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ORIGINAL ARTICLE

The Role of O^6-methylguanine-DNA Methyltransferase Polymorphisms in Prostate Cancer Susceptibility: a Meta-Analysis

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Abstract

To assess the associations between O^6-methylguanine-DNA methyltransferase(MGMT) polymorphisms and prostate cancer risk. We retrieved PubMed, Cochrane Library and Embase electronic database to search for all eligible studies published from Jan 1, 1970 to Sep 31, 2017 to conduct a Meta-analysis. we identified 11 independent studies in 5 eligible reports, including 5143 cases and 8118 controls. The data suggested that rs12917 was associated with higher PCa risk under the contrast of TT vs CC and recessive model in overall population (TT vs CC: OR = 1.599, 95%CI: 1.007–2.539, $P = 0.047$; TT vs CC + CT: OR = 1.627, 95%CI: 1.026–2.580, $P = 0.038$). In subgroup analyses stratified by ethnicity, the remarkable association with higher PCa risk was detected under allelic model, dominant model, the contrast of TC vs CC, and the contrast of TC vs CC + TT in Asian population. (T vs C: OR = 1.911, 95%CI: 1.182–3.090, $P = 0.008$; TC vs CC: OR = 1.948, 95%CI: 1.152–3.295, $P = 0.013$; TC + TT vs CC: OR = 1.994, 95%CI: 1.190–3.342, $P = 0.009$; TC vs CC + TT: OR = 1.926, 95%CI: 1.140–3.255, $P = 0.014$). However, the data suggest the rs2308327 and rs2308321 polymorphisms of the MGMT gene were nor associated with the susceptibility of prostate cancer. Based on the meta-analysis, MGMT rs12917 polymorphism increase the susceptibility to prostate cancer, which can be taken for a diagnosis and screening molecular biomarker for prostate cancer patients.

Keywords MGMT · PCa · Prostate cancer · Risk · Meta-analysis

Introduction

DNA repair pathway is a known defense mechanism with a fundamental role in maintenance of genomic integrity and resistance to human carcinogenesis [1]. The O^6-methylguanine-DNA methyltransferase (MGMT) is one of the most important proteins in DNA repair. It is a 207 amino acid protein encoded by the MGMT gene on 10q26 on chromosome 10 and spans about 300 KB. Studies have shown that MGMT has basic methylation activity, which plays a central role in the direct reversal of human DNA repair [2, 3]. In addition, because of its promoter methylation, the inactive MGMT gene may be involved in epigenetic regulation of gene expression, which has been observed in many human cancers. Therefore, MGMT plays an important role in the pathogenesis of cancer [4–6].

Prostate cancer (PCa) is one of the most common malignancies and is the second most common cause of cancer mortality in men in Europe and the United States [7, 8]. Identifying the risk factors for PCa is essential to broaden our understanding of the disease and to investigate possible therapeutic measures. Although the complex etiology of PCa remains unclear, various risk factors play an important role in the development of PCa, such as advanced age, environmental changes, cultural changes and genetic variations. The host factors, including genetic polymorphism, have aroused interest in the etiology of PCa [9, 10].

Recently, many studies have studied the role of MGMT polymorphism in PCa. Studies found that the MGMT gene had multiple polymorphic sites and associated with PCa, including rs2308321 (Ile143Val), rs12917 (Leu84Phe) and rs2308327 [11]. However, the results of these studies are still

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uncertain. A single study may not be enough to detect the effect of this polymorphism on the PCa, especially in relatively small samples. Different types of research groups and research designs may also result in different results. To clarify the effect of gene polymorphism of MGMT on the risk of PCa, we conducted a meta-analysis of all eligible case-control studies.

Material and Methods

Search Strategy

We used the keyword "MGMT" OR "O^6-methylguanine-DNA methyltransferase" AND "polymorphism" OR "variant" OR "allele" OR "genotype" OR "cancer" OR "prostate cancer" OR "tumor tumor" to research the ariticles in PubMed, Cochrane Library and Embase electronic database and and all eligible studies were published before September 31, 2017. At the same time, the reference lists of reviews and retrieved articles were hand searched, so as to obtain more favorable qualified literatures. When more than one study of the same population was included in several publications, only the most recent or complete study was used in the meta-analysis.

Inclusion Criteria and Exclusion Criteria

For inclusion criteria, the study must follow the following criteria: (1) The relationship between the genetic polymorphism of MGMT and the risk of PCa can be evaluated; (2)case-control studies; and (3) The control group was in line with the Hardy-Weinberg Law. For exclusion criteria, the study must follow the following criteria: (1) lack of valid raw data; (2) The data can be seriously biased and the gender difference of the study population is too large; and (3) Repeated reports of the same population.

Data Extraction

The data was extracted by two investigators from each article independently. Discrepancies were not solved until consensus was reached on every item. From each study, the following data were collected: author's name, year of publication, country of origin, racial descent, cancer type, source of the control population, genotyping methods, matched factors as well as adjusted factors, number of cases and controls, genotype frequencies for cases and controls, characteristics of cancer cases, and controls. If data of subpopulation from different ethnicities was available in one paper, we took each subpopulation as an individual study.

Statistical Analysis

In this study, two independent researchers read the collected information and strictly followed the inclusion and exclusion criteria to discuss whether they could be included in the meta-analysis. The effect measure of choice was the odds ratio (OR) with its corresponding 95% confidence interval (CI). To evaluate whether the results of the data sets were homogeneous, we used the Q test. P values of heterogeneity below 0.05 were considered statistically significant for heterogeneity. Subgroup analysis based on race, divided into Asian, Caucasian, African American. If the result of the heterogeneity test is $P > 0.1$, then the random effect model is applied, otherwise the fixed effect model. The significance of the intercept was determined by the t-test suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias). All control groups were detected the Hardy-WeinbergLaw. All meta-analyses were conducted using STATA software (version 14.0; College Station, Tex., USA). All tests were two sided.

Results

Study Selection

As detailed in Fig. 1, we identified 571 relevant records through the bibliographical database search. After several rounds of screening, 43 literatures were retrieved to meet the retrieval requirements. After the evaluation of the inclusion and exclusion criteria, a total of 11 case-control studies in 5 literatures were eligible [11–15].

Study Characteristics

According to the inclusion and exclusion criteria defined above, we identified 11 independent studies in 5 eligible reports [11–15], including 5143 cases and 8118 controls. Main characteristics for all eligible studies were listed in Table 1. There are 5 case-control studies on rs2308321 [11–13, 15], 4 case-control studies on rs12917 [11, 13, 15] and 2 case-control studies on rs2308327 [11]. 11 independent studies consisted of 2 Asian [15], 3 African-American [14] and 6 Caucasian populations [11, 13–15].

Meta-Analysis

MGMT rs12917

Table 2 listed the main results of this meta-analysis. The data suggested that rs12917 was associated with higher PCa risk under the contrast of TT vs CC and recessive model in overall

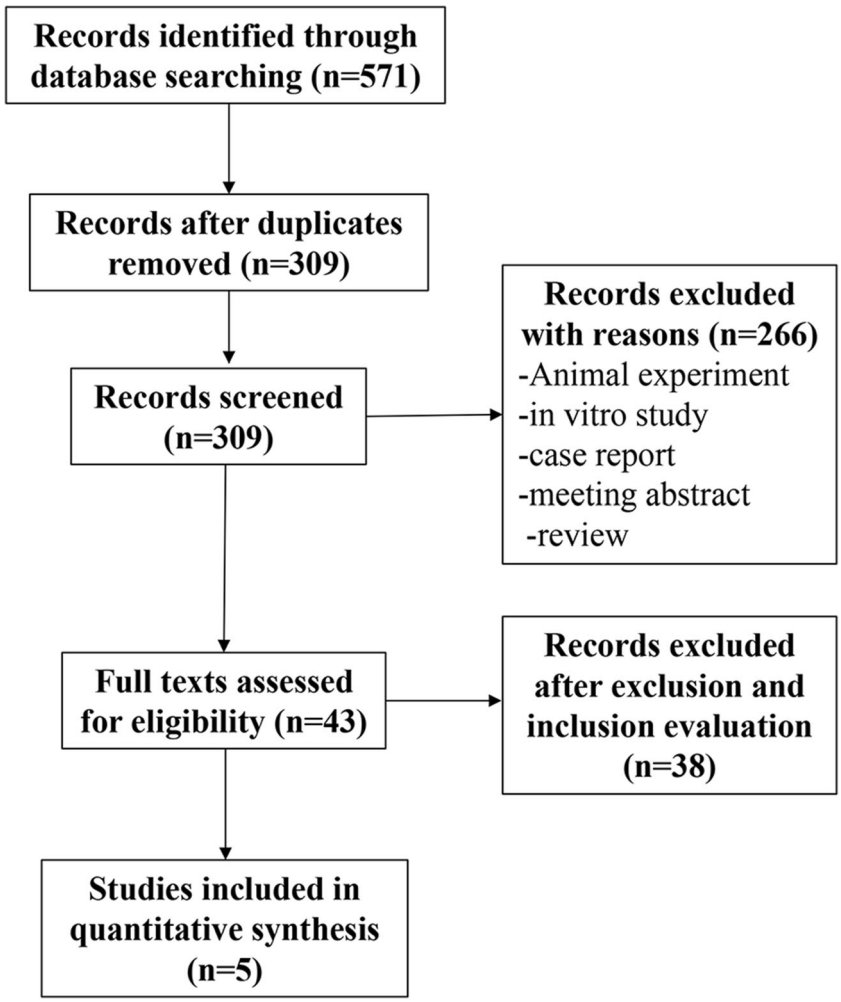

Fig. 1 Flow diagram detailing procedures of selecting eligible studies

Table 1 Basic information of the original articles included in this meta-analysis

Site	First author	Ethnicity	Year	Study design	Methods	Case			Control		
rs12917						CC	CT	TT	CC	CT	TT
	Yet Hua Loh, et al.	Caucasians	2011	PBC	PCR-RFLP	146	37	5	894	212	14
	Jamie D. Ritchey, et al.	Asian	2005	PBC	PCR-RFLP	123	36	2	213	32	1
	Ilir Agalliu, et al.	Caucasians	2010	PBC	ABI-SNPlex	949	269	32	916	298	23
	Ilir Agalliu, et al.	African-American	2010	PBC	ABI-SNPlex	106	35	6	60	20	1
rs2308321						AA	AG	GG	AA	AG	GG
	Yet Hua Loh, et al.	Caucasians	2011	PBC	PCR-RFLP	149	34	1	859	228	9
	Yet Hua Loh, et al.	Caucasians	2010	PBC	PCR-RFLP	238	72	2	1176	296	14
	Jamie D. Ritchey, et al.	Asian	2005	PBC	PCR-RFLP	155	5	1	243	5	0
	Ilir Agalliu, et al.	Caucasians	2010	PBC	ABI-SNPlex	926	267	14	922	256	17
	Ilir Agalliu, et al.	African-American	2010	PBC	ABI-SNPlex	130	10	0	73	7	0
rs2308327						AA	AG	GG	AA	AG	GG
	Ilir Agalliu, et al.	Caucasians	2010	PBC	ABI-SNPlex	950	276	22	960	266	20
	Ilir Agalliu, et al.	African-American	2010	PBC	ABI-SNPlex	134	11	0	75	8	0

PCR—RFLP: polymerase chain reaction—restriction fragment length polymorphism; ABI-SNPlex: applied Biosystems-SNPlex; PBC: population-based study

Table 2 Summary ORs(95%CI) of MGMT polymorphisms and prostate cancer risk

Site	Genetic model	Subgroup analysis	Number of studies	OR (95%CI)	*P*	*P* (*Q* test)
rs12917	T vs C	Total	4	1.204(903–1.606)	0.206	0.043
		Asian	1	1.911(1.182–3.090)	**0.008**	1.000
		Caucasian	2	1.013 (0.832–1.234)	0.898	0.236
		African-American	1	1.211(0.701–2.093)	0.493	1.000
	TT vs CC	Total	4	1.599(1.007–2.539)	**0.047**	0.655
		Asian	1	3.463(0.311–38.588)	0.313	1.000
		Caucasian	2	1.465(0.900–2.386)	0.124	0.412
		African-American	1	3.396(0.399–28.882)	0.263	1.000
	TC vs CC	Total	4	1.107(0.794–1.542)	0.550	0.041
		Asian	1	1.948(1.152–3.295)	**0.013**	1.000
		Caucasian	2	0.905(0.764–1.073)	0.251	0.356
		African-American	1	0.991(0.525–1.868)	0.977	1.000
	TC + TT vs CC	Total	4	1.167(0.842–1.617)	0.353	0.036
		Asian	1	1.994(1.190–3.342)	**0.009**	1.000
		Caucasian	2	0.955(0.790–1.156)	0.640	0.279
		African-American	1	1.105(0.598–2.042)	0.750	1.000
	TT vs CC + CT	Total	4	1.627(1.026–2.580)	**0.038**	0.717
		Asian	1	3.082(0.277–34.269)	0.360	1.000
		Caucasian	2	1.501(0.924–2.439)	0.101	0.455
		African-American	1	3.404(0.403–28.781)	0.261	1.000
	TC vs CC + TT	Total	4	1.088(0.783–1.511)	0.617	0.045
		Asian	1	1.926(1.140–3.255)	**0.014**	1.000
		Caucasian	2	0.896(0.757–1.061)	0.204	0.315
		African-American	1	0.953(0.507–1.793)	0.882	1.000
rs2308321	G vs A	Total	5	1.021(0.894–1.166)	0.758	0.502
		Asian	1	2.182(0.687–6.936)	0.186	1.000
		Caucasian	3	1.015(0.887–1.161)	0.831	0.480
		African-American	1	0.810(0.302–2.170)	0.674	1.000
	GG vs AA	Total	4	0.840(0.465–1.518)	0.565	0.746
		Asian	1	4.698(0.190–116.049)	0.344	1.000
		Caucasian	3	0.778(0.422–1.434)	0.421	0.965
	GA vs AA	Total	5	1.048(0.905–1.215)	0.530	0.653
		Asian	1	1.568(0.447–5.504)	0.483	1.000
		Caucasian	3	1.049(0.903–1.218)	0.535	0.409
		African-American	1	0.802(0.293–2.197)	0.668	1.000
	GA + GG vs AA	Total	5	1.037(0.898–1.199)	0.618	0.571
		Asian	1	1.881(0.564–6.270)	0.304	1.000
		Caucasian	3	1.034(0.892–1.198)	0.658	0.421
		African-American	1	1.037(0.898–1.199)	0.668	1.000
	GG vs AA+GA	Total	4	0.831(0.461–1.501)	0.540	0.746
		Asian	1	4.645(0.188–114.723)	0.348	1.000
		Caucasian	3	0.770(0.418–1.417)	0.401	0.965
	GA vs AA+GG	Total	5	1.052(0.908–1.218)	0.502	0.654
		Asian	1	1.558(0.444–5.468)	0.489	1.000
		Caucasian	3	1.052(0.906–1.222)	0.506	0.408
		African-American	1	0.802(0.293–2.197)	0.668	1.000
rs2308327	G vs A	Total	2	1.041(0.883–1.228)	0.634	0.535
	GG vs AA	Total	1	1.109(0.609–2.019)	0.735	1.000
	GA vs AA	Total	2	1.036(0.859–1.250)	0.708	0.533

Table 2 (continued)

Site	Genetic model	Subgroup analysis	Number of studies	OR (95%CI)	*P*	*P* (*Q* test)
	GA + GG vs AA	Total	2	1.041(0.868–1.249)	0.664	0.527
	GG vs AA+GA	Total	1	1.100(0.597–2.026)	0.760	1.000
	GA vs AA+GG	Total	2	1.034(0.858–1.246)	0.725	0.536

OR, odds ratio; *CI*, confidence interval; vs: versus; P (*Q* test) P value of *Q* test for heterogeneity test. If *P*<0.05, we used a specific bold type

population (TT vs CC: OR = 1.599, 95%CI: 1.007–2.539, *P* = 0.047, Fig. 2; TT vs CC + CT: OR = 1.627, 95%CI: 1.026–2.580, *P* = 0.038, Fig. 3). In subgroup analyses stratified by ethnicity, the remarkable association with higher PCa risk was detected under allelic model, dominant model, the contrast of TC vs CC, and the contrast of TC vs CC + TT in Asian population. (T vs C: OR = 1.911, 95%CI: 1.182–3.090, *P* = 0.008, Fig. 4; TC vs CC: OR = 1.948, 95%CI: 1.152–3.295, *P* = 0.013; TC + TT vs CC: OR = 1.994, 95%CI: 1.190–3.342, *P* = 0.009, Fig. 5; TC vs CC + TT: OR = 1.926, 95%CI: 1.140–3.255, *P* = 0.014).

MGMT rs2308321 and rs2308327

The data suggest the rs2308327 and rs2308321 polymorphisms of the MGMT gene were nor associated with the susceptibility of PCa (Table 2). In overall population, there were heterogeneous in both rs2308321 and rs2308327 for dominant model, co-dominant model, over-dominant model and allelic model comparison. After subgroup analyses by ethnicity, there was heterogeneous in rs2308321 for dominant model, co-dominant model, over-dominant model and allelic model comparison (Table 2).

Sensitivity Analyses

One-way sensitivity analyses of the pooled ORs and 95% CIs involved in the meta-analysis were performed. A single study for all the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs, and the corresponding pooled ORs were not materially altered.

Publication Bias

Begg's funnel plot and Egger's test were utilized to evaluate the publication bias. The Begg funnel plot compared with the allele model is shown in Fig. 6 (T vs C), and the results of the Egger's test are *P* = 0. 144. In addition, no evidence of publication bias was observed in any subgroup analyses under various comparison models.

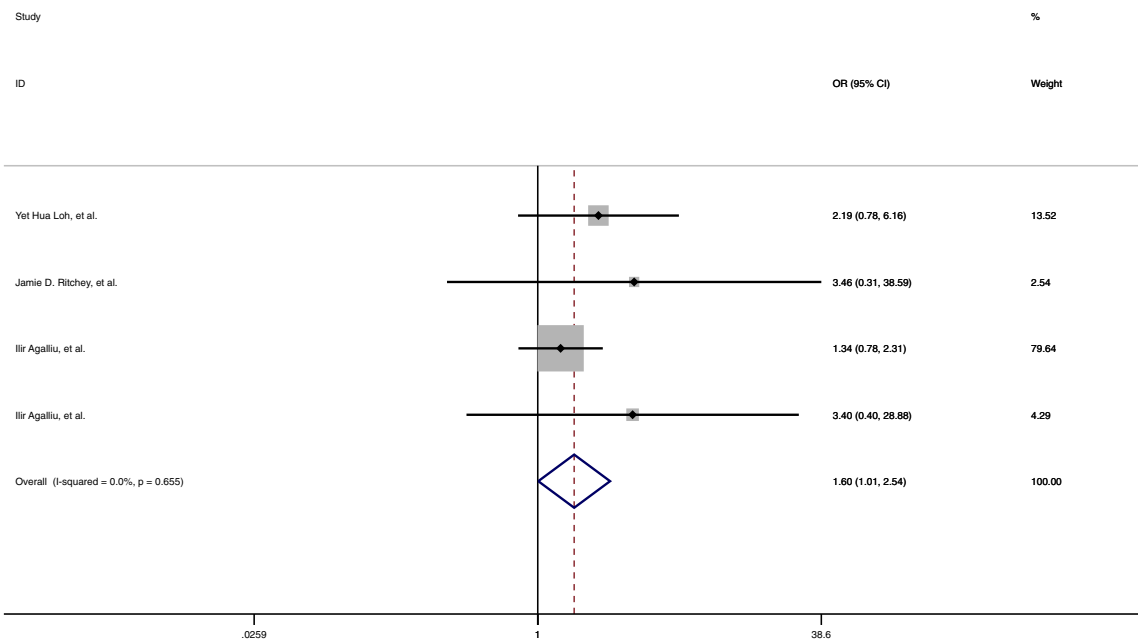

Fig. 2 Fixed-effects meta-analysis on prostate cancer risk and MGMT rs12917 polymorphism in overall population (TT versus CC). Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI representing its width

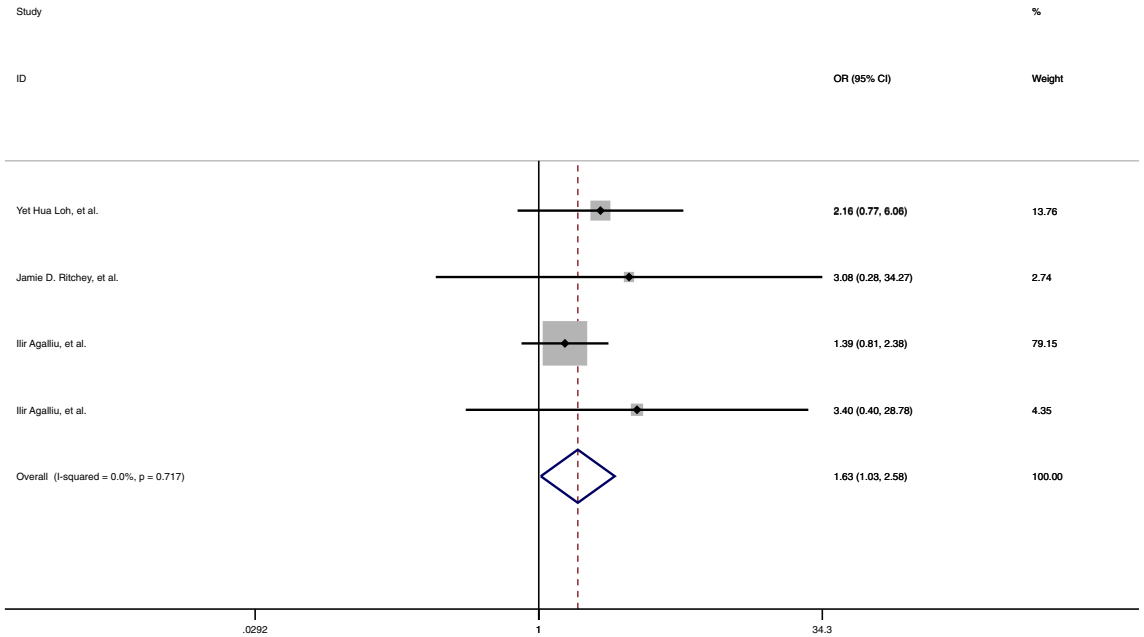

Fig. 3 Fixed-effects meta-analysis on prostate cancer risk and MGMT rs12917 polymorphism under recessive model in overall population (TT versus CC + CT). Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI representing its width

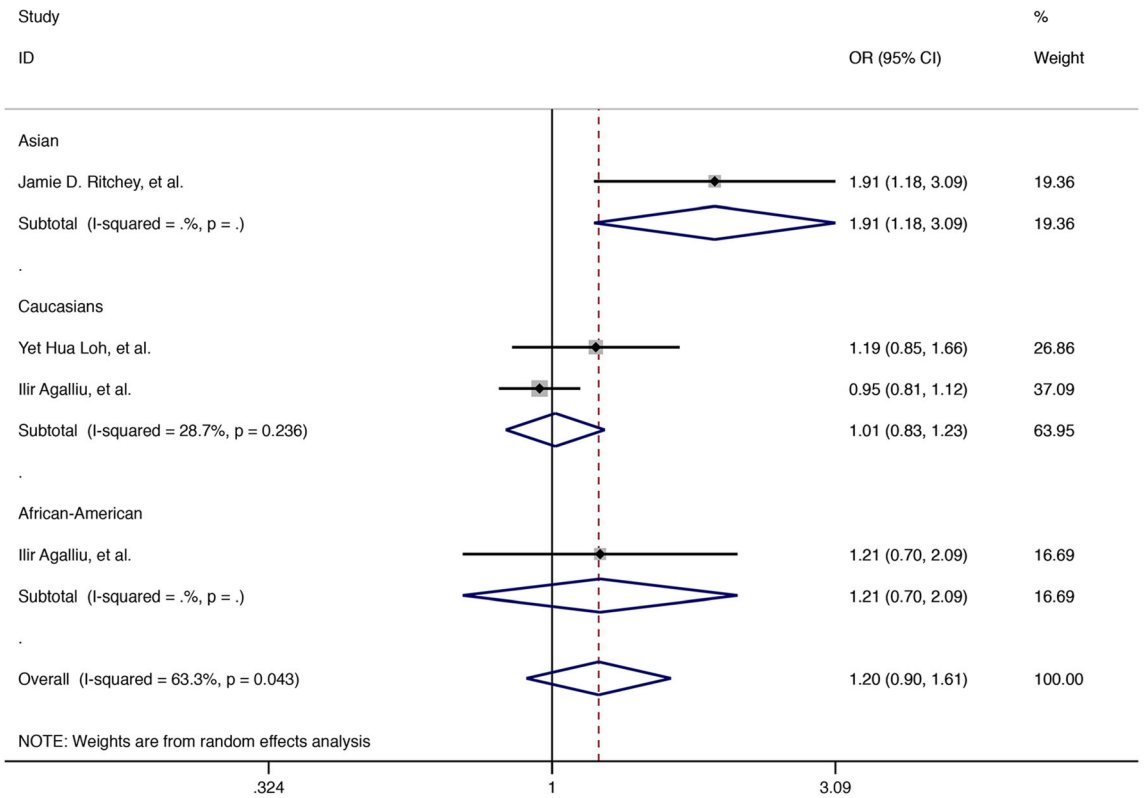

Fig. 4 Random-effects meta-analysis on prostate cancer risk and MGMT rs12917 polymorphism in Asian population (T versus C). Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI representing its width

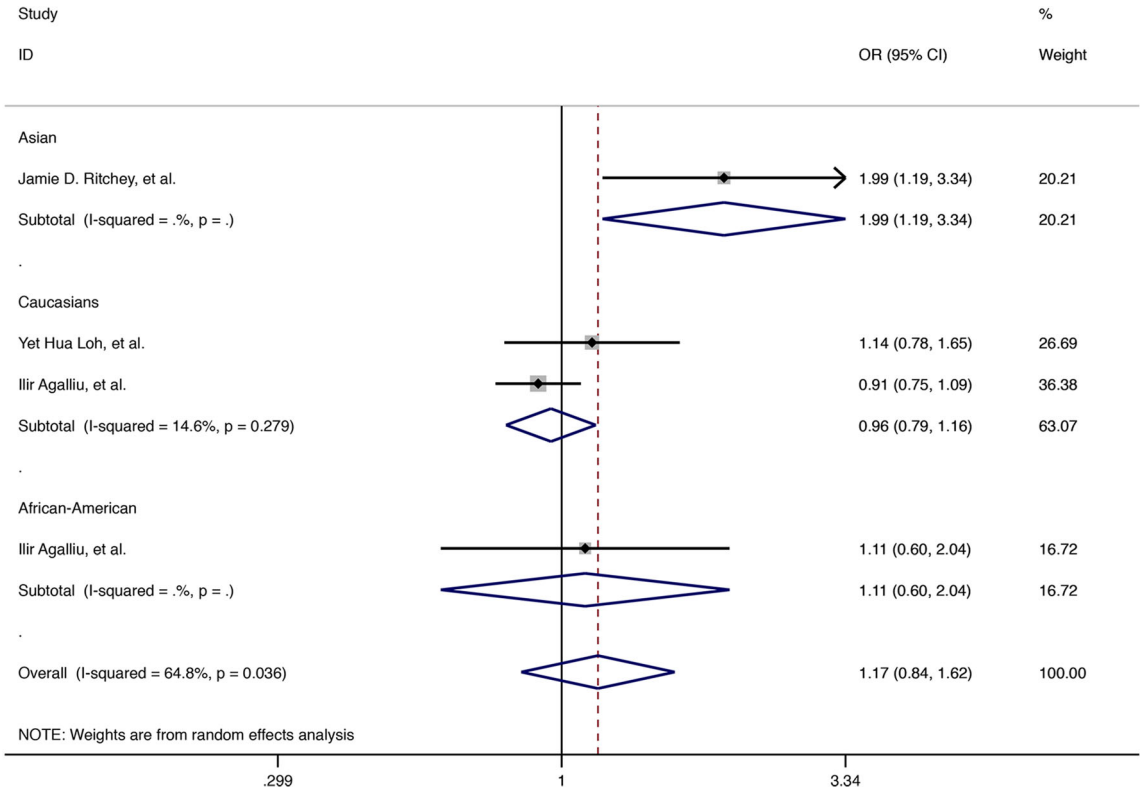

Fig. 5 Random-effects meta-analysis on prostate cancer risk and MGMT rs12917 polymorphism under dominant model in Asian population (TT + CT versus CC). Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI representing its width

Discussion

Prostate cancer (PCa) is one of the most common malignancies and the second most common cause of cancer mortality in men in Europe and the United States [7, 8]. It has been showed that the polymorphisms in genes might have a pronounced effect on cancer risk [16–18]. MGMT gene is an important gene for DNA repair and plays an important role in the pathogenesis of cancer. Some studies [2, 19–25] investigated the combined effects of Lue84Phe, Ile143Val, and other

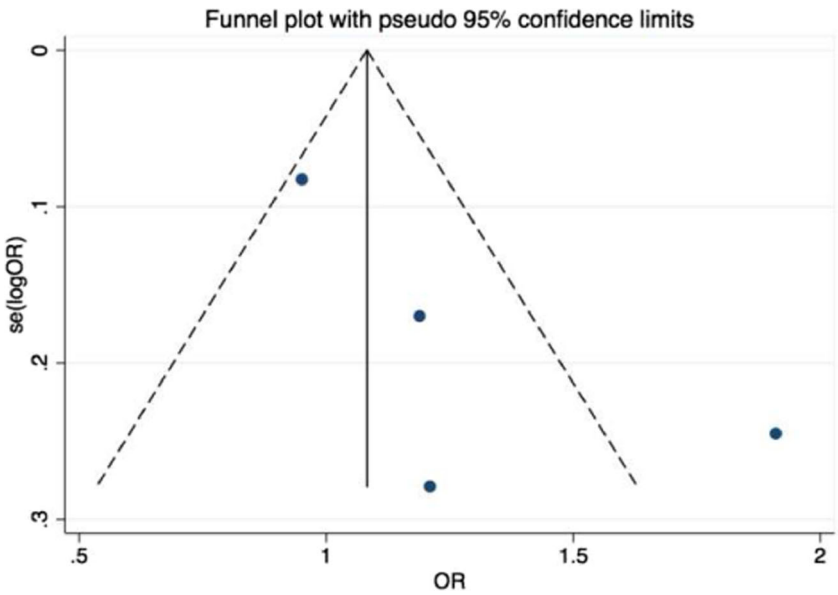

Fig. 6 Funnel plot analysis to detect publication bias (MGMT: rs12917 T versus C). Each point represents a separate study for the indicated association. Logor represents natural logarithm of OR. Horizontal line represents the mean effects size

polymorphisms in MGMT on cancer risk. Some polymorphisms of the MGMT gene may contribute to PCa development. Individual studies of the relationship between genes and cancer risk always produce inconsistent and controversial results. Meta-analysis can solve problems caused by low statistical capacity in a single study, and can draw stronger conclusions. Meta-analysis has confirmed that MGMT gene polymorphism is associated with the incidence of lung and rectal cancer [26–30]. This study based on a meta-analysis of 11 case-control studies, showed rs12917 MGMT gene polymorphism was associated with the risk of PCa for recessive model and the contrast of TT vs CC in overall population. The rs2308327 and rs2308321 polymorphisms of the MGMT gene were not associated with the susceptibility of PCa.

Population grouping analysis is a disturbing issue, and it may cause the evidence is not very reliable, indicating that the environment and different ethnicities have different effects on the genetic background [31]. At the same time, because the subgroup analysis based on race, the same polymorphism in different populations' cancer susceptibility plays a different role. In this study, the subgroup analysis showed that the MGMT gene rs12917 polymorphisms were significantly associated with PCa for allelic model, dominant model, the contrast of TC vs CC, and the contrast of TC vs CC + TT in Asian population.

However, there are some limitations to this meta-analysis. First, heterogeneity can interfere with the results of meta-analysis. In spite of this, we based on the research of the published researches to minimize this possibility, using specific criteria for research, and implement strictly the data extraction and analysis. The existence of heterogeneity is caused by the selection of control, age distribution and lifestyle factors. Although most of the controls were selected from healthy people, some studies have already selected PCa patients or other patients with a patient or family as a control. In addition, this meta-analysis included only published research findings, and the presence of bias indicates that the results of meaningless or negative results may not be published. Finally, our results are unadjusted. If you can provide more personal information, it should be a more accurate analysis, which will allow us to adjust using other variables including age, race, family history, lifestyle and environmental factors [32].

Despite these limitations, this meta-analysis found that the MGMT gene rs12917 polymorphisms were associated with PCa's susceptibility. Subgroup analysis showed that the MGMT gene rs12917 polymorphisms were significantly associated with PCa in Asia. So it can be a screening marker for prostate cancer risk. The rs2308327 and rs2308321 polymorphisms of the MGMT gene have nothing to do with the susceptibility of PCa. In future studies, we should consider the study of larger sample sizes of different races to determine the results of our meta-analysis. In addition, the effects of gene - gene and gene-environment interaction must be studied. The study of these factors may lead to better and more comprehensive understanding of the link between these factors, namely the association between them and the risk of prostate cancer.

Conclusions

Based on the meta-analysis, MGMT rs12917 polymorphism increase the susceptibility to prostate cancer, which can be taken for a diagnosis and screening molecular biomarker for prostate cancer patients. MGMT rs2308327 and rs2308321 polymorphisms of the MGMT gene were not associated with the susceptibility of prostate cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study protocol has been approved by the local ethics committee.

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