

Correlation of MMP2-C1306T (rs243865) and MMP7-181A/G (rs11568818) with cervical cancer: a meta-analysis

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Summary

Objective: We aimed to determine whether a correlation exists between the polymorphisms of matrix metalloproteinases (MMPs) MMP2-C1306T (rs243865) and MMP7-181A/G (rs11568818) and cervical cancer (CC). **Methods:** A literature search up to September 28, 2018, in PubMed, the Cochrane Library, and Embase was conducted. Odds ratio (OR) and 95% confidence interval (CI) were used as effect models. The quality, heterogeneity, and publication bias of the included studies were assessed. **Results:** Five studies with a total of 1,630 participants were included. For the G vs. A and GG vs. AA model of the rs11568818 gene, no significant heterogeneity was found ($p < 0.05$, $I^2 > 50\%$). No statistical significance was found for all the rs243865 models, indicating no significant association between rs243865 and CC. The meta-analysis of the rs11568818 gene polymorphism revealed a statistical significance for G vs. A (OR = 1.3719; 95% CI, 1.1480–1.6395; $P = 0.0005$), GG vs. AA (OR = 1.8561; 95% CI, 1.2682–2.7165; $P = 0.0015$), and GG vs. AA+GA (OR = 1.7448; 95% CI, 1.0104–3.0130; $P = 0.0458$). No publication bias was found for all the rs11568818 and rs243865 models, which suggested that the present results were reliable. **Conclusions:** MMP7-181A/G (rs11568818) was associated with CC; however, MMP2-C1306T (rs243865) was not associated with CC.

Key words: Cervical cancer; Gene polymorphism; Matrix metalloproteinases; Meta-analysis.

Introduction

Cervical cancer (CC) is the fourth most common cancer and cause of cancer deaths in women [1]. In 2012, approximately 528,000 new cases and 266,000 deaths were reported [1]. Approximately 95% of cases result from persistent infection with carcinogenic human papillomavirus (HPV) infections [2]. CC in the early stages can be treated with radiotherapy or surgery, whereas metastatic CC is incurable [3]. Understanding the molecular mechanisms underlying this disease may provide insights into the treatment of CC.

Abnormal genetic variation in certain genes of the susceptible population was confirmed to change the risk of CC in this population [4]. Matrix metalloproteinases (MMPs) play major roles in cell proliferation, differentiation, apoptosis, angiogenesis, migration, and host defense [5]. MMPs are the main component of proteolytic enzymes, which are involved in cancer metastasis and invasion [6]. Four polymorphisms, including MMP9-1562 C > T, MMP7-181 A > G, MMP-2 1306 C > T, and MMP1-16071G/2G, may be associated with genetic susceptibility to cancers [7, 8]. The correlation between MMP gene polymorphisms and CC has been studied by many researchers [9–11]. For example, Singh *et al.* [12] indicated that the -1306 C > T functional polymorphism in MMP-2 showed protective roles against HPV-mediated CC based on the data of 150 patients with invasive CC and 150 healthy controls. Su *et al.* [13] suggested that people with the MMP-7-181G/G homozygous genotype had a higher risk of CC by studying 217 cases.

However, in the previous studies, the research was incomplete, as some studies only focused on MMP7-181A/G and others investigated only MMP2-C1306T, with small sample sizes. Therefore, further research is needed to study the correlation of MMP polymorphisms and CC.

In the present study, we conducted a meta-analysis to evaluate the results of published studies about the association between the polymorphisms of MMP2-C1306T (rs243865) and MMP7-181A/G (rs11568818) and CC.

Materials and Methods

In accordance with our search strategy, articles from electronic databases, including PubMed, the Cochrane Library, and Embase, were retrieved to find related studies. The literature tracing method was also used in the search. The literature search was performed using the following keywords: (“cervical squamous cell carcinoma” OR “cervical cancer” OR “cervical carcinoma” OR “carcinoma of cervix” OR “carcinoma of uterine cervix”) AND MMP-related genes (“MMPs” OR “matrix metalloproteinases” OR “matrix metalloprotei*” OR “MMP” OR “rs243865” OR “rs11568818” OR “MMP2” OR “MMP7” OR “MMP-2” OR “MMP-7”) AND gene polymorphism (“poly-morphi*” OR “genetic” OR “variant”). The articles searched were those published up to September 28, 2018, without language restriction.

The searched studies were included in the analysis if they (1) reported the distribution of rs243865 and rs11568818 mutation gene frequencies in patients with and without CC,

Table 1. — Characteristics of the included studies

Author	Public year	Study location	Detection method	Studyyear	Controlsource	CC	C	CC	C	CC	C	Gene	NOS
						N	Age (y)	Smoking					
Baltazar-Rodriguez LM [20]	2008	Mexico	PCR	2005.4-2006.7	Healthy	54	126	43.5 ± 14.5	41.8 ± 9.1	13	27	rs243865	8
Singh HO [19]	2008	India	PCR-RFLP	2005.1-2007.4	Healthy	137	146	47.2 ± 8.8	48.3 ± 8.3	51	17	rs11568818	6
Singh N [11]	2015	India	ARMS-PCR	NA	Healthy	150	150	Mean: 50	Mean:50	NA	NA	rs243865	8
Wu SH [12]	2011	China	ARMS-PCR	2008.1-2008.12	Without history of gynecology diseases	217	190	50 (25-75)	NA	NA	NA	rs11568818	6
Xie BB [1]	2015	China	PCR-RFLP	2013.1-2015.1	Healthy	230	230	53.6 ± 7.3	54.3 ± 9.8	42	57	rs243865, rs11568818	7

CC: Cervical cancer; C: Control; NOS: Newcastle-Ottawa Scale; N: The total number of including; ARMS-PCR: Amplification refractory mutation system polymerase chain reaction; RFLP: Restriction fragment length polymorphism.

Table 2. — Results of Meta-analysis

SNP	Model	Sample size		Test of association		Model	Test of heterogeneity ^{a,b}				Egger's test ^c	
		Cases	Control	OR(95%CI)	Z		p-value	Q	p-value	I ² (%)		t
rs243865	T vs. C	960	1012	0.7752 [0.2820; 2.1307]	0.49	0.6216	Random	38.18	< 0.01	94.8	0.8369	0.5564
	TC vs. CC	426	454	0.4222 [0.0899; 1.9825]	1.09	0.2745	Random	29.53	< 0.01	93.2	61.113	0.01042
	TT vs. CC	392	387	1.0871 [0.3313; 3.5672]	0.14	0.8905	Random	12.75	< 0.01	84.3	0.1683	0.8938
	TT vs. CC+TC	480	506	1.1586 [0.4655; 2.8835]	0.32	0.7517	Random	7.66	0.02	73.9	0.3172	0.8045
	TT+TC vs. CC	480	506	0.6545 [0.1877; 2.2830]	0.66	0.5061	Random	36.76	< 0.01	94.6	1.5311	0.3683
rs11568818	G vs. A	1194	1164	1.3719 [1.1480; 1.6395]	3.48	0.0005	Fixed	1.08	0.58	0	1.172	0.4497
	GA vs. AA	501	518	1.2807 [0.7502; 2.1862]	0.91	0.3646	Random	8.18	0.02	75.5	0.05544	0.9647
	GG vs. AA	372	373	1.8561 [1.2682; 2.7165]	3.18	0.0015	Fixed	2.38	0.3	16.1	5.7725	0.1092
	GG vs. AA+GA	597	582	1.7448 [1.0104; 3.0130]	2	0.0458	Random	4.23	0.12	52.7	1.3086	0.4154
	GG+GA vs. AA	597	582	1.3736 [0.9647; 1.9558]	1.76	0.0783	Random	4.24	0.12	52.8	0.2225	0.8606

^aRandom-effects model was used when the p-value for heterogeneity test < 0.05, otherwise the fixed-effect model was used. ^bp-value < 0.05 is considered statistically significant for Q statistics. ^cEgger's test to evaluate publication bias, p-value < 0.05 is considered statistically significant. OR: Odds ratio; CI: confidence interval.

(2) provided data on an accurate genotype or allele frequency, and (3) were case-control studies. Furthermore, studies with incomplete data that could not be applied to the statistical analysis, reviews, reports, letters, and comments were excluded. If one article was published repeatedly or the same data were used for multiple studies, only the latest published article or article with the most complete information was included.

The following data were extracted from each study by two investigators independently: study location, year of study, publication year, first author, detection method of the gene polymorphism, source population of the control samples, numbers of case samples (CC) and control samples (non-CC), some demographic characteristics (age, number of smokers, etc.), as well as rs243865 and rs11568818 gene distributions. The Newcastle-Ottawa Scale (NOS) [14] was applied to assess the quality of the articles included in the present study. Discrepancies were resolved through a discussion with the third investigator.

Hardy-Weinberg equilibrium (HWE) tests [15] were performed using the chi-square test. The R 3.12 software was used for the meta-analysis, and odds ratio (OR) and 95% confidence interval (95% CI) were applied as effect models [16]. The heterogeneity across the studies was characterized using the I^2 and Cochran Q statistics [17]. If the p value < 0.05 or the I^2 value $> 50\%$, which indicated no heterogeneity between the studies, the random-effect model was applied. Otherwise, the fixed-effect model was applied [18]. Publication bias was assessed as inferred from the Egger test result [19].

Results

As presented in Figure 1, the authors found 93 articles in the initial search. After the preliminary screening, 93 articles (PubMed, 43; Embase, 39; and the Cochrane Library, 11) were included. A total of 20 articles remained after eliminating 24 duplicate studies and 49 obviously unrelated studies. Then, one letter/editorial and two case series/reports were removed after abstract screening, and 12 articles were eliminated after full-text screening. Finally, five studies [11-13, 20, 21] were included in this meta-analysis.

A total of 1,630 participants (788 patients with CC and 842 patients without CC) were included in the meta-analysis. Among these patients, 842 without CC included female healthy controls and women who visited gynecology outpatient department clinics for routine checkup, without any medical history of gynecological diseases, including cervical diseases. The publications dates of the included studies ranged from 2008 to 2015, and the study locations included India, Mexico, and China. The detection methods were mainly amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP). The NOS scores of the participants in the two groups ranged from 6 to 8, indicating that all the included studies were

high quality. The HWE test results showed that only the participants in the control groups of Singh *et al.* [20] and Baltazar-Rodriguez *et al.* [21] were in accordance with the HWE (Table 1).

We performed a meta-analysis for the different gene models of rs243865 and rs11568818, which included the allelic genetic model (rs243865, T vs. C; rs11568818, G vs. A), the co-dominant genetic model (rs243865, TC vs. CC, TT vs. CC; rs11568818, GA vs. AA, GG vs. AA), the recessive genetic model (rs243865, TT vs. CC+TC; rs11568818, GG vs. AA+GA), and the dominant genetic model (rs243865, TT+TC vs. CC; rs11568818, GG+GA vs. AA).

The pooled effect model was calculated using p and I^2 values. The heterogeneity test revealed no significant heterogeneity for the “G vs. A” and “GG vs. AA” models of the rs11568818 gene ($P < 0.05$, $I^2 > 50\%$); thus, we used the fixed-effect model to calculate the pooled 95% CI and OR. Furthermore, the random-effect model was selected to calculate the values for the other models (Table 2).

The meta-analysis for the rs243865 gene polymorphism revealed no statistically significant differences for all the models (T vs. C: OR = 0.7752; 95% CI, 0.2820–2.1307; $P = 0.6216$; TC vs. CC: OR = 0.4222; 95% CI, 0.0899–1.9825; $P = 0.2745$; TT vs. CC: OR = 1.0871; 95% CI, 0.3313–3.5672; $P = 0.8905$; TT vs. CC+TC: OR = 1.1586; 95% CI, 0.4655–2.8835; $P = 0.7517$; TT+TC vs. CC: OR = 0.6545; 95% CI, 0.1877–2.2830; $P = 0.5061$), indicating no significant association between rs243865 and CC (Figure 2, Table 2). The meta-analysis for the rs11568818 gene polymorphism revealed statistically significant differences for G vs. A (OR = 1.3719; 95% CI, 1.1480–1.6395; $P = 0.0005$), GG vs. AA (OR = 1.8561; 95% CI, 1.2682–2.7165; $P = 0.0015$), and GG vs. AA+GA (OR = 1.7448; 95% CI, 1.0104–3.0130; $P = 0.0458$). No statistically significant difference was found for the other models. Therefore, “G” in rs11568818 might be a risk factor (Figure 3, Table 2).

No publication bias was found as inferred from the Egger test result for all the models of rs11568818 and rs243865, which suggested that the present results were reliable (Table 3).

Discussion

Several research studies have reported the possible relationship between MMP polymorphisms and the risk of CC, whereas the previous research studies are incomplete and included small samples [12, 13]. Meta-analysis is recognized as a useful method for examining inconsistent results because it can increase the statistical power and sample size of a study [22]. In this study, we performed a meta-analysis to determine whether a correlation existed between the polymorphisms of MMP2-C1306T (rs243865) and MMP7-181A/G (rs11568818) and CC. Our results suggested that the rs11568818 gene was associated with CC, but showed no significant correlation between rs243865

and CC.

MMP7 and MMP2 were found to be overexpressed in cancers [23]. Yao *et al.* [24] reported a close correlation between the MMP7-181A/G polymorphism and early-stage CC. Some other studies suggested the correlation between the MMP7 polymorphism and cancers such as colorectal [25] and endometrial cancers [26]. Adabi *et al.* [27] reported no association between the MMP2 polymorphism and susceptibility to cancers. Furthermore, the results of a meta-analysis suggested that the MMP7 polymorphism had a significant association with metastasis in some cancers, but no significant associations was found between MMP2-C1306T and metastasis [6]. The result of the meta-analysis by Zhu *et al.* [28] concerning the correlation between the MMP1 and MMP7 polymorphisms and CC confirmed the significant association between the MMP7 polymorphism and susceptibility to CC. Thus, the results of the present meta-analysis were in line with the results of the previous studies. In addition, an *in vitro* experiment revealed that the basal transcriptional activity of the G allele was greater than that of the A allele [29], which suggested that the transition from A to G at the -181 base pair might affect the development of CC by increasing the basal transcriptional activity. On the basis of the present results, we concluded that there was a relationship between MMP7-181A/G (rs11568818) and the development of CC.

Some limitations of the present study should be discussed as follows: (1) Owing to some studies with incomplete data and the small sizes of the samples included, no corrections were made for the covariate and subgroup analyses. (2) Only the participants in the control group of Singh *et al.* [20] and Baltazar-Rodriguez *et al.* [21] were in accordance with the HWE, which suggested that the representativeness of the study populations was relatively poor. (3) A significant heterogeneity was found in some models. The possible sources of heterogeneity might be the different regions such as living environments, economic development, and regional living habits, and the effect of other factors such as age. Further high-quality studies with large sample sizes are needed.

The present study shows that MMP7-181A/G (rs11568818) is associated with the development of CC and, thus, may be regarded as a risk factor for CC.

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Conflict of Interest

The authors declare no conflict of interest.

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