Associations Between M235T Polymorphism in the AGT Gene and Cancer: An Updated Systematic Review and A Meta-analysis

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Research

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Abstract

Background: We assessed the relationship between AGT gene M235T polymorphism and the susceptibility to cancer by performing an updated meta-analysis.

Methods: This study retrospectively searched related articles in the electronic databases. Afterwards, we determined combined odds ratios (ORs) and related 95% confidence intervals (CIs) by the fixed- or random-effects model.

Results: The present meta-analysis enrolled altogether 9 articles. On the whole, the relationship between AGT M235T polymorphism and the cancer risk was not significant among the entire population(TT vs MM:OR=1.28,95%CI=0.80-2.04;TM vs MM: OR=0.90, 95%CI = 0.53-1.52;Recessive model: OR= 1.13, 95%CI = 0.83-1.52; Dominant model: OR=0.93, 95%CI =0.55-1.57). But the relationship of AGT M235T polymorphism with the digestive cancer risk was significant upon subgroup analysis stratified according to cancer type (TT vs MM:OR=1.68,95%CI=1.11-2.54;TM vs MM: OR=1.34, 95%CI = 0.97-1.85;Recessive model: OR= 1.27, 95%CI = 0.95-1.70; Dominant model: OR=1.45, 95%CI =1.07-1.96).

Conclusion: According to findings in the present meta-analysis, AGT M235T polymorphism may be possibly related to digestive cancer susceptibility.

Introduction

Cancer greatly affects the global economy and public health. According to statistics, 14 million cancer patients are diagnosed in 2012, and the cancer morbidity is predicted to increase to nearly 22 million in 2030[1]. At present, the cancer pathogenic mechanism remains largely unclear, and cancer is reported as a complicated condition induced by numerous factors, such as genetic factors, smoking, excessive drinking, chemical dyes, high calorific diet, or their combination[2]. Typically, genetic factors are recognized to exert vital parts in cancer risk, with numerous cancer pathogenesis-related genes being identified as the cancer risk genes[3].

Renin-angiotensin system (RAS) is the hormone signaling pathway, which has been suggested to modulate blood pressure (BP) and cardiovascular homeostasis. Besides, RAS within local tissues is possibly associated with cancer genesis and progression[4]. In brief, renin can release 10 amino acids (aa) in angiotensinogen (AGT) for forming Ang I as well as the great protein (des (Ang I) AGT). Both des (Ang I) AGT and AGT have been recognized as the non-inhibitory serpins inhibiting new blood vessel formation[5]. Then, ACE can eliminate the above 2 aa from Ang I for generating Ang II. Notably, Ang II represents a major RAS active peptide that can promote cell proliferation and new blood vessel formation via angiotensin II type 1 receptor (AGTR1)[6].

AGT gene is 12,068 bp in length and located on chromosome 1q42.2, and there are 4 introns and 5 exons in the gene coding region. Mutations in AGT gene mostly result from thymine nucleotide (T) substitution by cytosine nucleotide (C) at the + 704 position in exon 2. Therefore, the codon 235-encoded methionine (Met) is replaced by threonine (Thr) (also referred to as M235T), and 2 alleles are formed, including 235T (variant type) and 235M (wild type). Altogether 3 genotypes are detected among the population, which are homozygous 235TT and 235MM, as well as heterozygous 235M[7]. As discovered by Paillard and colleagues, AGT-235 T allele elevated the plasma AGT content[8], which induced smooth muscle proliferation and contraction of small arteries, lipid deposition and hypertrophy of vascular smooth muscle cells (VSMCs), increased norepinephrine production and excited the sympathetic nervous system.

According to previous meta-analysis, the M235T variant in AGT gene is not related to the susceptibility to cancer[9]. But that meta-analysis only involves a small sample size and does not take into account some latest studies. The aim of the present study was to compile case-control research and updated meta-analyses to explore the association between AGT M235T polymorphism and susceptibility for cancer, so as to more accurately assess the cancer risk.

Methods

Retrieval protocol

This meta-analysis was carried out independently in line with guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[10]. Electronic databases, like PubMed, CNKI, Web of Science, Embase, Wanfang, and Cochrane library were searched for identifying articles that examined the association of AGT M235T polymorphism with cancer risk from inception to March 1st, 2021, using the keywords below, “Angiotensinogen”, “M235T”, “AGT”, “polymorphism or mutation” and “cancer”. At the same time, the reference lists in related studies were manually searched to avoid omitting any eligible study. No language restriction was applied in literature retrieval.

Inclusion and Exclusion

Eligible researches were enrolled according to the inclusion criteria:(1) studies that assessed the relationship of AGT M235T polymorphism with cancer risk, (2) case-control studies, (3) those with available genotyping information. The following was the exclusion criteria: (1) articles not related to cancer, (2) reviews, (3) articles with no available data, (4) duplicates.

Data extraction

Two investigators reviewed the related articles and collected data, and any disagreement between them was settled by the opinion of a third reviewer. The following information was collected, including first author, region, publication year, case and control numbers, case and control genotype frequencies, together with Hardy–Weinberg equilibrium (HWE) of control group.

Quality assessment

According to Table 1, the quality assessment rules were used for quality evaluation of the articles.[11] In brief, study quality was evaluated based on control source, sample size, case representativeness, diagnosis of cancer, genotyping quality evaluation and HWE, and the overall score was between 0 and 15. Studies that had a score $\geq$ 10 were deemed as high quality, while those that had a score $<$ 10 as “low quality”.

Table 1
Scale for quality assessment.

Criteria	Score
Source of cases	3
Selected from population or cancer registry	2
Selected from hospital	1
Selected from pathology archives, but without description	0
Not described	
Source of controls	3
Population-based	2
Blood donors or volunteers	1
Hospital-based (cancer-free patients) 1	0
Not described 0	
Specimens of cases determining genotypes	3
White blood cells or normal tissues	0
Tumor tissues or exfoliated cells of tissue	
Hardy-Weinberg equilibrium in controls	3
Hardy-Weinberg equilibrium	0
Hardy-Weinberg disequilibrium	
Total sample size	3
≥ 1000	2
≥ 500 but < 1000	1
≥ 200 but < 500	0
> 0 but < 200	

Statistical analysis

- Meta-analysis was carried out by adopting STATA12.0. ORs together with related 95% CIs were employed for evaluating correlation of AGT M235T polymorphism with cancer susceptibility under different comparisons, including heterozygote (TM vs MM), homozygote (TT vs MM), recessive model (TT vs MM + TM) and dominant model(TT + TM vs MM) between groups.Moreover, χ^2 test was utilized for determining HWE regarding the distribution of genotype among all the enrolled researches. Heterogeneity was analyzed by I^2 statistic, and $I^2 > 50\%$ suggested heterogeneity. Subgroup analyses according to cancer type, ethnicity and quality scores were also conducted. Afterwards, this study also conducted sensitivity analysis through eliminating a single study each time, showing suspect on one study of excessive sensitivity because the omission of this specific study yielded to the estimation beyond the 95%CI of the pooled analysis. Finally, we evaluated Begg's funnel plot for possible publication bias.

Results

Characteristics of Included Studies

Altogether 699 related studies were searched; at last, nine of them were included int othe present meta-analysis according to the pre-determined study inclusion and exclusion criteria[12–20]. All our collected articles were published from 2007 to 2020. Figure 1 shows the study screening flow chart. In brief, HWE test was carried out in the nine studies to examine the distribution of genotype in control group. As a result, all studies did not deviate from the HWE, with the exception of John et al and Pringle et al. All the enrolled studies had the quality score > 10 points, with the exception of John et al, indicating that these studies had high study quality. With regard to cancer type, 3 studies were on digestive cancer and 3 were on breast cancer (BC) to examine AGT M235T polymorphism. Table 2 displays the study features and methodological quality.

Table 2
Characteristics of the included studies of AGT M235T polymorphism.

Study included	Year	Cancer type	Race	Cases/ Controls	Genotypes for cases	Genotypes for controls	HWE test	Quality scores
					TT TM MM	TT TM MM		
González-Zuloeta	2007	Breast cancer	Caucasian	962/760	244 492 226	225 354 181	0.07	12
Vairaktaris	2008	Oral cancer	Caucasian	163/124	23 87 53	15 61 48	0.51	10
Vasku	2009	Colorectal cancer	Caucasian	102/101	50 100 50	31 96 73	0.95	10
Shibata	2011	Gastric cancer	Asian	206/210	140 57 9	142 60 8	0.60	10
Mendizábal-Ruiz	2011	Breast cancer	Mixed	50/224	21 17 12	75 118 31	0.15	10
Fishchuk	2013	Breast cancer	Caucasian	131/102	29 66 36	15 55 32	0.27	10
Pringle	2016	Endometrial cancer	Caucasian	183/133	78 83 22	40 54 39	0.03	7
Wang	2016	Mixed	Asian	104/1178	62 40 2	838 315 25	0.47	12
John	2019	Basal Cell Carcinoma	Caucasian	91/99	0 20 71	4 67 28	0.00	6

Meta-analysis results

Table 3 lists the major findings from this meta-analysis and the heterogeneity. On the whole, AGT M235T polymorphism did not show significant relationship with cancer under each genetic model (TT vs MM:OR = 1.28,95%CI = 0.80–2.04;TM vs MM: OR = 0.90, 95%CI = 0.53–1.52;Recessive model: OR = 1.13, 95%CI = 0.83–1.52; Dominant model:OR = 0.93, 95%CI = 0.55–1.57).

Table 3
Summary ORs and 95%CI of AGT M235T polymorphism with cancer risk.

Variables	N[a]	TT vs MM	TM vs MM	Dominant model	Recessive model
		OR(95%CI) Model	OR(95%CI) Model	OR(95%CI) Model	OR(95%CI) Model
Total	9	1.28(0.80–2.04) R	0.90(0.53–1.52) R	0.93(0.55–1.57) R	1.13(0.83–1.52) R
Race					
Asian	2	0.89(0.40–2.01) F	1.06(0.47–2.39) F	0.94(0.42–2.08) F	0.78(0.46–1.31) R
Caucasian	6	1.50(0.81–2.80) R	0.97(0.52–1.83) R	1.01(0.53–1.93) R	1.27(0.83–1.97) R
Cancer type					
Breast cancer	3	0.91(0.72–1.16) F	0.86(0.50–1.47) R	0.94(0.65–1.36) F	1.14(0.69–1.89) R
Digestive cancer	3	1.68(1.11–2.54) F	1.34(0.97–1.85) F	1.45(1.07–1.96) F	1.27(0.95–1.70) F
Quality					
high	7	1.19(0.82–1.74) R	1.13(0.95–1.35) F	1.11(0.94–1.32) F	1.08(0.80–1.45) R
low	2	0.49(0.01–41.59) R	0.57(0.03–12.34) R	0.58(0.02–14.93) R	0.66(0.05–8.64) R

[a] Number of comparisons.

As revealed by subgroup analysis stratified by ethnicity, AGT M235T polymorphism did not show significant relationship with cancer susceptibility in the Caucasian or the Asian population. Meanwhile, subgroup analysis stratified by quality score suggested that AGT M235T polymorphism did not show significant relationship with cancer susceptibility. According to subgroup analysis based on cancer type, significant association was found in digestive cancer (Fig. 2,GG vs AA: OR = 2.38, 95% CI = 1.24–4.55; GA vs AA: OR = 1.34, 95% CI = 0.82–2.20; recessive model: OR = 2.17, 95% CI = 1.54-3.0; dominant model: OR = 1.59, 95% CI = 1.06–2.39), rather than breast cancer.

Sensitivity Analysis

- When each individual study was eliminated, the pooled results were not changed, which indicated statistical significance of our results(Fig. 3).

Publication bias

We drew the Begg's funnel plot for assessing the possible publication bias among the enrolled articles. No evident asymmetry was observed in the funnel plot(Fig. 4).

Discussion

At present, cancer is recognized to be a major cause leading to mortality in the world. It has brought severe social and economic burdens on the health-care system across diverse countries; what's worse, it has deteriorated the patient life quality[21]. Regardless of the progresses made in cancer treatment, cancer prognosis is still poor. Cancer represents a kind of multifactorial disorder. As reported in some studies, the interaction between polymorphisms and environmental factors exerts a vital part in cancer genesis. More and more studies find that RAS affects cell proliferation, inflammation, apoptosis and tissue angiogenesis. However, most existing case-control studies are conducted to examine the relationship of AGT M235T polymorphism with the susceptibility to cancer. Nonetheless, no consistent results are obtained. This meta-analysis was carried out for assessing the relationship of AGT M235T polymorphism with the susceptibility to cancer.

Our findings suggest that this polymorphism was not related to a higher susceptibility to cancer. As revealed by subgroup analysis stratified by race, AGT M235T polymorphism was significantly associated with cancer risk among the Asian and Caucasian populations. When stratified by cancer type, AGT M235T polymorphism was significantly associated with digestive cancer risk, but not the breast cancer.Discrepancies between study could possibly due to a different role of this polymorphism in different cell types or tissues. It remains unknown about the mechanism regarding the connection of AGT M235T polymorphism with digestive cancer risk. Firstly, AGT M235T polymorphism is linked with AGT content in plasma. AGT participates in cardiovascular remodeling, vascular tone, water and salt homeostasis, while high salt consumption represents one of the risk factors for digestive cancer.[17] Secondly, AGT A-20C polymorphism is reported previously to predict a higher susceptibility to gastric cancer. There is a linkage disequilibrium of A-20C with M235T polymorphism sites of AGT gene. These two polymorphisms may be cooperate with each other to add the risk of disease[22].

Certain limitations must be noted in the present meta-analysis. Firstly, raw data from the enrolled articles were lacking, which restricted our ability to better evaluate the associations between genes and between genes and the environment. Secondly, each of the enrolled articles was of retrospective nature, which might inevitably lead to subject selection bias, finally impacting our result reliability. Thirdly, the present meta-analysis just enrolled the published articles, while the related unpublished articles were not enrolled, which might cause a potential publication bias.

To sum up, our meta-analysis reveals that AGT M235T polymorphism is related to susceptibility to digestive cancer. More large-scaled case-control studies should be conducted to explore the potential relationships between genes and between genes and the environment with cancer incidence.

Declarations

Conclusions section

According to findings in the present meta-analysis, AGT M235T polymorphism may be possibly related to digestive cancer susceptibility.Relevance of the study reported:Jianjun Lin, Jiayu Chen, Chibo Liu.AGT M235T variant is not associated with risk of cancer. J Renin Angiotensin Aldosterone Syst. 2015;16:448-52.

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Authors' contributions

Jun-Yan Kou designed the study and drafted the manuscript. Jun-Yan Kou was responsible for the collection and analysis of the experimental data. Jing Huang revised the manuscript critically for important intellectual content. The authors read and approved the final manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hangzhou Cancer Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

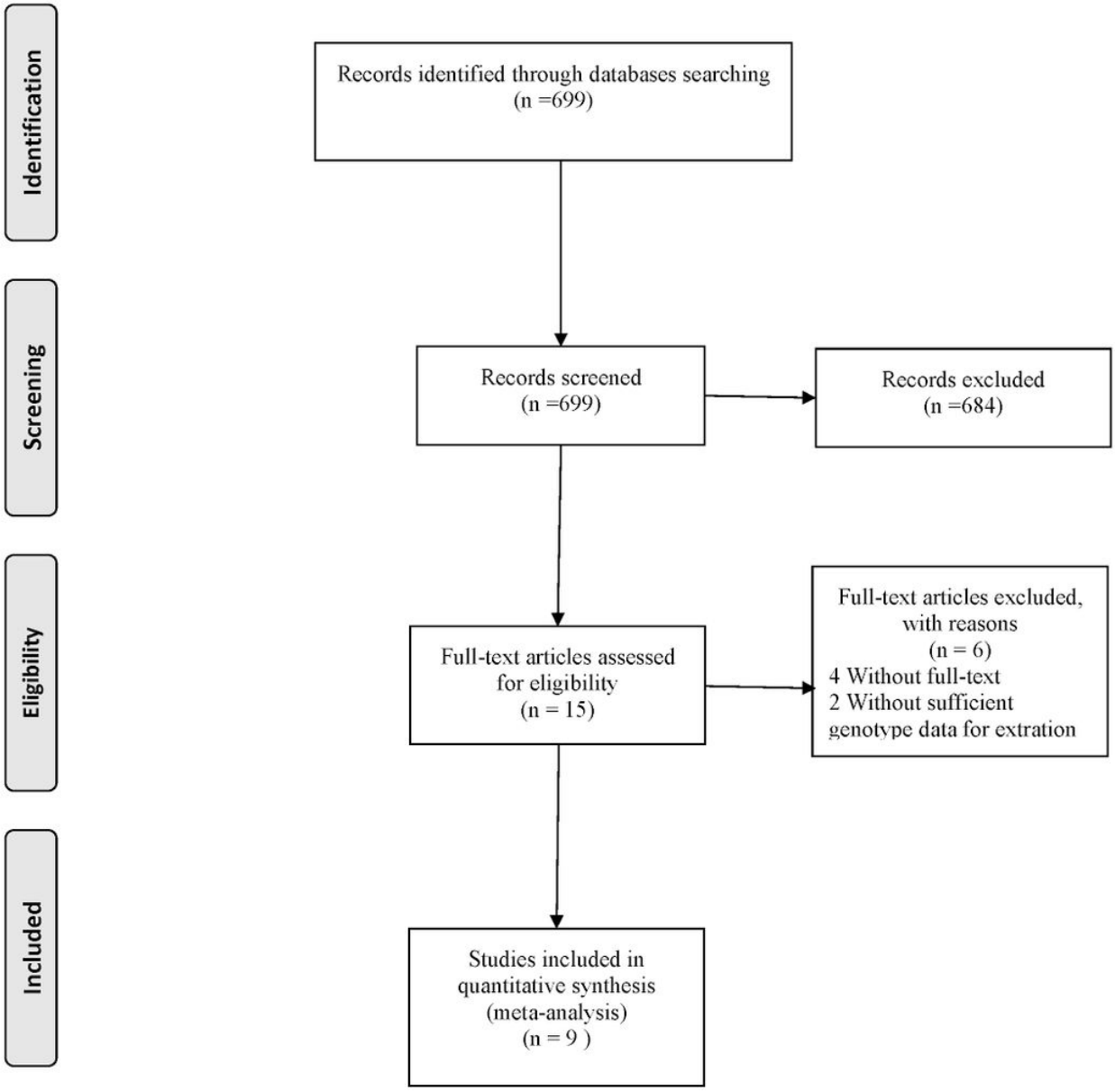

Figure 1

The flow diagram of included/excluded studies.

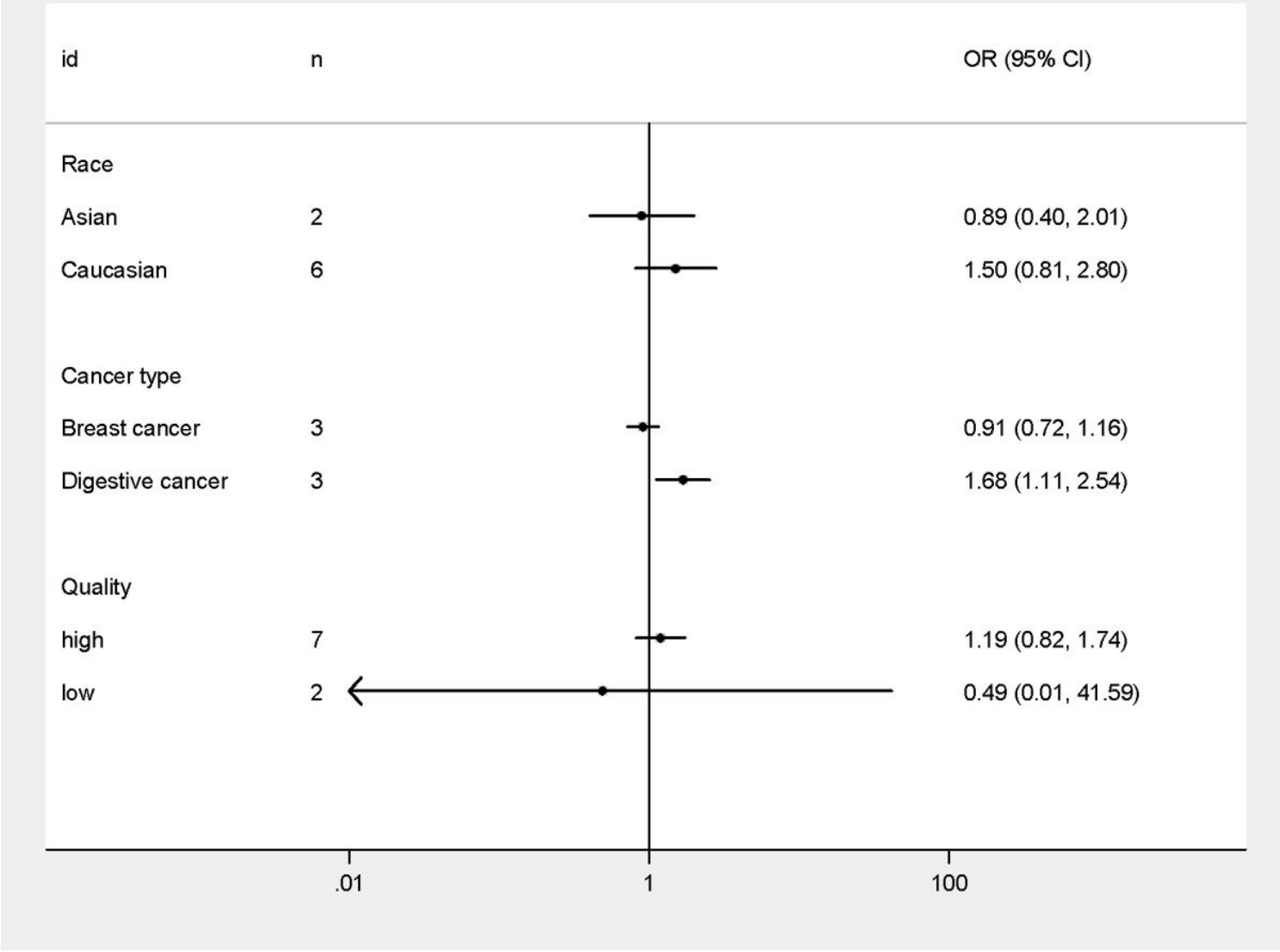

Figure 2

Forest plot for meta-analysis of the association between the M235T polymorphism and cancer risk with TT vs MM.

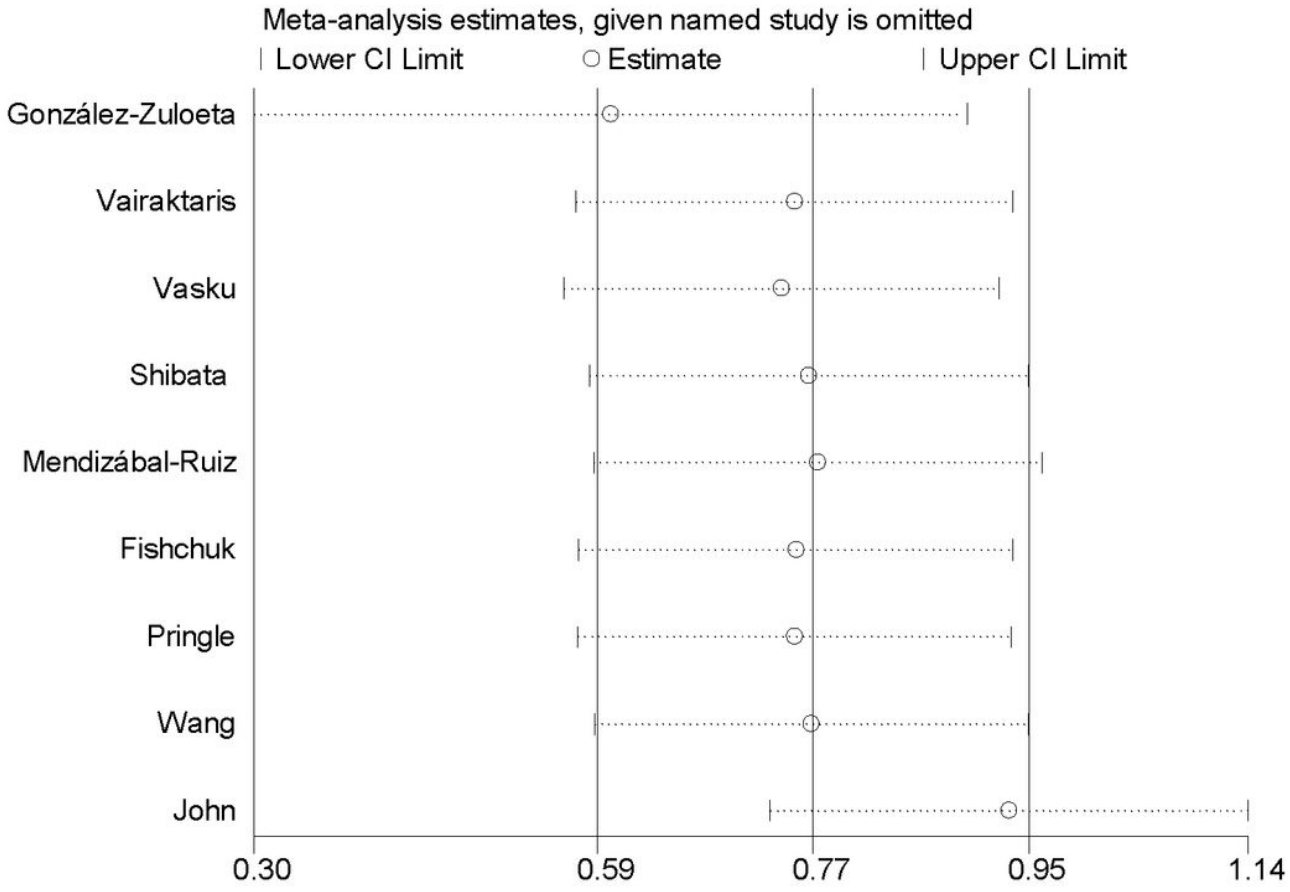

Figure 3

Sensitivity analysis of the association between the M235T polymorphism and cancer risk.

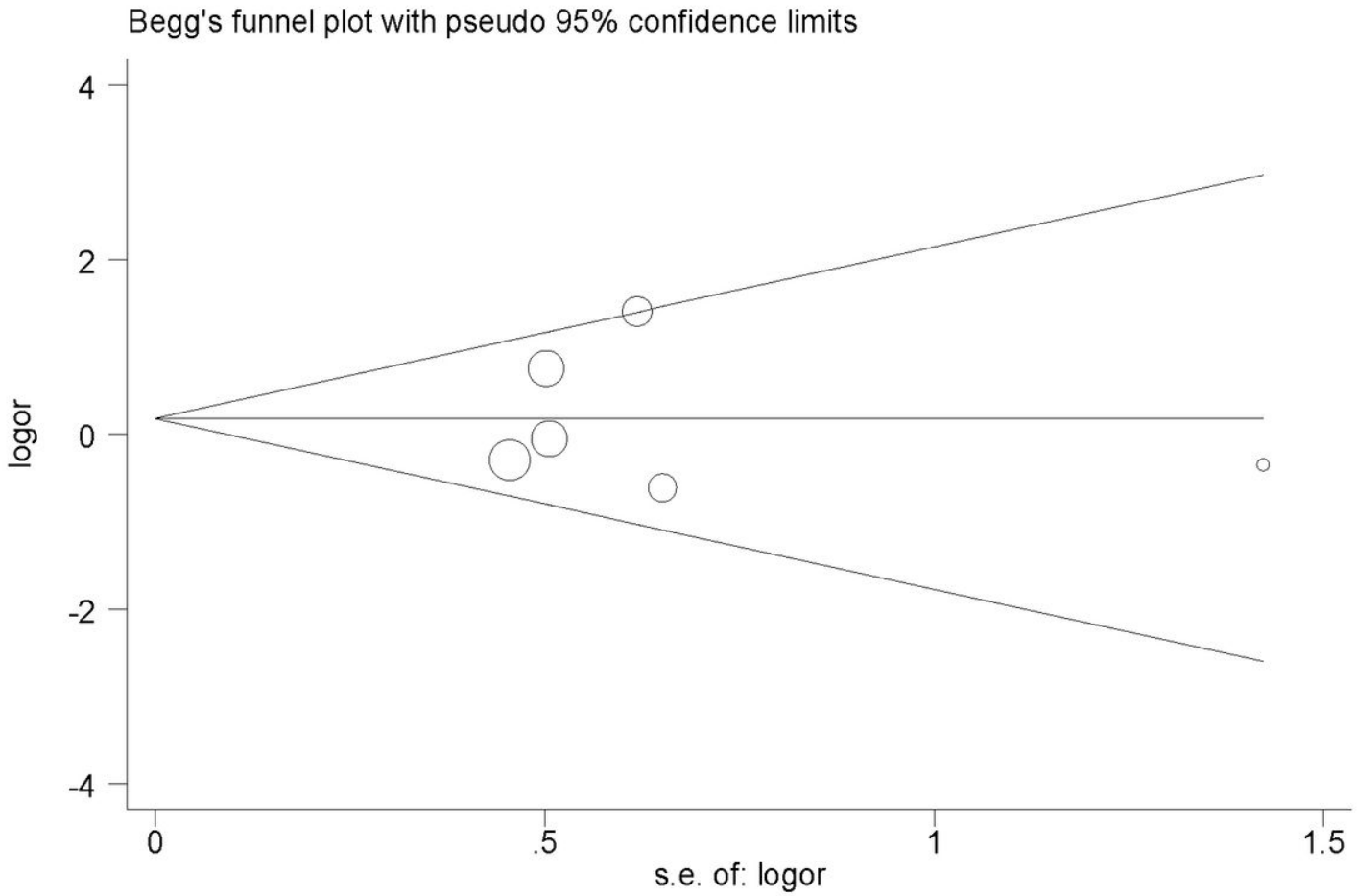

Figure 4

Begg’s funnel plot analysis to detect potential publication bias for M235T polymorphism.