A Meta-Analysis of Association Between the MMP-13 rs2252070 Promoter Polymorphism and Cancer Risk

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Abstract

Background Originally detected in breast cancer tissue, MMP-13 has been showed to be closely related to cancer development. Increasing evidence has also suggested that rs2252070, one of its SNP, can profoundly influence cancer risk by regulating the expression while the conclusion still remained controversial. Therefore, this meta-analysis was conducted to assess the carcinogenesis effect of this SNP quantitatively. Methods Studies about association between rs2252070 polymorphism and cancer risk by March 15, 2020 had been collected in PubMed, Web of Science, Cochrane Library and CNKI. R scripts and STATA software were applied to calculate estimates. Pooled ORs and corresponding 95% CIs were used to evaluate the strength of association. Results Twenty studies meeting pre-defined criteria were retrieved for the final statistical analysis, including 8,215 cancer patients and 8,480 healthy controls. The pooled estimates revealed no statistical significance for the association between this polymorphism and the risk of cancer in all 5 genetic models. Similarly, no significance had been detected in stratified analyses by region, cancer type, sample size and genotyping method. Conclusion The association between MMP-13 rs2252070 and carcinogenesis was not statistically significant. To elucidate this conclusion, future studies including gene-gene and gene-environment interaction are needed to verify the study results.

Background

Collagenase-3, a member of matrix metalloproteinases, is widely distributed in various tissues and organs and can degrade multiple components of basement membrane and extracellular matrix, including collagen I, II, III, VII, X and other proteoglycans[1, 2]. It's a Zn^{2+} dependent matrix metalloproteinase and normally inactive. Besides activating other subtypes of MMPs (such as MMP-2 and MMP-9), it can also be activated by other MMPs (such as MMP-2 and MMP-3) [3]. Therefore, slight changes in the activity or expression level of MMP-13 can be amplified by influencing the activation of other ECM decomposition enzymes. Because of participating in the degradation of ECM, it is considered to play an important role in various pathological processes like rheumatoid arthritis and liver fibrosis[4]. Originally identified in breast cancer tissues, increasing evidence has also suggested that this enzyme is closely related to cancer development [5, 6]. By comparing the level of collagenase-3 in normal and cancer tissues, the result demonstrated that the content of this enzyme in normal tissues is extremely low[7, 8]. And other researchers had found that there is a positive correlation between collagenase-3 level and tumor aggressiveness[9].

Encoding collagenase-3, the MMP-13 gene is located on 10q22 and consists of 10 exons and 9 introns[10]. As mentioned above, even the smallest variation of genome, such as single nucleotide polymorphism, may significantly affect the regulation of MMP-13. At present, 3662 single nucleotide polymorphisms of MMP-13 have been reported, of which rs2252070 (A > G), located 77 bps upstream of the promoter region, is the most widely studied one. In vitro, it has been proved that the G allele of rs2252070 had significantly lower corresponding promoter activity, approximately half of A allele[11]. Consequently, this A to G SNP has been linked to lower cancer susceptibility by influencing the expression level of MMP-13. Given the essential biological effects of rs2252070, it is necessary to evaluate its carcinogenic impact. Some researchers had already investigated the relationship between this SNP and cancer risk in various cancers such as lung cancer, gastric cancer, colorectal cancer, liver cancer and prostate cancer[12, 13].However, due to the unavoidable differences in research design and implementation, the research results were incongruous and there's no consensus has been reached about the impact of *MMP-13* rs2252070 on carcinogenic risk by far. Therefore, to summarize the existed evidence and draw a more credible conclusion, we performed this meta-analysis based on current relevant datasets.

Materials And Methods

Searching Strategy

Pertinent studies about association between *MMP-13* rs2252070 polymorphism and cancer risk were identified through searching in web of Science, PubMed Cochrance Library CNKI And Wanfang Data. The Boolean query formula was composed of following three keyword parts: cancer ("neuroblastoma", "melanoma", "lymphoma", "osteosarcoma", "leukemia", "tumor", "cancer", "carcinoma" and "adenocarcinoma"), polymorphism ("polymorphism", "SNP", and "variant") and polymorphism ID, gene name and symbol ("MMP13", "MMP-13", "matrix metalloproteinase-13", and "rs2252070"). All articles identified by our searching strategy were published before March 15, 2020.

Eligibility Criteria

Titles and abstracts of all relevant papers were reviewed by three auxiliary members respectively. For a study to be included in this meta-analysis had to meet the following pre-defined inclusion criteria: (1) manuscripts published on peer-reviewed journals; (2) case-control studies search on the effect of *MMP-13* rs2252070 polymorphism on the susceptibility of malignant tumors; (3) researches with enough genotype data to calculate or value and 95% confidence interval in at least one genetic model; (4) the case group does not contain any benign tumor samples. According to the literature screening criteria described in the previous section, we preliminarily screened out the irrelevant research that obviously needs to be excluded, and then read the full text and check the data to determine whether to include it.

Data Extraction

Retrieval work of this study was conducted by three reviewers independently. Group discussion would be organized to reach an agreement in case of inconsistent information about screening results. And if there was overlapping or duplication data in different researches, the most recent publication or that with the largest study population would be selected for our meta-analysis. For each study, the following information were documented : a) first author's surname (b) year of publication (c) the geographical area of samples involved (d) the frequency of polymorphism in the case group and the control group (E) the sample size (f) the genotyping method (g) the cancer type. In addition, the deviation from Hardy Weinberg equilibrium (HWE) in each study was measured statistically ($P < 0.05$ indicates statistical significance), and then was qualitatively marked as the study characteristic.

Statistics Analysis

Association between cancer risk and rs2252070 polymorphism were analyzed by pooling odds ratio (ORs) and corresponding 95% confidence interval (CIs) in five genetic models including allele model (G vs A), dominant model (AG + GG vs AA), recessive model (G vs AG+AA), heterozygous model (AG vs AA) and homozygous model (GG vs AA). Cochran's Q test was performed to assess the state of heterogeneity between studies, with a significance level of 0.10. Between-study heterogeneity was not considered to be significant when P_h< 0.10, and the data would be pooled by the fixed effects (Mantel–Haenszel) algorithm[14]. Otherwise, random effects (DerSimonian and Laird) model would be adopted to calculate and 95% confidence interval[15]. Galbraith plot was generated to directly find out which studies significantly contribute to the overall heterogeneity[16]. Moreover, in order to explore the source of heterogeneity further, subgroup analyses were performed for cancer type (lung cancer, digestive system cancer or others), region (Asian or others), sample size (greater than 1000 or not), and method of genotyping (PCR-RFLP or others).To evaluate the potential publication bias quantitatively, Begg's test and Egger's test were both conducted and the threshold set as 0.05[17,18]. Also, corresponding funnel plots were applied to demonstrate the degree of publication bias visually. (Studies with larger sample population and higher-quality were distributed at the bottom of funnel, whereas those with smaller sample population and lower precision were located closer to the horizontal axis). Additionally, the sensitivity analysis was carried out to make sure the stableness of our study by using the leave-one-out method. All statistical tests were performed by applying our pre-developed R script (version 3.5.2) and STATA software (version 14.2).

Results

Characteristics of Included Studies

A total of 139 publications were preliminarily obtained by applying our searching strategy in five databases. Twenty-two studies were remained for further examination after the duplication removal and initial screening. While performing the final eligibility checking, we found that three ovarian cancer datasets from the Fourth People's Hospital of Hebei Medical University overlapped. According to our strategy, the two studies published earlier with smaller sample sizes were excluded, and the latest research data from December 2001 to December 2008 were retained[19].

Finally, 20 publications were qualified for the statistical analyses, including 4 in Chinese and 16 in English[19-39]. A total of 16,995 samples were enrolled, including 8,215 cancer patients in the case group and 8,480 healthy people in the control group. Among all the eligible papers, thirteen of them were conducted in China and seven others had people from Greece, Spain, Turkey, Sweden, Mexico, Polish and Brazil involved. And all studies were published between 2006 and 2019.The literature retrieval and screening process are shown in Figure 1. The basic characteristics of the included literatures are shown in Table 1.

Main Analysis Results

As demonstrated in Table 2, all the 95% confidence interval of the combined estimates contained OR = 1, indicating no statistically significant association between this polymorphism and cancer susceptibility (allele model: OR = 0.99, 95% CI 0.89-1.10; homozygous model: OR = 0.96, 95% CI 0.78-1.17; heterozygous model: OR = 1.00, 95% CI 0.91-1.10 Figure 2; dominant model: OR = 1.00, 95% CI 0.88-1.13; recessive model: OR = 0.98, 95% CI 0.83-1.16)

Subsequently, subgroup analyses for cancer type, origin area, genotyping method and sample size had been conducted to assess the impact of rs2252070 on cancer risk further. When stratified by cancer types, no significant association had been detected in the digestive system cancer group. Similarly, it revealed no significance in both lung cancer group and other cancer group. Next, in the analyses based on origin area and genotyping method, the pooled results also showed that this polymorphism had no significant effect on cancer incidence. Finally, we assessed the associations in sample size subgroups and set cut-off at 200, 400, 500, 600, 800 and 1000 respectively. However, the effect of rs2252070 polymorphism on cancer risk was still not statistically significant by applying all cut-offs.

Publication Analysis and Sensitivity Analysis

In order to validate the robustness of our study, the sensitivity analysis was conducted by leave-one-out method (Figure 3). By removing one certain study each time and re-calculating the summary statistic successively, the pooled ORs did not materially altered, showing that our results were not subject to any certain research.

In addition, when applying Begg's test for appraisal of the publication bias, no significance in all genetic models had been detected. While when Egger's test was used, there was significant publication bias in homozygous model (P = 0.030, Figure 4) and recessive model (P = 0.019, Figure 5). Asymmetric distribution was also observed in the corresponding funnel diagram. Using trim-fill method, four suppositional studies were added in homozygous model and five were added in recessive model severally. Moreover, the re-calculated OR value and corresponding 95% CI remained stable (homozygous model: OR = 1.09, 95% CI: 0.88 -1.35; recessive model: OR = 1.15, 95% CI: 0.96-1.37).

Between-study Heterogeneity Analysis

Based on the criterion of heterogeneity P-value greater than 0.1, significant heterogeneity was observed in all five genetic models (allele model P_h< 0.01; homozygous model P_h < 0.01; heterozygous model P_h = 0.06; dominant model P_h < 0.01; recessive model P_h < 0.01). Therefore, all of the analyses were conducted by applying the random effects model.

Since heterogeneity in the subgroup could not be completely eliminated in subgroup analyses, therefore, we drew Galbraith plots to find out the source of heterogeneity between studies. Eight studies [24-26,30,33,34,36,39] in the allele model, seven studies [24-27,32,36,39] in the homozygous model, one study [35] in the heterozygous model (Figure 6), five studies in the dominant model, and six studies [24-26, 32,36,39] in the recessive model have been identified as the main causes of between-study heterogeneity.

After removing these data sets, no significant heterogeneity was detected (allele model P_h = 0.75; homozygous model P_h = 0.20; heterozygous model P_h = 0.31; dominant model P_h = 0.36; recessive model P_h = 0.46). The recomputed combined estimates also remained stable which meant the results were unchanged (allele model: OR= 1.01, 95% CI: 0.95 – 1.07; homozygous model: OR = 1.09, 95% CI: 0.97-1.22; heterozygous model: OR = 1.03, 95% CI: 0.96 – 1.11; dominant model: OR = 0.99, 95% CI: 0.92 – 1.08; recessive model: OR= 1.07，95%CI，0.97-1.17).

Discussion

Based on the key role of MMP-13 gene and the inconsistency of existing evidence, the current meta-analysis was conducted to systematically assess the relationship between rs2252070 gene polymorphism of MMP-13 and cancer susceptibility.16695 samples (including 8215 cases and 8480 controls) from 20 related datasets were analyzed. The results suggested that the association between rs2252070 polymorphism and the risk of cancer is insignificant.

Heterogeneity plays an important role in evaluating the strength of a meta-analysis and it should be eliminated as much as possible to avoid erroneous interpretation of analysis results. For our study, significant between-study heterogeneity had been detected in all five genetic models. Therefore, we performed subgroup analyses by cancer type, region, sample size and genotyping method. In subgroup analyses of cancer type, because of the diversity of included cancer types, we combined colorectal, esophageal, gastric cardia and oral cancer studies as digestive cancer subgroup. And except for lung cancer researches, the remaining ones were converged as another group. While there was still no significant differential cancer susceptibility between wild type and mutant type in none of the subgroups. In addition, considering that most of the included samples were from Asian area and even the same SNP can have a totally different effect among different races, we stratified the overall population according to geological source area and the results suggested no statistical difference had been found. As for stratified analyses based on genotyping method, no statistical significance in association between rs2252070 and cancer risk had been detected. Similarly, no significant associations were found in neither subgroup when stratified according to sample size.

It should be noted that there were several limitations in our analysis. Firstly, only Chinese and English databases had been involved in the literature searching and screening process and this may lead the exclusion of other pertinent studies. On the other hand, most of the available studies we found were about Chinese populations, which restricted us to investigate potential biases caused by racial genetic differences. Secondly, another major limitation of the systematic review was the statistical heterogeneity between involved studies, which limited the ability to evaluate the size of the effects in a more precise way. Finally, due to data limitations, this study did not take the possible SNP-SNP and gene-gene interactions into consideration. Also, we didn't evaluate the impact of other confounding factors like alcohol or cigarette using.

In spite of the limitations mentioned above, the main superiority of high-quality meta-analysis was the methodology. No matter in the process of literature search, study screening, data extraction or result interpretation, we all adhered to the system evaluation and Meta-Analysis Guide (PRISMA) strictly[40]. Moreover, by integrating the data sets of previously published studies, the sample size of the study was expanded and possible small-sample-effect had been eliminated, which improved the statistical power greatly. Last but not least, by performing sensitivity analyses and publication bias analyses, the results of this meta-analysis were proved to be stable and reliable.

Conclusion

The results of this meta-analysis showed that there was no statistically significant association between *MMP-13* rs2252070 and cancer susceptibility, suggesting the inappropriateness of listing this polymorphism as a biomarker for cancer risk. However, this is only a preliminary conclusion. Further designed studies with larger sample size are needed to clarify the relationship between rs2252070 polymorphism and cancer risk.

Abbreviations

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; HWE: Hardy Weinberg equilibrium ; ECM: extracellular matrix.

Declarations

Ethics approval and consent to participate

This study was approved by the Institute Ethical Committee of the Affiliated Cancer Hospital of Zhengzhou University, China. Written informed consents were obtained from all patients.

Consent for publication

Not applicable.

Avaliability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

PY and BX have designed the research and wrote the paper; YC, YM, CZ and PR searched and analyzed the data. All authors read and gave final approval of this version for publishing.

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Tables

Table 1: Principal characteristics of studies included in this meta-analysis.

Author	Year	Reference ID	Country	Region	Cancer Type	Genotyping Method	Cancer			Control			HWE
							AA	AG	GG	AA	AG	GG	
Zhang	2006	[17]	China	China	Mixed	PCR-RFLP	125	281	153	133	316	160	0.33
Lei	2006	[27]	Sweden	other	breast cancer	TaqMan	443	408	103	449	417	84	0.36
Zhai	2007	[28]	China	China	hepatocellular cancer	DNA Sequencing	99	212	116	123	225	129	0.22
Vairakataris	2007	[29]	Greek and German	other	oral cancer	PCR-RFLP	75	78	8	40	47	10	0.48
Zhou	2007	[30]	China	China	nasopharyngeal cancer	polymerase chain reaction (PCR) direct sequencing	201	367	200	195	353	204	0.09
Gonzalez-Arriaga	2008	[26]	Spain	Other	lung cancer	PCR-RFLP	248	208	45	267	197	42	0.51
Jia	2010	[31]	China	China	epithelial ovarian cancer	PCR-RFLP	75	154	71	61	149	90	0.96
Li	2010	[24]	China	China	Mixed	PCR-RFLP	136	293	163	137	324	163	0.31
Peng	2010	[32]	China	China	lung cancer	PCR-RFLP	105	207	108	91	227	101	0.08
Wang	2013	[16]	China	China	lung cancer	PCR-RFLP	85	132	83	55	156	89	0.35
Sanli	2013	[33]	Turkey	other	lung cancer	PCR-RFLP and DNA sequencing	118	7	7	80	0	0	NA
Yao	2013	[34]	China	China	colorectal cancer	PCR-LDR	25	64	40	10	28	36	0.24
Nguyen	2013	[35]	Sweden	other	colorectal cancer	TaqMan	185	158	42	276	276	67	0.87
Moreno-Ortiz	2014	[15]	Mexico	other	colorectal cancer	PCR-RFLP	48	50	4	60	49	16	0.24
Yang	2014	[36]	China	China	laryngeal squamous cell cancer	PCR-LDR	32	61	55	20	56	72	0.1
Shi	2016	[37]	China	China	esophageal squamous cancer	MassArray	259	730	599	348	821	431	0.25
Lu	2017	[38]	China	China	lung cancer	PCR-RFLP	82	69	31	119	72	24	0.01
Bialkowska	2018	[39]	Polish	other	prostate cancer	TaqMan	92	87	18	104	78	15	0.94
Li	2019	[25]	China	China	lung cancer	PCR-RFLP	108	94	43	140	87	31	<0.01
de-Matos	2019	[40]	Brazil	other	oropharyngeal squamous cell cancer	TaqMan	53	64	8	46	65	19	0.61

Table 2: Association between the *MMP-13* polymorphism and cancer risk

Comparison	Allele model (G vs. A)			Homozygote model (GG vs. AA)			Heterozygote model (AG vs. AA)			Dominant model (GG+AG vs. AA)			Recessive model (GG vs AA+AG)	
	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*
Overall	0.99 (0.89, 1.10)	0.83	<0.01	0.96 (0.78, 1.17)	0.67	<0.01	1.00 (0.91, 1.10)	1.00	0.06	1.00(0.88,1.13)	0.97	<0.01	0.98(0.83,1.16)	0.83
Region														
China	1.00 (0.87, 1.14)	0.95	<0.01	0.99 (0.76, 1.28)	0.93	<0.01	0.98 (0.85, 1.13)	0.78	0.02	0.98 (0.82, 1.17)	0.85	<0.01	1.02 (0.84, 1.24)	0.87
Other	0.98 (0.85, 1.13)	0.75	0.04	0.88 (0.61, 1.27)	0.51	0.02	1.02 (0.91, 1.14)	0.76	0.41	1.03 (0.92, 1.15)	0.65	0.18	0.88 (0.62, 1.25)	0.47
Cancer Type														
lung	1.13 (0.89, 1.43)	0.31	<0.01	1.19 (0.79, 1.79)	0.42	<0.01	1.02 (0.73, 1.43)	0.89	<0.01	1.09 (0.77, 1.55)	0.64	<0.01	1.16 (0.97, 1.38)	0.11
digestive	0.95 (0.80, 1.12)	0.51	<0.01	0.85 (0.60, 1.20)	0.36	<0.01	1.03 (0.92, 1.14)	0.64	0.50	1.00 (0.84, 1.18)	0.96	0.02	0.86 (0.64, 1.16)	0.33
others	0.94 (0.80, 1.10)	0.44	0.02	0.89 (0.65, 1.23)	0.49	0.03	0.99 (0.87, 1.13)	0.86	0.53	0.98 (0.87, 1.11)	0.80	0.15	0.91 (0.72, 1.17)	0.48
Method														
PCR-PFLP	1.01(0.88, 1.15)	0.93	<0.01	0.95 (0.73, 1.23)	0.71	<0.01	0.98 (0.82, 1.16)	0.81	0.02	0.99 (0.82, 1.19)	0.88	<0.01	1.02 (0.84, 1.23)	0.88
others	0.96(0.82, 1.13)	0.66	<0.01	0.95 (0.69, 1.31)	0.76	<0.01	1.04 (0.94, 1.14)	0.45	0.44	1.02 (0.86, 1.20)	0.85	<0.01	0.94 (0.71, 1.24)	0.65
Sample Size														
>1000	1.07 (0.94, 1.21)	0.31	<0.01	1.15 (0.91, 1.47)	0.24	<0.01	1.02 (0.94, 1.12)	0.62	0.43	1.06 (0.92, 1.21)	0.44	0.02	1.15 (0.95, 1.40)	0.16
<=1000	0.93 (0.79, 1.09)	0.37	<0.01	0.81 (0.59, 1.11)	0.19	<0.01	0.99 (0.82, 1.19)	0.88	0.03	0.94 (0.76, 1.17)	0.60	<0.01	0.85 (0.67, 1.09)	0.20

Figures

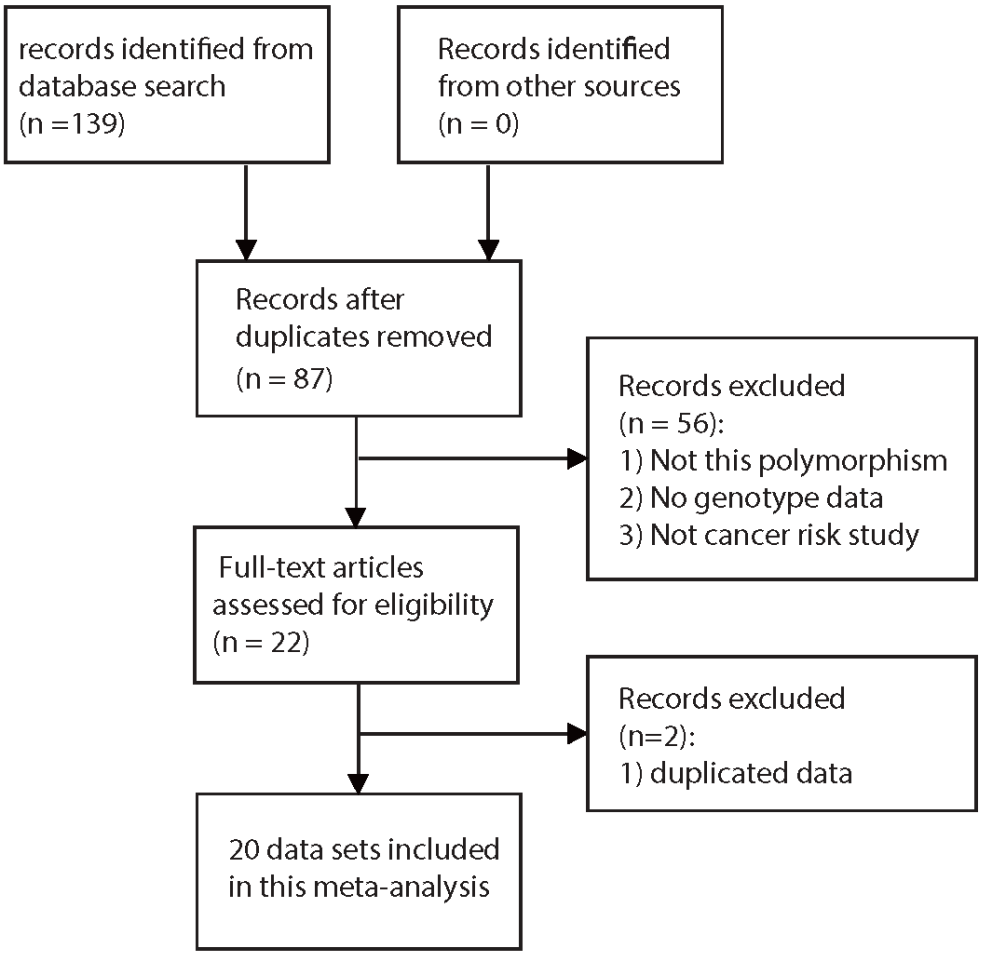

Figure 1

Flowchart shows detailed processes of literature screening.

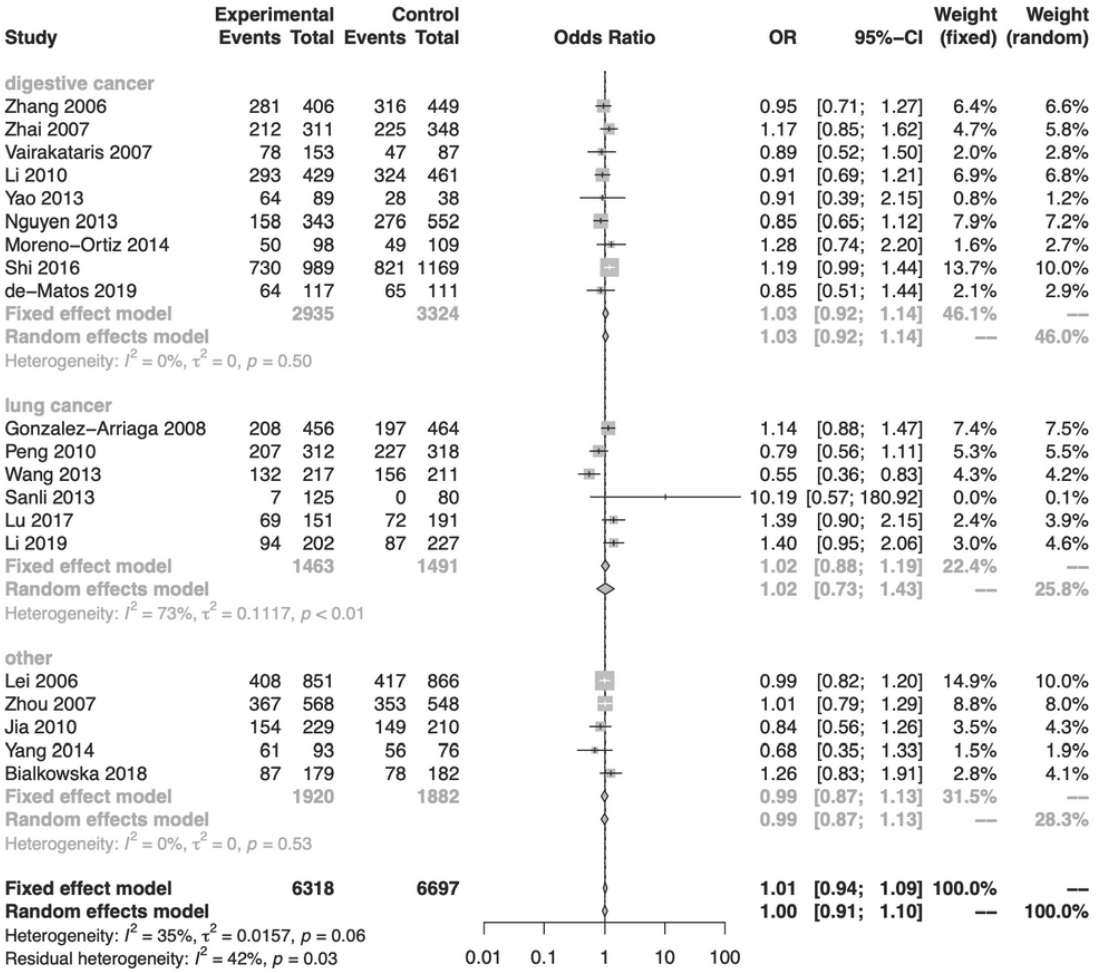

Figure 2

Forest plot shows the association between MMP-13 RS2252070 polymorphism and cancer risk under heterozygous model. The results were calculated using a random effects model. Each square represents an independent study, and the first author's last name and year of publication for each study were noted. The center of the square corresponds to its Odds ratio (OR), the range of horizontal lines corresponds to the 95% confidence interval (95% CI). The area of the square is proportional to the combined weight (shown in the weight column).The bottom diamond represents the pooled result, the center of the diamond corresponds to the pooled Odds ratio (OR), and the left and right vertices of the diamond correspond to the 95% confidence interval (95% CI). An invalid vertical line (OR=1) intersected by a diamond indicates that the result is not statistically significant.

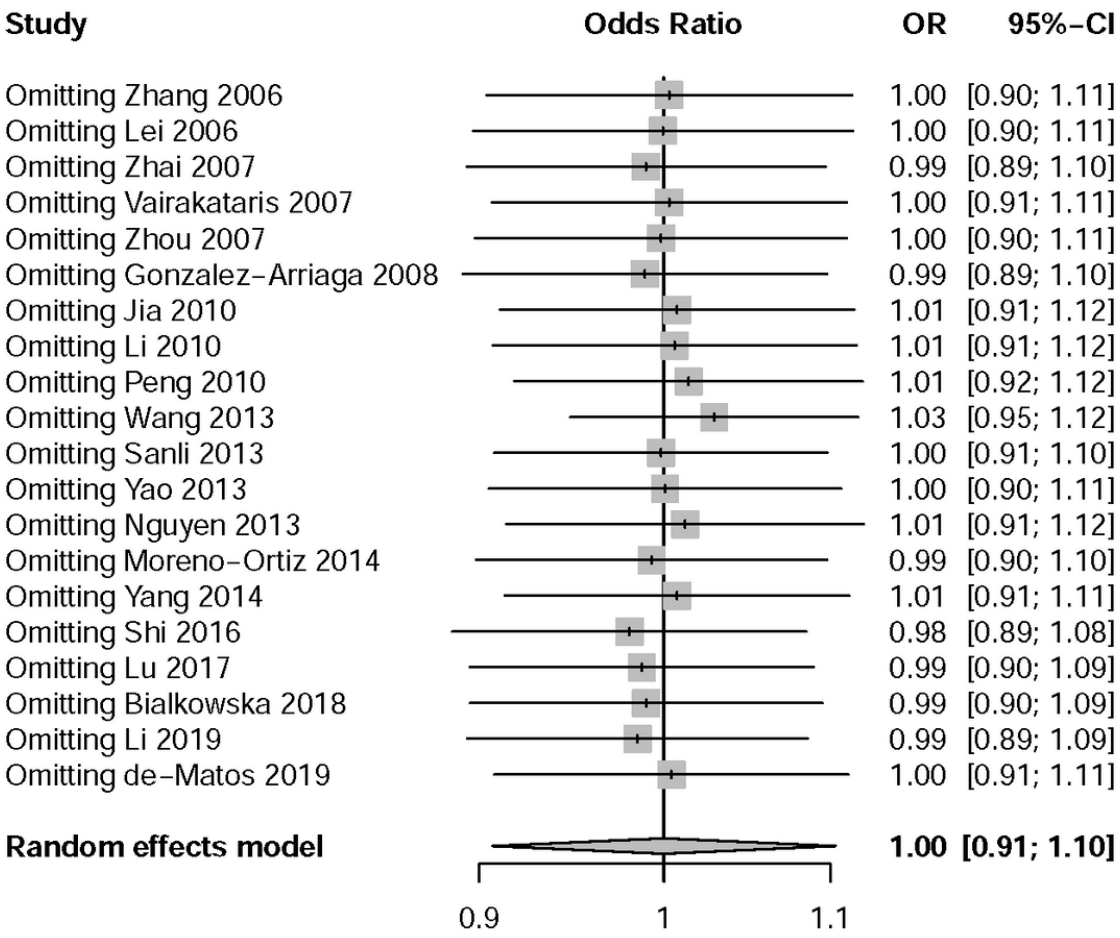

Figure 3

Forest plot of sensitivity analysis of MMP-13 RS2252070 polymorphism under heterozygote model with random effects. Row represents the pooled odds ratio (OR) and corresponding 95% confidence interval (95% CI) of all studies after eliminating the corresponding study for each row.

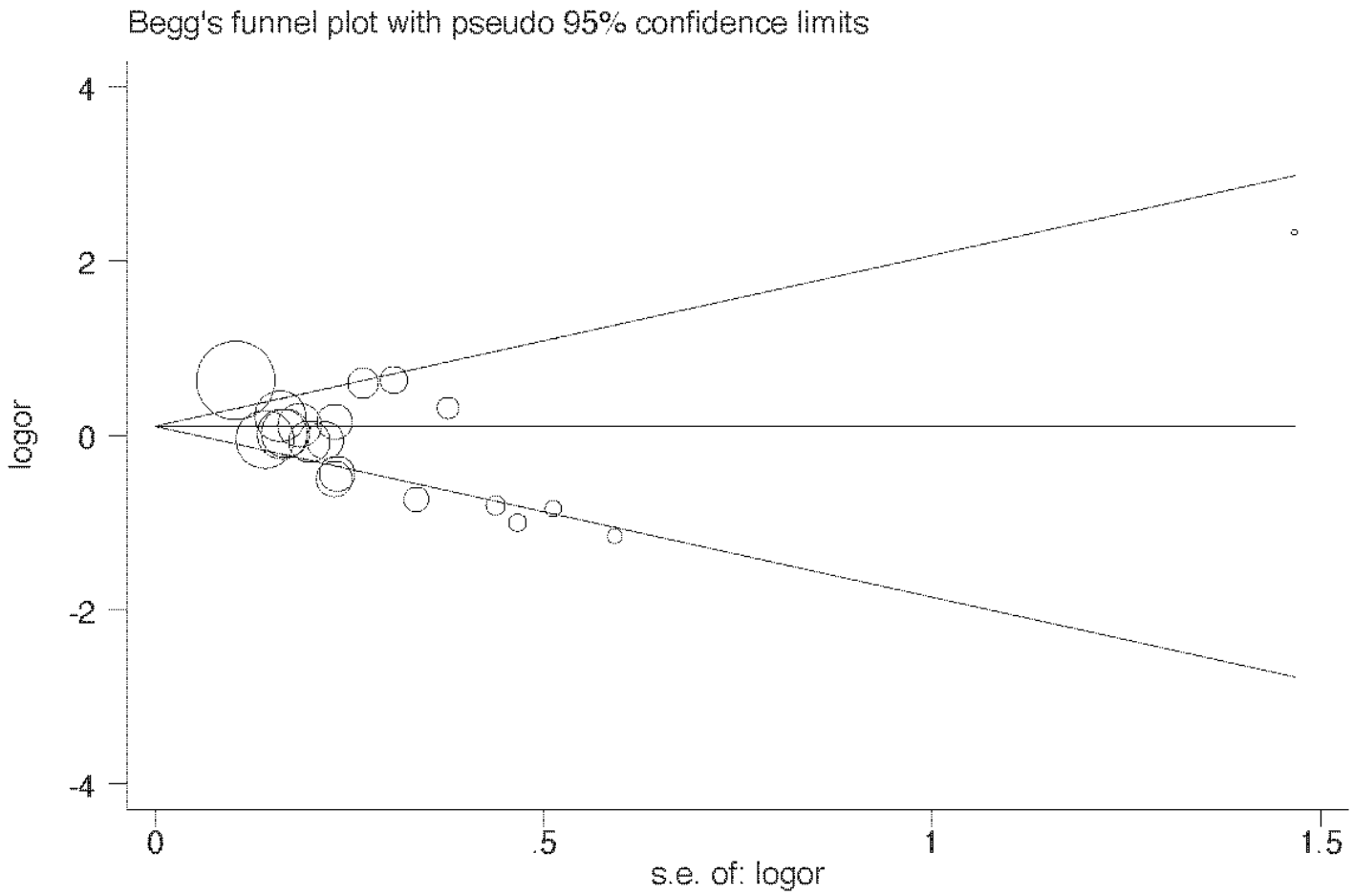

Figure 4

Funnel plot represents the results of the meta-analysis of MMP-13 rs2252070 polymorphism under heterozygous model using begg method. The X-axis represents the standard error of the log OR, and the Y-axis represents the log odds ratio (OR) stands. Each circle in the figure represents a study, and the size of the circle is proportional to the size of the sample.

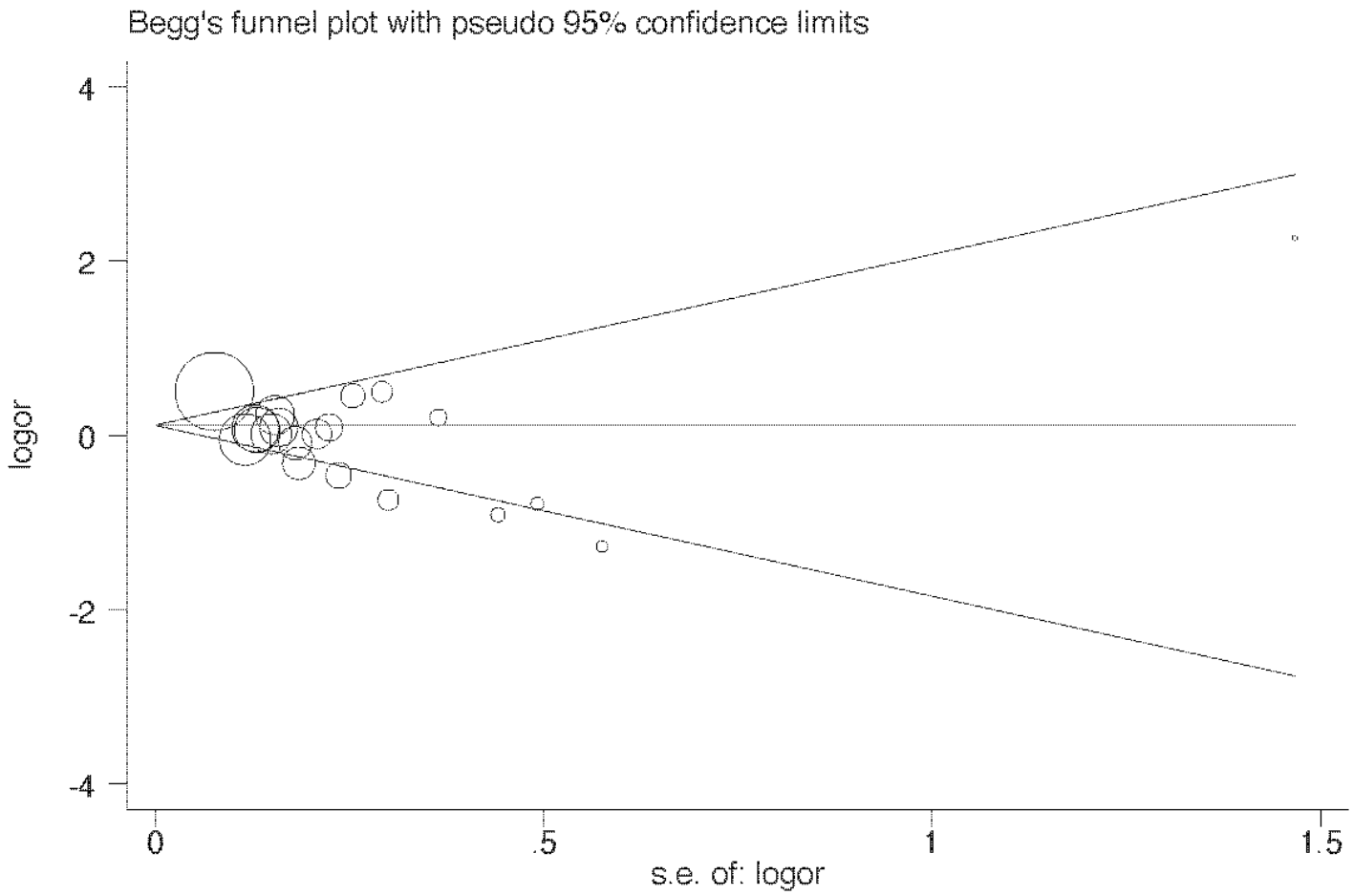

Figure 5

Funnel plot represents the results of the meta-analysis of MMP-13 rs2252070 polymorphism under recessive model using begg method. The X-axis represents the standard error of the log OR, and the Y-axis represents the log odds ratio (OR) stands. Each circle in the figure represents a study, and the size of the circle is proportional to the size of the sample.

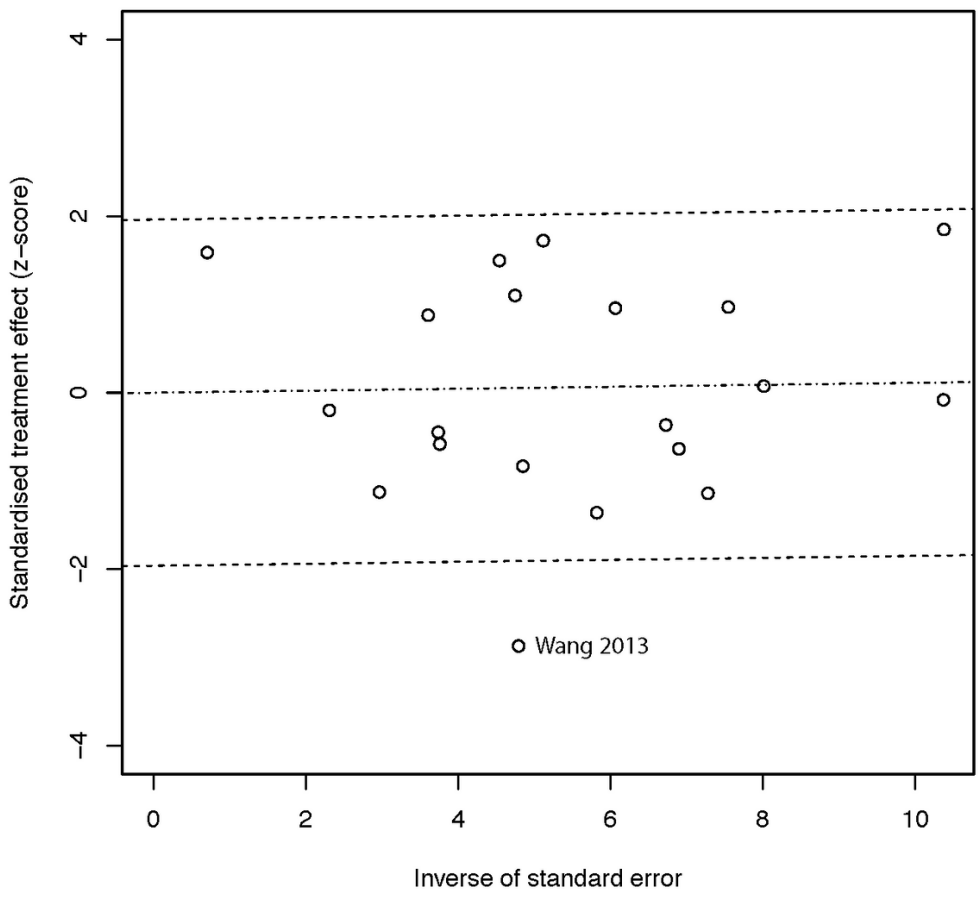

Figure 6

The Galbraith diagram shows the heterogeneity analysis results of MMP-13 rs2252070 under heterozygote model. The X-axis represents the inverse of the standard error of the effect value, and the Y-axis is the standardized treatment effect (z-score). Each point represents a study. There are three oblique lines in the figure, the slope of the middle line represents the pooled value of the random effect, and the line on both sides represents the 95% confidence interval (95% CI). Studies outside the bilateral line indicate the source of inter-study heterogeneity. They were tagged with the first author's last name and year of publication.