Review Article

A Matrix Metalloproteinase-1 Polymorphism, \textit{MMP1}–1607 (1G>2G), Is Associated with Increased Cancer Risk: A Meta-Analysis Including 21,327 Patients

Zhonghan Zhou\textsuperscript{\textregistered}, Xiaocheng Ma\textsuperscript{\textregistered}, Fangming Wang\textsuperscript{\textregistered}, Lijiang Sun\textsuperscript{\textregistered}, and Guiming Zhang\textsuperscript{\textregistered}

Department of Urology, The Affiliated Hospital of Qingdao University, Qingdao, China

Correspondence should be addressed to Lijiang Sun; slijiang999@126.com and Guiming Zhang; zhangguiming9@126.com

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1. Introduction

Single-nucleotide polymorphisms (SNP) are variations in single nucleotides that occur at specific positions in the genome and influence protein structure, gene splicing, transcription factor binding, messenger RNA degradation, or sequences of noncoding RNAs [1]. SNPs reportedly contribute to interindividual variability in susceptibility to common diseases such as cancer.

Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes that can degrade extracellular matrix components, thereby affecting various physiological and pathological processes such as embryonic development, wound healing, arthritis, atherosclerosis, and tumor progression [2]. Increasing evidence shows that MMPs play significant roles in cancer development, including cell growth, differentiation, apoptosis, angiogenesis, invasion, and metastasis [3].

MMP1, a member of the MMP family, can degrade interstitial collagen types I, II, and III, clearing a path for cancer cells to invade matrix barriers and migrate through tissue stroma [4]. The \textit{MMP1} gene is located at 11q22.3, and MMP1 expression can be regulated by the \textit{MMP1} promoter. The gene polymorphism \textit{MMP1}–1607 (1G>2G) or rs1799750 in the \textit{MMP1} promoter has been associated with increased susceptibility for various cancers [5, 6]. However, the results were controversial because of variations in cancer types and patient demographics. Therefore, we conducted this meta-analysis to further explore the association between \textit{MMP1}–1607 (1G>2G) polymorphism and cancer susceptibility.

2. Materials and Methods

2.1. Identification and Eligibility of Studies. We conducted a systematic search of literature published until December...
2017 that investigated the association of MMP1–1607 (1G>2G) polymorphism with cancer risks, through PubMed, Embase, ISI Web of Knowledge, and Google Scholar, using the terms “Matrix metalloproteinase-1 or MMP-1 or rs1799750,” “polymorphism or variation or mutation or SNP,” and “cancer or carcinoma or tumor or neoplasm.” Only case–control studies with sufficient genotype distribution data to calculate odds ratios (ORs) with 95% confidence interval (CIs) in different gene models were included. Letters, case reports, animal studies, and reviews were excluded. When overlapping populations were included in different articles, only the publication with the largest sample size was selected.

2.2. Data Extraction. Two investigators independently reviewed the articles to exclude irrelevant and overlapping studies. The following data were extracted from eligible publications: first author, published year, cancer type, country, ethnicity, control source, genotyping method, and genotype distribution. Any disagreements were resolved by discussion or by consultation with another investigator.

2.3. Statistical Analysis. The meta-analysis was conducted using SATAT (version 13.0). The Hardy–Weinberg equilibrium (HWE) for control groups was checked by the chi-square goodness-of-fit test \( P > 0.05 \). The associations between MMP1–1607 (1G>2G) polymorphism and cancer risks were calculated by OR and 95% CI with the following models to avoid assuming only one suboptimal genetic model: an allele model (2G vs. 1G), a dominant model (2G2G/1G2G vs. 1G1G), and a recessive model (2G2G vs. 1G2G/1G1G). Subgroup analyses were performed by cancer type and ethnicity.

The heterogeneity of studies was assessed by \( Q \) test using \( P \) value and \( I^2 \) value. A fixed-effects model was adopted when \( Q \) test indicated a lack of heterogeneity \( (P > 0.05); \) otherwise, a random-effects model was used. We considered 0–40% of \( I^2 \) value to indicate low heterogeneity, 30–60% to indicate moderate heterogeneity, 50–90% to indicate substantial heterogeneity, and 75–100% to indicate considerable heterogeneity. Publication bias was measured with funnel plots and Harbord’s and Peter’s tests.

3. Results

3.1. Characteristics of Eligible Studies. The study selection procedure is shown in Figure 1. We included 77 articles with 21,327 cancer patients and 23,245 controls in this meta-
| Author                  | Year | Cancer type       | Country | Ethnicity | Control | Genotype | N of case | N of control | HWE (P) |
|------------------------|------|-------------------|---------|-----------|---------|----------|-----------|-------------|---------|
| Kanamori et al. [7]    | 1999 | Ovarian cancer    | Japan   | Asian     | HB      | PCR-RFLP | 163       | 150         | 0.033   |
| Biondi et al. [8]      | 2000 | Other cancer      | Italy   | Caucasian | HB      | TaqMan   | 160       | 164         | 0.813   |
| Nishioka et al. [9]    | 2000 | Endometrial cancer| Japan   | Asian     | HB      | Sequencing| 100       | 150         | 0.033   |
| Ye et al. [10]         | 2001 | Cutaneous melanoma| England | Caucasian | HB      | TaqMan   | 139       | 132         | 0.849   |
| Zhu et al. [11]        | 2001 | Lung cancer       | America | Caucasian | HB      | PCR-RFLP | 456       | 451         | 0.028   |
| Ghiairi et al. [12]    | 2002 | Breast cancer     | America | Caucasian | HB      | Sequencing| 86        | 110         | 0.652   |
| Hinoda et al. [13]     | 2002 | Colorectal cancer | Japan   | Asian     | PB      | PCR-RFLP | 101       | 127         | 0.949   |
| Hirata et al. [14]     | 2003 | Renal cell cancer | Japan   | Asian     | HB      | Sequencing| 119       | 210         | 0.993   |
| Nishioka et al. [15]   | 2003 | Endometrial cancer| Japan   | Asian     | HB      | Sequencing| 109       | 150         | 0.033   |
| Wenham et al. [16]     | 2003 | Ovarian cancer    | America | Caucasian | PB      | TaqMan   | 311       | 387         | 0.536   |
| Hashimoto et al. [17]  | 2004 | Head and neck cancer| Japan   | Asian     | HB      | PCR-RFLP | 140       | 223         | 0.852   |
| Hirata et al. [18]     | 2004 | Renal cell cancer | Japan   | Asian     | PB      | PCR-RFLP | 156       | 230         | 0.871   |
| Lin et al. [19]        | 2004 | Oral cancer       | Taiwan  | Asian     | HB      | Sequencing| 121       | 147         | 0.336   |
| Matsumura et al. [20]  | 2004 | Gastric cancer    | Japan   | Asian     | HB      | PCR-RFLP | 215       | 166         | 0.432   |
| Zinnozdohoué et al. [21]| 2004 | Head and neck cancer| France  | Caucasian | HB      | PCR-RFLP | 125       | 249         | 0.978   |
| Fang et al. [22]       | 2005 | Lung cancer       | China   | Asian     | HB      | PCR-RFLP | 243       | 350         | 0.000   |
| Jin et al. [23]        | 2005 | Gastric cancer    | China   | Asian     | HB      | PCR-RFLP | 417       | 350         | 0.000   |
| Ju et al. [24]         | 2005 | Cervical cancer   | Korea   | Asian     | HB      | TaqMan   | 232       | 332         | 0.695   |
| Lai et al. [25]        | 2005 | Cervical cancer   | Taiwan  | Asian     | HB      | Other    | 197       | 197         | 1.000   |
| McCready et al. [26]   | 2005 | Glioblastoma      | America | Caucasian | HB      | PCR-RFLP | 81        | 57          | 0.916   |
| Cao and Li [27]        | 2006 | Oral cancer       | China   | Asian     | HB      | PCR-RFLP | 96        | 120         | 0.657   |
| Elander et al. [28]    | 2006 | Colorectal cancer | Sweden  | Caucasian | HB      | Other    | 127       | 208         | 0.918   |
| Kader et al. [29]      | 2006 | Bladder cancer    | America | Caucasian | HB      | TaqMan   | 556       | 555         | 0.565   |
| Li et al. [30]         | 2006 | Ovarian cancer    | China   | Asian     | HB      | PCR-RFLP | 122       | 151         | 0.008   |
| Liëvre et al. [31]     | 2006 | Colorectal cancer | France  | Caucasian | HB      | Other    | 591       | 561         | 0.900   |
| O-charoenrat et al. [32]| 2006 | Head and neck cancer| Thailand| Asian     | HB      | PCR-RFLP | 300       | 300         | 0.988   |
| Su et al. [33]         | 2006 | Lung cancer       | America | Caucasian | PB      | TaqMan   | 2014      | 1323        | 0.597   |
| Sugimoto et al. [34]   | 2006 | Endometrial cancer| Japan   | Asian     | HB      | PCR-RFLP | 107       | 213         | 0.768   |
| Xu et al. [35]         | 2006 | Colorectal cancer | China   | Asian     | HB      | Other    | 126       | 126         | 0.938   |
| Albayrak et al. [36]   | 2007 | Prostate cancer   | Turkey  | Caucasian | HB      | PCR-RFLP | 55        | 43          | 0.000   |
| Ju et al. [37]         | 2007 | Ovarian cancer    | Korea   | Asian     | HB      | TaqMan   | 133       | 332         | 0.695   |
| Lei et al. [38]        | 2007 | Breast cancer     | Sweden  | Caucasian | PB      | TaqMan   | 954       | 947         | 0.151   |
| Lu et al. [39]         | 2007 | Other cancer      | China   | Asian     | HB      | PCR-RFLP | 221       | 366         | 0.000   |
| Nasr et al. [40]       | 2007 | Nasopharyngeal cancer| Tunisia| Caucasian | HB      | PCR-RFLP | 174       | 171         | 0.091   |
| Nishizawa et al. [41]  | 2007 | Oral cancer       | Japan   | Asian     | HB      | TaqMan   | 170       | 164         | 0.493   |
| Piccoli et al. [42]    | 2007 | Renal cell carcinoma| Brazil  | Caucasian | PB      | PCR-RFLP | 99        | 118         | 1.000   |
| Vairaktaris et al. [43]| 2007 | Oral cancer       | Greece  | Caucasian | HB      | PCR-RFLP | 156       | 141         | 0.276   |
| Woo et al. [44]        | 2007 | Colorectal cancer | Korea   | Asian     | HB      | PCR-RFLP | 185       | 304         | 0.488   |
| Zhai et al. [45]       | 2007 | Hepatocellular cancer| China  | Asian     | HB      | Sequencing| 431       | 479         | 0.559   |
| Zhou et al. [46]       | 2007 | Nasopharyngeal cancer| China  | Caucasian | PB      | Sequencing| 829       | 759         | 0.634   |
| Dos Reis et al. [47]   | 2008 | Prostate cancer   | Brazil  | Caucasian | PB      | TaqMan   | 100       | 100         | 0.293   |
| González-Arriaga et al. [48]| 2008 | Lung cancer       | Spain   | Caucasian | HB      | PCR-RFLP | 501       | 510         | 0.934   |
| Kouhkan et al. [49]    | 2008 | Colorectal cancer | Iran    | Asian     | HB      | PCR-RFLP | 150       | 100         | 0.935   |
| Shimizu et al. [50]    | 2008 | Tongue cancer     | Japan   | Asian     | HB      | TaqMan   | 69        | 91          | 0.585   |
| Tasci et al. [51]      | 2008 | Bladder cancer    | Turkey  | Caucasian | HB      | PCR-RFLP | 102       | 94          | 0.740   |

**Table 1:** The main characteristics of studies included in the meta-analysis.
analysis (Table 1) [7–83]. Of these, 43 articles were conducted among Asian populations and 34 among Caucasian populations; 67 studies were hospital-based and 10 were population-based. Of the different genotyping methods used in these studies, 45 used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), 18 used TaqMan real-time PCR, 8 used sequencing, and 6 used other methods. Sixteen of the 77 articles showed deviations from HWE in control groups.

3.2. Quantitative Analysis. The main results of this meta-analysis are listed in Table 2. The association between the MMP1–1607 (1G>2G) polymorphism and cancer risks was seen in the allele model (2G vs. 1G, OR: 1.174, 95% CI: 1.107–1.244; Figure 2), the dominant model (2G2G/1G2G vs. 1G1G, OR: 1.192, 95% CI: 1.109–1.303; Figure 3), and the recessive model (2G2G vs. 1G2G/1G1G, OR: 1.231, 95% CI: 1.141–1.329; Figure 4).

3.3. Risk by Cancer Type. When we considered different cancer types, elevated risk was found in lung cancer in the allele model (2G vs. 1G, OR: 1.127, 95% CI: 1.002–1.268) and the dominant model (2G2G/1G2G vs. 1G1G, OR: 1.127, 95% CI: 1.005–1.264).

Significant association was also found in colorectal cancer in the allele model (2G vs. 1G, OR: 1.281, 95% CI: 1.033–1.588), and the recessive model (2G2G vs. 1G2G/1G1G, OR: 1.368, 95% CI: 1.094–1.712).
Five articles addressed the MMP1-1607 polymorphism in nervous system cancers, including astrocytoma, glioblastoma, hypothalamic adenoma, and malignant gliomas. Significantly elevated risks were observed in all the three different models (2G vs. 1G, OR: 1.799, 95% CI: 1.493–2.168; 2G2G vs. 1G1G, OR: 2.070, 95% CI: 1.474–2.906; and 2G2G vs. 1G2G/1G1G, OR: 1.935, 95% CI: 1.498–2.501).

In renal cancer, the association was found in the allele model (2G vs. 1G, OR: 1.351, 95% CI: 1.149–1.590) and the recessive model (2G2G vs. 1G2G/1G1G OR: 1.674, 95% CI: 1.351–2.073). In bladder cancer, only in the recessive model (2G2G vs. 1G2G/1G1G, OR: 1.431, 95% CI: 1.013–1.821) was significant association detected (2G2G vs. 1G2G/1G1G, OR: 1.126, 95% CI: 1.015–1.249; and 2G2G vs. 1G2G/1G1G, OR: 1.249, 95% CI: 1.013–1.573). In the random-effects model, or homozygous model, but showed a decreasing trend in the recessive model (Table 2).

3.4. Risk by Ethnicity. In the Asian population, the association between the variation and cancer risks was detected in the allele model (2G vs. 1G, OR: 1.228, 95% CI: 1.130–1.334), the dominant model (2G2G/1G2G vs. 1G1G, OR: 1.256, 95% CI: 1.084–1.456), and the recessive model (2G2G vs. 1G2G/1G1G, OR: 1.297, 95% CI: 1.176–1.431).

In the Caucasian population, evaluated risk was also found in the allele model (2G vs. 1G, OR: 1.109, 95% CI: 1.023–1.202), the dominant model (2G2G/1G2G vs. 1G1G, OR: 1.126, 95% CI: 1.015–1.249), and the recessive model (2G2G vs. 1G2G/1G1G, OR: 1.431, 95% CI: 1.013–1.289). Although significant differences were observed in both Asian and Caucasian populations, the Asian population showed higher risk than the Caucasian for the allele, dominant model, or homozygous model, but showed a decreasing trend in the recessive model (Table 2).

3.5. Heterogeneity and Sensitivity Analysis. Heterogeneity was observed in overall analyses in all comparison models with $P<0.05$ and $I^2$ range from 50.2% to 74.0% (indicating moderate or substantial heterogeneity). We therefore used the random-effects model. Sensitivity analysis to assess influence of individual studies showed no individual study to greatly affect the pooled OR.

3.6. Publication Bias. The forest plot seemed to be symmetrical (Figure 5). Harbord’s and Peter’s tests revealed no statistical significance in publication bias (Harbord’s: $P = 0.093$; Peter’s: $P = 0.153$).

4. Discussion

The MMP1-1607 (1G>2G) polymorphism has been associated with increased transcription of MMP1 due to an insert...
of a guanine base that creates a core-binding site for the EST family of transcription factors, which leads to increased susceptibility for tumor occurrence and progress. The significant association between the variation of MMP1–1607 (1G>2G) with some cancer types has been reported by different meta-analyses [3, 4, 84–86].

In the current meta-analysis of 77 articles with 21,327 cancer patients and 23,245 controls, the MMP1–1607 (1G>2G) polymorphism was a strong risk factor in various cancers. Although both Asian and Caucasian individuals with 2G alleles or 2G2G genotypes may be more susceptible to cancer development, several studies revealed significant
associations in Asians, but not Caucasians [5, 6]. These discrepancies might be due to limited sample sizes. Moreover, the Asian population seemed to show increased risk compared with Caucasian populations when the allele or dominant models were adopted, whereas a decreasing trend was observed in a recessive model, which implies different susceptibilities.

The association was found in lung, colorectal, nervous system, renal, bladder, and nasopharyngeal cancers, but not gastric, oral, ovarian, breast, prostate, head-and-neck, endometrial, hepatocellular, or esophageal cancers, which indicates that the variation plays different roles in various cancers, in accordance with previous meta-analyses [4, 85, 87, 88]. However, these papers only focused on single types.
of cancer or one specific ethnicity. Our meta-analysis included all the cancers, analyzed the overall pooled OR, and performed subgroup analyses. Our findings imply a complex relationship between cancer susceptibility and gene variation, influenced by cancer sites and ethnicities.

Recently, the functional studies of SNPs have moved fast. For instance, a study reported that a missense variant rs149418249 in the TTP1 gene confers colorectal cancer risk by interrupting TTP1–TIN2 interaction and influencing telomere length [89]. An expression quantitative trait locus-based analysis revealed that a mutation rs27437, residing in the upstream of SLC22A5, can affect colorectal cancer risk by regulating SLC22A5 expression [90]. Another article reported that a TCF7L2 missense variant rs138649767...

**Figure 4:** Forest plot of MMP1–1607 (1G>2G) polymorphism and cancer risks in the recessive model (2G2G vs. 1G2G/1G1G).
associates with colorectal cancer risk by interacting with a GWAS-identified regulatory variant rs698326 in the MYC enhancer [91]. However, the biological mechanisms of functional SNPs still remain challenging. Therefore, further studies are required to promulgate the real functions by which the MMP1–1607 (1G>2G) polymorphism may influence cancer susceptibility and progression.

Our study had some limitations. First, moderate or substantial heterogeneity was detected between studies, which was not significantly decreased by subgroup analysis. When all variations were included in the meta-regression analysis, no obvious factors were detected. More subgroup analyses should be performed, based on factors such as tobacco or alcohol consumption. This conclusion should be interpreted with caution. Second, this analysis was performed with candidate gene strategy in which the MMP1–1607 (1G>2G) polymorphism was selected for study based on a priori knowledge of the gene’s biological functional impact on the trait or disease in question [92]. Genome-wide association studies (GWAS) which scan the entire genome for genetic variation include immense amounts of SNPs. Published papers usually reported those SNPs with highly statistical significance (usually $P < 10^{-6}$). We have retrieved literature through PubMed in order to search the evidence of association between the MMP1–1607 (1G>2G) polymorphism and cancer risks in GWAS results [92, 93]. However, we did not acquire any positive findings. We speculate that ethnic discrepancy, population stratification, and different standards of statistical significance might lead to negative findings in GWAS. Third, due to the innate shortage of case–control designed studies, the quantity of studies was limited. Third, gene–gene and gene–environment interactions should be considered in analyses of the effects of genes. Fourth, more original papers with large sample sizes were required due to lack of eligible studies in specific cancers in this analysis.

5. Conclusions

In conclusion, an association between the MMP1–1607 (1G>2G) polymorphism and cancer risks was detected in both Asians and Caucasians. After stratification by cancer types, associations were found for lung cancer, colorectal cancer, nervous system cancer, renal cancer, bladder cancer, and nasopharyngeal cancer. More original studies with larger sample size are required for future analysis.

Conflicts of Interest

The authors declare no competing financial interests.

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