SX and XL conducted the literature search, data extraction and quality assessment. SX and CH designed the study, performed the statistical analyses and wrote the manuscript. XL contributed to the interpretation of the data and critically revised the manuscript for important intellectual content. SX and CH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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