Observational Study

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MMP-3 gene regulates the carcinogenesis and metabolic process of ovarian cancer, evidence from a Chinese population

Observational study and meta-analysis

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Abstract

The current investigation aims to explore the relationship between matrix metalloproteinase-3 (MMP-3) gene polymorphism and ovarian cancer (OC) risk. Two hundred forty pathologically confirmed OC patients and 390 healthy controls participated in the present investigation. Polymerase chain reaction-restriction fragment length polymorphism was applied to investigate the present polymorphism. At the same time, the meta-analysis was also performed to comprehensively explore the relationship. Three genotypes (5A/5A, 5A/6A, and 6A/6A) were observed for MMP-3 gene polymorphism. 6A/6A genotype and 6A allele displayed significant increase in OC patients (all $P < .05$). Meta-analysis found that no significant results (all $P > .05$). In conclusion, our results indicate that MMP-3 gene polymorphism contributes increased risk to OC for southern Chinese population. And meta-analysis indicates that MMP-3 gene polymorphism contributes no risk to OC in other populations.

Abbreviations: DNA = deoxyribonucleic acid, MMP-3 = matrix metalloproteinase-3, OC = ovarian cancer.

Keywords: gene polymorphism, immunotherapy, metabolism, MMP-3, ovarian cancer.

1. Introduction

With insidious onset, rapid disease progression, and high mortality, ovarian cancer (OC) causes great harm to women's life and health.[1,2] Despite the continuous improvement of medical level and the continuous optimization of epithelial ovarian cancer treatment plans, the 5-year survival rate of advanced OC remains lower than 30%.[3,4] Therefore, early prediction of the prognosis of OC patients and early treatment are of great significance to improve the survival rate of patients.

The pathogenesis of OC has not been clearly defined so far, which involves the abnormal expression of various oncogene and tumor suppressor genes. Studies have reported that tumor metastasis is the main risk factor for ovarian cancer progression, and the polymorphism of genes regulating OC metastasis participates in OC pathogenesis.[5,6] Single nucleotide polymorphism is a common form of gene variation, with one single nucleotide polymorphism locus for every 1000 nucleotides, which has a crucial role in the tumor pathogenesis. The abnormal expression of matrix metalloproteinase-3 (MMP-3) participates in the occurrence of OC. However, the previous results about MMP-3 gene polymorphism and OC risk were inconsistent.[7–9] Therefore, we would like to investigate the above association by conducting experiment and meta-analysis to further explore the relationship.

2. Materials and methods

2.1. Research objects

Totally, 240 OC patients hospitalized in Suzhou Municipal Hospital from March 1, 2020 to March 31, 2023 were selected. Inclusion criteria: (1) compliance with the International Federation of Gynecology and Obstetrics classification criteria and World Health Organization classification criteria,[10] and pathological diagnosis of OC; (2) Suitable for tumor cell reduction surgery, and able to cooperate with this study and complete medical records. Exclusion criteria: (1) patients who had received preoperative radiotherapy, chemotherapy or

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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hormone therapy; (2) patients with other malignant tumors and autoimmune diseases were lost to follow-up during the follow-up and were unable to cooperate with this researcher. Three hundred ninety normal healthy women were enrolled as the group of control population. The current investigation was authorized by the ethics committee of Suzhou Municipal Hospital, and we also have obtained the informed consent from all patients.

2.2. Gene polymorphism analysis

One venous blood tube (about 3 mL) was collected in the morning and was placed in ethylenediaminetetraacetic acid anticoagulant tube for deoxyribonucleic acid (DNA) extraction. DNA extraction was conducted by applying whole blood DNA purification kit (Thermo Fisher Company, Waltham). Shanghai Tianhao Biotechnology Co., Ltd. was responsible for Primer synthesis. Polymerase chain reaction-restriction fragment length polymorphism method was used for amplification. The polymerase chain reaction system was based on reports from previous literatures. ABI3730XL was sampled and its Gene polymorphism was analyzed with gene Mapper 4.1, and the results were further verified by sequencing.

2.3. Meta-analysis process

All eligible studies included in the present meta-analysis should be searched, reviewed and extracted by 2 experienced authors. The famous databases consisted of Pubmed database, Cochrane library, Embase database. Some important information should be reviewed and extracted including name of first author, publication year, and ethnic, source of control, genotyping method, sample size, genotype frequency, allele frequency and Hardy–Weinberg equilibrium conformity. All methods applying the present meta-analysis were based on published literatures.[11–24]

2.4. Statistical analysis

SPSS17, STATA11 software, t test, $\chi 2$ test statistic tools were applied in our investigation, as reported by previous literatures.[11,15,16,25,26] Only $P < .05$ was deemed to have a significant association.

3. Results

3.1. General information of study subjects

The important information was shown in Table 1, which consisted of age, menstruation status, history of abortion, number of births. The general information indicated that no significant difference was observed ($P > .05$).

3.2. Results of MMP-3 gene polymorphism

Three genotypes were observed for MMP-3 gene polymorphism. 6A/6A genotype and 6A allele displayed significant increase (all $P < .05$). Table 2 showed the whole data and information.

3.3. Meta-analysis results

Figure 1 showed the flow diagram for the present meta-analysis. A total of 3 literatures were enrolled and Table 3 showed the detailed information and data, which was extracted from the above literatures. Table 4 was the literature assessment by NOS. The population of 4 literatures was Caucasians and Asians. They showed different sample size, genotyping methods, genotype frequency, and allele frequency. No significant associations were found by any genetic model (Figs. 2–5). We found that MMP-3 gene polymorphism conferred no risk for patients with OC. What's more, 6A/6A genotype and 6A allele were not risk factors for patients.

4. Discussion

OC mortality rate ranks the first in the mortality rate of malignant tumor of female reproductive system.[27,28] Its pathogenesis is still unclear. In addition to reproductive endocrine factors such as nonbirth, infertility, early menarche and late menopause, it is also related to genetics, environment and the use of hormone drugs. Due to various reasons, most cases have developed to International Federation of Gynecology and Obstetrics III or IV stage, so it is necessary to conduct in-depth research on its pathogenesis.

Table 1

The participates characteristics of both ovarian cancer group and control group.

Basic information		Control (N = 390)	Ovarian cancer (N = 240)	*P*
Age		38.4 ± 8.9	36.9 ± 11.3	.28
Number of births	0–1	264	149	.44
	≥2	126	91	
History of abortion	0–1	269	179	.41
	≥2	121	61	
Menstruation status	Premenopause	347	200	.28
	Menopause	43	40	
BMI	BMI < 18.5 kg/m^2	125	35	.09
	BMI ≥ 18.5 kg/m^2	265	205	

BMI = body mass index.

Table 2

Comparison of genotype and allele frequency between ovarian cancer group and control group.

	Control group (N = 390)		Ovarian cancer group (N = 240)			
MMP-3 polymorphism	n	Percentage (%)	n	Percentage (%)	OR (95%CI)[a]	*P**
5A/5A	98	25.3	32	13.3	1.00[REF]	
5A/6A	166	42.6	64	26.7	1.18 (0.72–1.93)	.508
6A/6A	126	32.3	144	60.0	3.50 (2.20–5.57)	0
5A	362	46.4	128	26.7	1.00[REF]	
6A	418	53.6	352	73.3	2.38 (1.86–3.05)	0

CI = confidential index, OR = odds ratio.

*Adjusted for sex and age by logistic regression model.

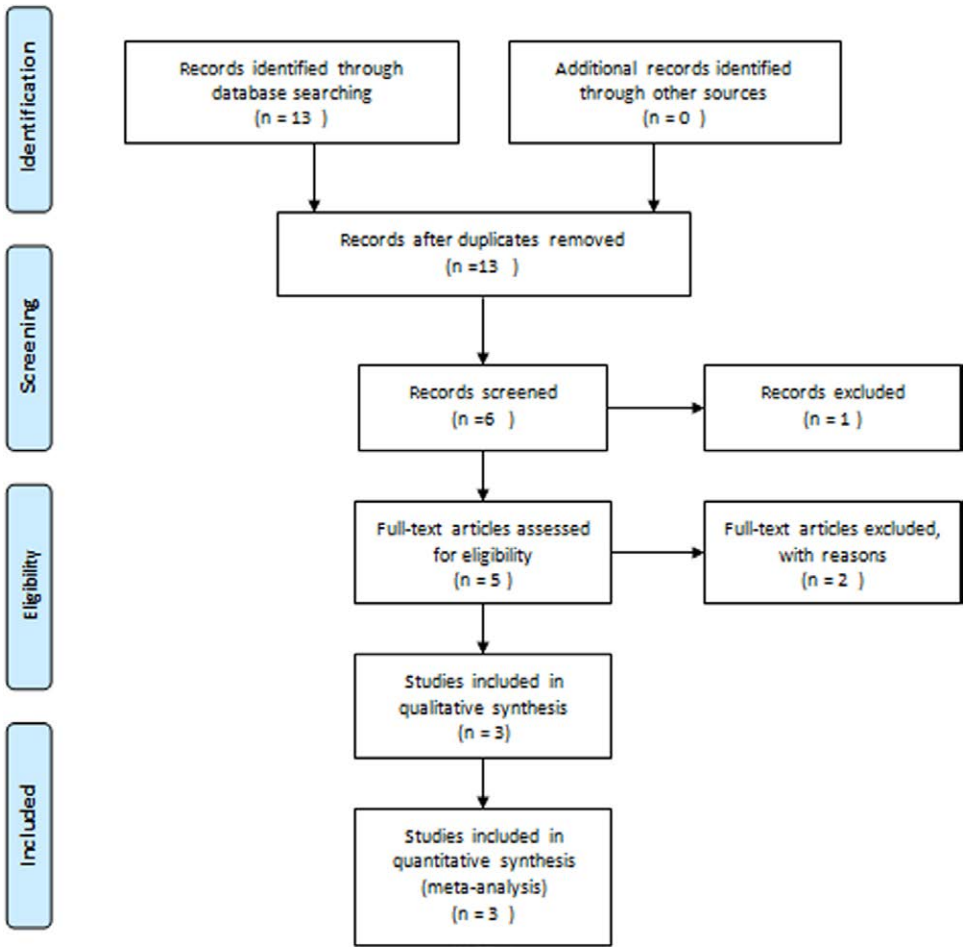

Figure 1. PRISMA 2009 flow diagram.

Table 3

Main characteristics of all case–control studies included in meta-analysis.

Literature	Ethnics (country)	Genotyping methods	Source of control	Sample size	HWE conformity	NOS	Year
Biondi et al	Caucasian (Italy)	PCR-RFLP	PB	100/236	Yes	8	2000
Smolarz et al	Caucasian (Poland)	PCR-RFLP	HB	100/100	Yes	7	2003
Li et al	Asian (China)	PCR-RFLP	PB	320/320	Yes	9	2006

HB = hospital-based, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle-Ottawa score, PB = population-based, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RFLP = restricted fragment length polymorphism.

Table 4

Quality assessment of the 7 case–control studies according to the Newcastle-Ottawa Scale.

Literature	Selection of enrolled study subjects	Between-group comparability	Exposure outcomes and factors	Total
Biondi et al	3	2	3	8
Smolarz et al	3	2	2	7
Li et al	4	3	2	9
Average	3.3	2.3	2.3	7.9

MMP-3 belongs to the MMP protein family and has protease activity, which can degrade extracellular matrix proteins and promote tumor cell metastasis. Our meta-analysis found no positive results. Interestingly; we found a significant association about the above association. At first, we were a little surprised and confused. But after deep thought and a review of previous published literatures, we decided that this was an explainable result. The results of gene polymorphism are affected by many factors such as region and race, which is an important reason why our results are different from those of previous studies. Although there is a study on Chinese population with negative results, China has more than 50 ethnic groups with 1.4 billion populations. The research population included in the present study belongs to the southern Chinese population, while the published literature studies the northern Chinese population. So we think current study is quite meaningful for enriching the library and are an encouraging finding.

There were no positive results in age, body mass index, birth time, abortion history or menstruation status between control group and OC group. The proportion of 6A allele and 6A/6A genotype of MMP-3 in the OC group was

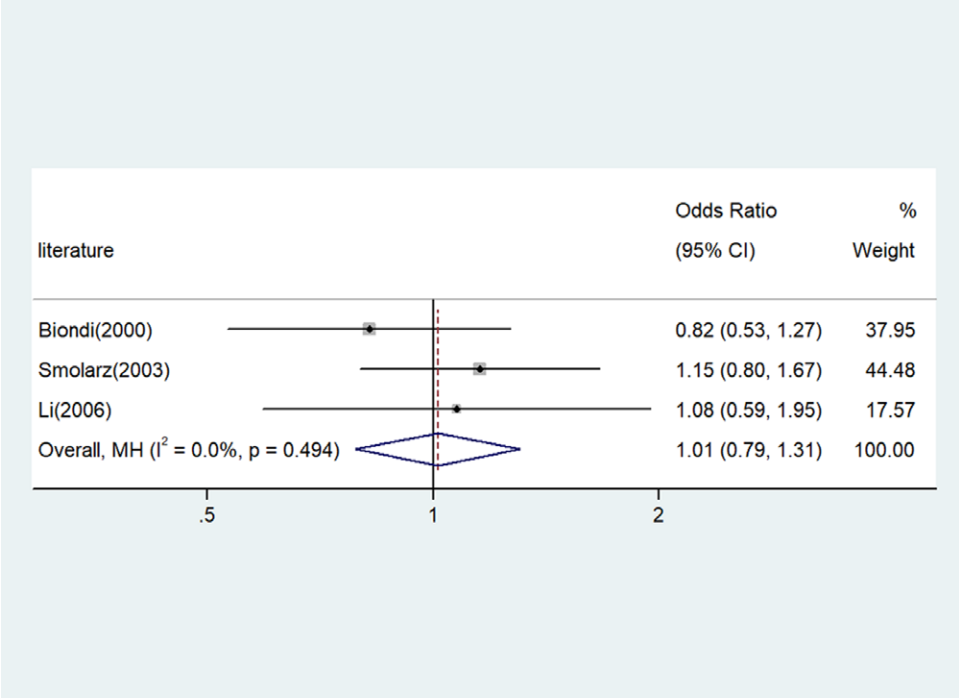

Figure 2. Forest plot for the associations between MMP-3 gene polymorphism and OC risk through allele contrast (6A vs 5A). CI = confidence interval; OC = ovarian cancer; OR = odds ratio.

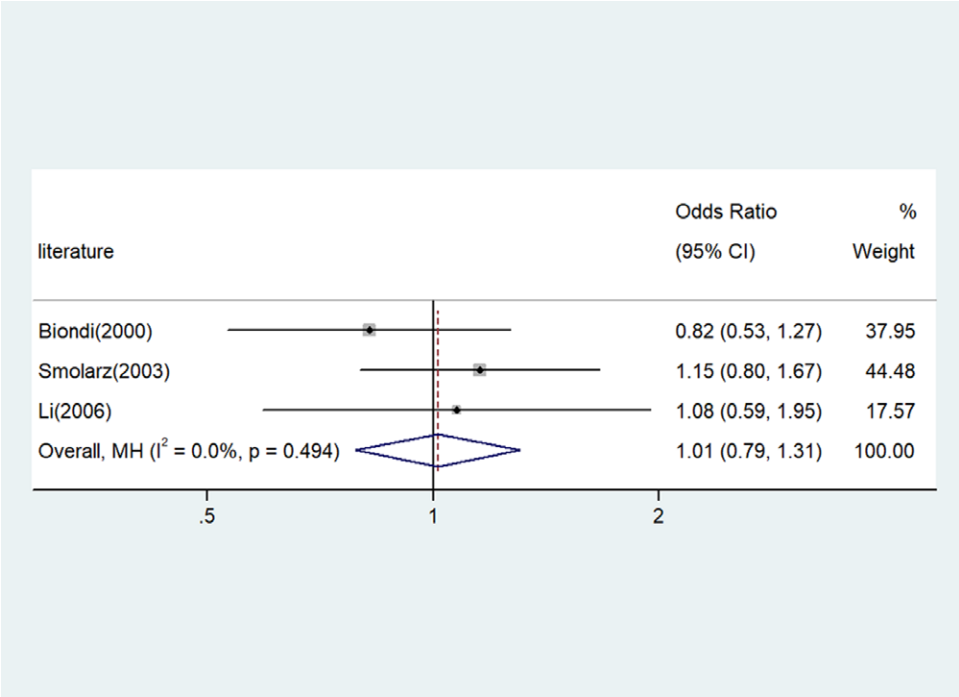

Figure 3. Forest plot for the associations between MMP-3 gene polymorphism and OC risk through homozygote comparison (6A/6A vs 5A/5A). CI = confidence interval; OC = ovarian cancer; OR = odds ratio.

significantly increased, indicating that OC occurrence was not related to clinical data such as age. It was related to MMP-3 gene polymorphism. The reason may be that MMP-3 is an oncogene, and MMP-3 includes 2 structural regions, the propeptide region and the catalytic region. The gene polymorphism of MMP-3 can up-regulates the expression of MMP-3 gene, and the promoter polymorphism of MMP-3 gene can up-regulate the expression of MMP-3. MMP-3 has extensive hydrolase activity in various extracellular matrix such as collagen, elastin, fibronectin, proteoglycan, and laminin.

We have to admit that the current research still has some shortcomings. First, some confounding factors were not included in the current study, which may affect the results to some extent. However, in future studies, we will include more epidemiological indicators to further improve our study. Second, bioinformatics

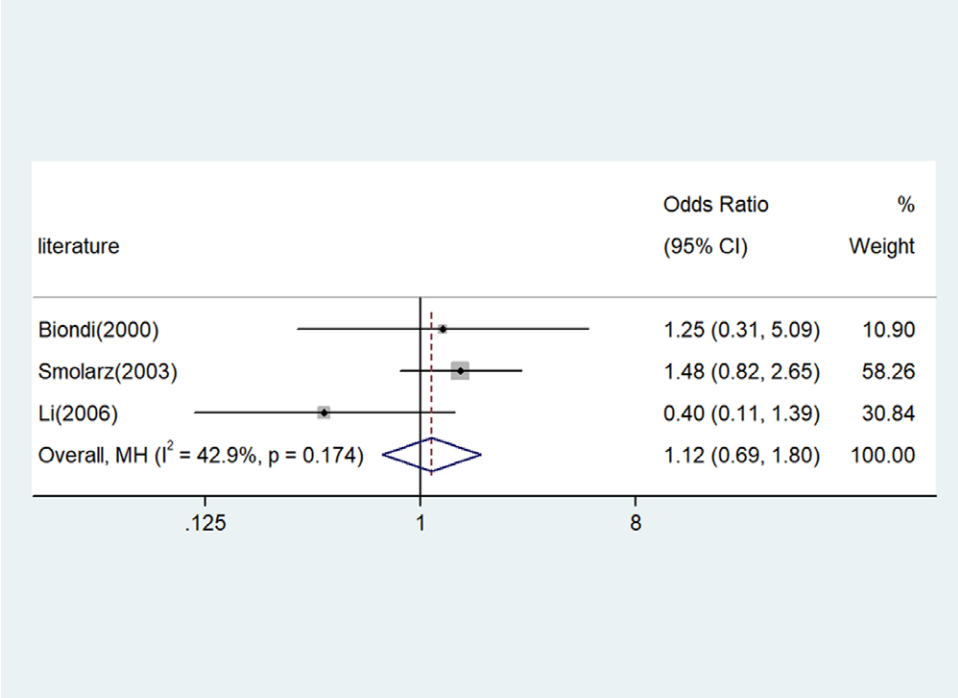

Figure 4. Forest plot for the associations between MMP-3 gene polymorphism and OC risk through recessive genetic model (6A/6A vs 6A/6A/5A/5A). CI = confidence interval; OC = ovarian cancer; OR = odds ratio.

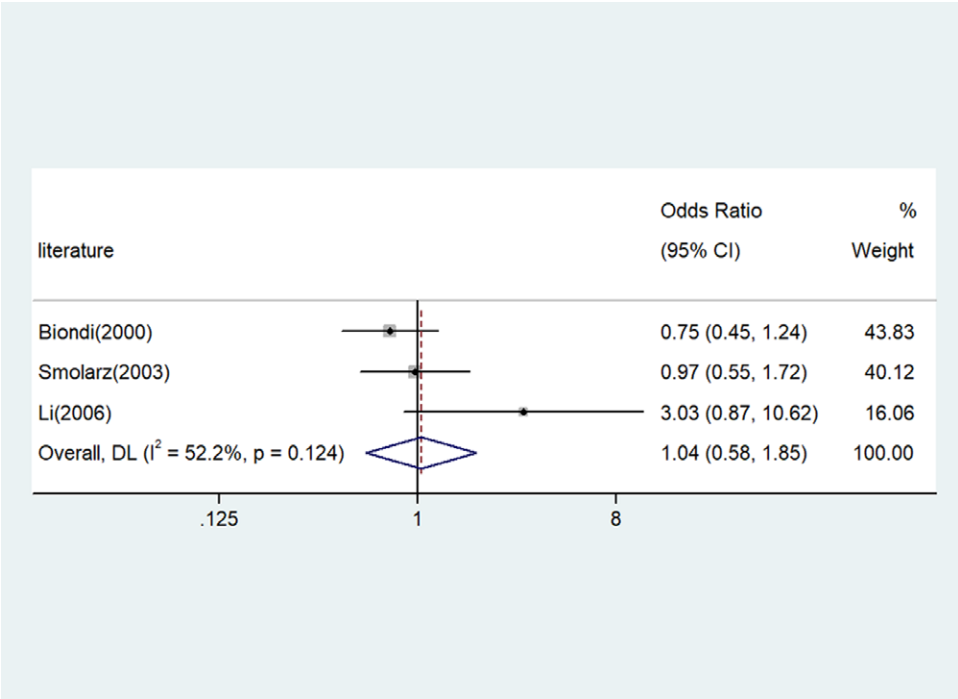

Figure 5. Forest plot for the associations between MMP-3 gene polymorphism and OC risk through dominate genetic model (6A/5A/5A/5A vs 6A/6A). CI = confidence interval; OC = ovarian cancer; OR = odds ratio.

analysis is a hot topic in current research. The same is true for bioinformatics analysis of OC. In future studies, we will combine gene polymorphism studies with biogenic analysis to further explore the pathogenesis of OC and guide clinical diagnosis and prognosis.

In a word, our results indicate that MMP-3 gene polymorphism contributes increased risk to OC for southern Chinese population. And meta-analysis indicates that there is no relationship between MMP-3 gene polymorphism and OC susceptibility in other populations.

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Author contributions

Conceptualization: Dan Si.
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Writing – original draft: Dan Si.
Writing – review & editing: Dan Si.

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