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Original Article

The associations of single nucleotide polymorphism rs2295080 in mTOR with cancer risk: an updated meta-analysis

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Abstract: Many studies have examined the association of the mTOR gene rs2295080 (T/G) polymorphism with cancer susceptibility, but the findings have been inconsistent. To evaluate the effect of the mTOR rs2295080 polymorphism on cancer risk, fifteen articles (containing 9207 cases and 10739 controls) were examined for this meta-analysis. To assess the degree of association, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random effects model. In total, our results indicated that rs2295080 is associated with a decreased risk of cancer in the dominant-model and in the heterozygous-model (TG + GG versus TT: OR = 0.88, 95% CI 0.79-0.99 P = 0.035; TG versus TT: OR = 0.89, 95% CI 0.81-0.98 P = 0.021). Performing a sub-group analysis based on systemic cancer type, we observed that the rs2295080 polymorphism decreased the cancer risk in urogenital system cancers (TG + GG versus TT: OR = 0.72, 95% CI 0.58-0.90 P = 0.004; G versus T: OR = 0.75, 95% CI 0.58-0.97 P = 0.026; TG versus TT: OR = 0.77, 95% CI 0.69-0.86 P = 0.000). It is noteworthy that we found the rs2295080 polymorphism significantly increased the risk in blood system cancers (GG versus TG + TT: OR = 2.25, 95% CI 1.30-3.91 P = 0.004; G versus T: OR = 1.24, 95% CI 1.05-1.47 P = 0.013; GG versus TT: OR = 2.25, 95% CI 1.33-3.82 P = 0.003). However, we did not find a correlation between the rs2295080 polymorphism and cancer risk of the digestive system in any of the five models. Thus, possible additional factors related to the risk of cancer of the digestive system should be investigated in further studies.

Keywords: mTOR, rs2295080, polymorphism, cancer, risk

Introduction

The mammalian target of rapamycin (mTOR) located on chromosome 1p36.2, is composed of 2549 amino acids and is arranged in a highly conservative structural domain [1, 2]. mTOR is a molecular downstream PI3K/AKT signaling pathway, which plays a vital role in cellular physiological processes, for example angiogenesis, metabolism, proliferation, migration, and apoptosis [3-8]. An abnormal mTOR signaling pathway is connected with the formation and progression of multiple tumors [9, 10]. It includes many malignancies, such as bladder tumors, acute lymphocytic leukemia (ALL), prostate gland cancer, colorectal cancer, esophageal cancer, etc. On the one hand, the mTOR pathway inhibits the apoptosis of normal cells and promotes the carcinogenesis of normal cells. On the other hand, it also promotes the proliferation rate of cancer cells [3], thus making people more susceptible to cancer. Most of these SNPs of mTOR, located in the unknown function effect of exons and introns, which affect the transcription factor (transcriptional factor, TF) after the combining ability and genetic transcription.

Many studies have found that the SNP rs2295080 is closely related to tumors [11-13], such as Zhao et al. found that the rs2295080 with the G allele was higher in the AL group than it was in the controls [14]. Earlier, only Shao et al. Jin et al. and Zhang et al. individually performed a meta-analysis said that the mTOR promoter region rs2295080 is associated with the

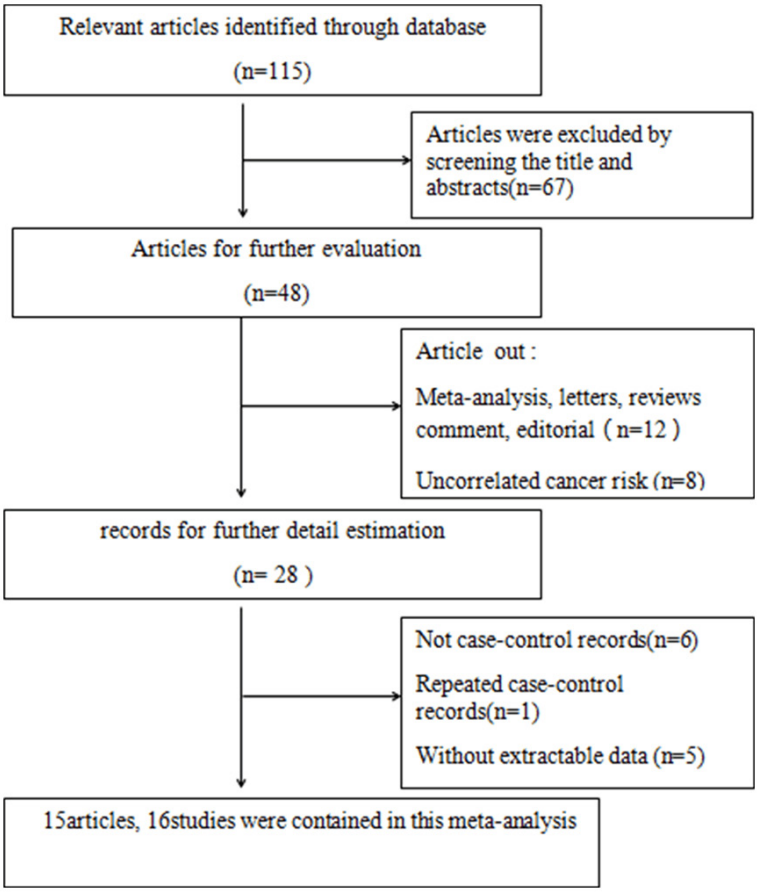

Figure 1. Flow diagram of the process for study selection. A total of 15 articles were identified and one of the articles contained two studies. So, there were 16 studies included in our meta-analysis.

risk of cancer. But their results were not consistent [15-17]. Since then, there have been 6 studies on the correlation between rs2295080 and tumors. For example, Liu et al. found that the GT genotype of mTOR rs2295080 G > T provided more protection against prostate cancer than the TT genotypes [18]. These newly published studies reveal potential features of rs2295080 polymorphisms and question the conclusions from the meta-analyses that were published before. Accordingly, we performed this updated meta-analysis to reevaluate the role of SNP rs2295080 in tumorigenesis and to provide a more accurate correlation assessment.

Materials and methods

Search identification and selection

The eligible studies was collected by searching the PubMed database, Google Scholar, and CNKI. WanFang Date, with We searched using the keywords "mTOR" or "rs-2295080", "Polymorphisms" or "SNP", "cancer or carcinoma or tumor" and "risk" as well as their combinations published up through December 2018 in any language. We looked for studies that revealed the correlation between SNP rs2295080 and the risk of cancer.

Inclusion and exclusion criteria

Studies were selected in this meta-analysis if they met the criteria: 1. Case-control studies; 2. Studies that offered genotype frequencies to count the value of odds ratios (ORs) and 95% confidence intervals (95% CI); 3. Studies that assessed the relevance between SNP rs2295080 and the risk of cancer. Exclusion criteria: 1. Reviews or editorials; 2. Animal studies. The titles and abstracts were viewed and the full articles were further estimated to verify their feasibility based on the inclusion and exclusion criteria, and all questions were discussed and handled by three reviewers.

Data extraction

Two researchers (K.H.W and L.Z.J) independently extracted data from all the eligible studies. If a dispute remained unresolved, the third investigator (J.J.X) would be take part to adjudicate the disagreements. All the selected data were drawn up in a unified format, and the following contents were collected: first author's name, year of publication, source of the controls, ethnicity, genotypic method, the number of cases and controls, genotype frequency (TT, TG, GG). Of course, the outcomes of the Hardy-Weinberg equilibrium (HWE) test were also included.

Statistical analysis

When the frequency of the control genotype meets HWE, a Chi-square (2) test is carried out.

Table 1. Main characteristics of studies (containing 9207 cases and 10739 controls) selected in the meta-analysis

Author	Year	Genotypic method	Country ethnicity	Cancer type	Source of controls	Cases			Controls			*P* value of HWE*
						TT	TG	GG	TT	TG	GG	
Chen et al. [24]	2012	RFLP-PCR	CHINA (Han)	Prostate	HB	429	209	28	413	259	36	0.69
Huang et al. [25]	2012	RFLP-PCR	CHINA (Han)	All	HB	254	140	23	353	180	21	0.52
Cao et al. [13]	2012	aqMan assay	CHINA (Han)	RCC	HB	454	218	38	438	277	45	0.08
Li et al. [26]	2013	RFLP-PCR	CHINA (Han)	Prostate	PB	653	311	40	617	382	52	0.70
Xu et al. [12]	2013	RFLP-PCR	CHINA (Han)	Gastric	HB	482	246	25	497	305	52	0.35
Xu et al. [27]	2015	RFLP-PCR	CHINA (Han)	Colorectal	HB	482	225	30	459	273	45	0.56
Zhu et al. [28]	2015	TaqMan assay	CHINA (Han)	ESCC	HB	674	390	49	702	362	49	0.43
Zhao et al. [14]	2015	RFLP-PCR	CHINA (Han)	ALL	HB	68	50	15	173	111	12	0.22
Zhao et al. [14]	2015	RFLP-PCR	CHINA (Han)	AML	HB	27	14	6	173	111	12	0.07
Wang et al. [29]	2015	RFLP-PCR	CHINA (Han)	Gastric	HB	568	394	40	607	355	41	0.00
Zhao et al. [30]	2016	Sequencing	CHINA (Han)	Breast	HB	351	197	12	345	212	26	0.01
Zhao et al. [21]	2017	TaqMan assay	CHINA (Han)	Gastric	HB	178	90	15	174	86	11	0.42
Liu et al. [18]	2017	RFLP-PCR	CHINA (Han)	Prostate	HB	236	145	32	454	316	37	0.15
Wen et al. [20]	2017	RFLP-PCR	CHINA (Han)	Thyroid	HB	366	170	24	295	176	29	0.45
Qi et al. [22]	2017	RFLP-PCR	CHINA (Han)	Gastric	HB	194	279	101	297	441	174	0.97
Bizhani et al. [23]	2018	RFLP-PCR	IRANIAN (Caucasian)	Bladder	PB	65	90	80	26	76	152	0.00

Note: RFLP-PCR, restriction fragment length Polymorphism-polymorphism chain reaction; ALL, Acute lymphocytic leukemia; AML, Acute myeloid leukemia; RCC, Renal cell cancer; ESCC, Esophageal squamous cell carcinoma; HB, Hospital based; PB, Population based; *HWE, Hardy-Weinberg equilibrium; P > 0.05 indicates that the participants in the case group met the HWE.

Table 2. Meta-analysis of the association between the rs4986790 polymorphism and cancer risk. The results were Odd ratio (OR), 95% confidence interval (95% CI) and *P*-value were tested to evaluate the association

Genotype	Number of studies [12-14, 18, 20-30]	OR (95% CI)	*P*-value	Pheterogeneity	I^2 (%)	Begg's test and egger's test	
						P_B	P_E
Systemic cancer type							
Overall	16						
TG + GG/TT		0.88 (0.79, 0.99)	0.035	0.000	72.6	0.558	0.535
GG/TG + TT		0.92 (0.72, 1.18)	0.519	0.000	75.6	0.192	0.122
GG/TT		0.88 (0.67, 1.15)	0.345	0.000	77.6	0.558	0.390
TG/TT		0.89 (0.81, 0.98)	0.021	0.004	55.4	1.000	0.407
G/T		0.90 (0.80, 1.01)	0.073	0.000	82.3	1.000	0.982
Urogenital system cancers	5						
TG + GG/TT		0.72 (0.58, 0.90)	0.004	0.002	77.1		
GG/TG + TT		0.80 (0.47, 1.37)	0.420	0.000	86.3		
GG/TT		0.69 (0.38, 1.27)	0.236	0.000	87.5		
TG/TT		0.77 (0.69, 0.86)	0.000	0.384	4.0		
G/T		0.75 (0.58, 0.97)	0.026	0.000	89.2		
Blood system cancers	3						
TG + GG/TT		1.17 (0.96, 1.44)	0.142	0.722	0.00		
GG/TG + TT		2.25 (1.30, 3.91)	0.004	0.225	33.0		
GG/TT		2.25 (1.33, 3.82)	0.003	0.263	25.1		
TG/TT		1.07 (0.86, 1.33)	0.574	0.691	0.0		
G/T		1.24 (1.05, 1.47)	0.013	0.48	0.0		
Digestive system cancers	6						
TG + GG/TT		0.96 (0.82, 1.12)	0.598	0.006	69.7		
GG/TG + TT		0.85 (0.69, 1.05)	0.126	0.241	25.8		
GG/TT		0.84 (0.65, 1.08)	0.175	0.108	44.6		

TG/TT		0.98 (0.85, 1.13)	0.773	0.026	60.7
G/T		0.95 (0.83, 1.08)	0.443	0.003	72.2
Other system cancers	2				
TG + GG/TT		0.81 (0.69, 0.97)	0.019	0.482	0.0
GG/TG + TT		0.61 (0.40, 0.95)	0.027	0.333	0.0
GG/TT		0.57 (0.37, 0.89)	0.013	0.400	0.0
TG/TT		0.85 (0.81, 0.98)	0.069	0.381	0.0
G/T		0.80 (0.69, 0.92)	0.002	0.928	0.0

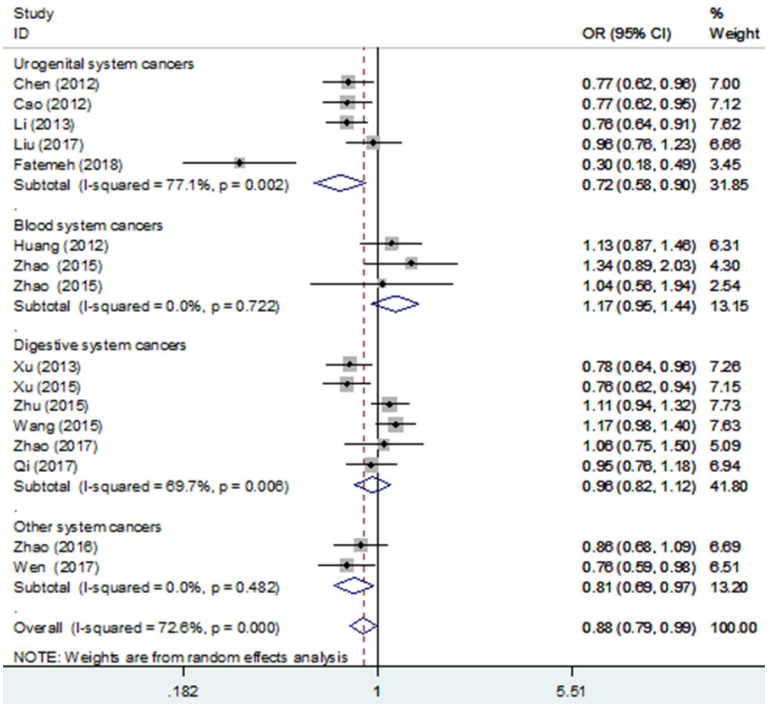

Figure 2. Overall and individual systemic meta-analysis of the mTOR rs0095080 polymorphism and cancer risk in the dominant-model.

ORs with 95% CIs were calculated to evaluate the assessment between the SNP rs2295080 and cancer risk [19]. The pooled ORs were calculated for the dominant model (TG + GG vs TT), recessive models (GG vs TG + TT), homozygote models (GG vs TT), heterozygote model (TG vs GG), additive model (G vs T). The statistical significance was evaluated using a Z test. On the side, a subgroup analysis was conducted according to the systematic tumor classification of the participants. Q and I^2 statistical magnitudes were customized to assess heterogeneity to measure the tightness of the genetic links. Theoretically speaking. The CIs ratio calculated by the random effects model is larger than the fixed effect model. In addition, the results of the random effect model are more conservative. Therefore, we selected random effects model. In addition, Begg's funnel plot test and Egger's regression test are used to assess publication bias, $P < 0.05$ is supposed to indicate publication bias. We used STATA software (version 12.0, Stata Corporation, College Station, TX). All values of test were two sided.

Results

Study characteristics

Figure 1 lists the detailed screening process. According to our inclusion and exclusion criteria, a total of 15 articles containing 16 case-control studies (containing 9207 cases and 10739 controls) were conformed to the meta-analysis study, respectively [12-14, 18, 20-30]. The studies include those written in the Chinese language [14, 20-22]. The studies and the main characteristics in this meta-analysis are presented in **Table 1**.

Meta-analysis results

We gathered statistics from 16 studies (containing 9207 cases and 10739 controls) to investigate the relationship between the mTOR rs2295080 polymorphism and cancer risk. The consequences of rs2295080 with cancer risk in five models are provided in **Table 2**. A forest plot of the overall and subgroup analyses with different models is shown in **Figures 2-6**. It demonstrated that the rs2295080 polymorphism has a connection with the reduction of cancer risk among the whole populace in the dominant-model and heterozygous-model (TG

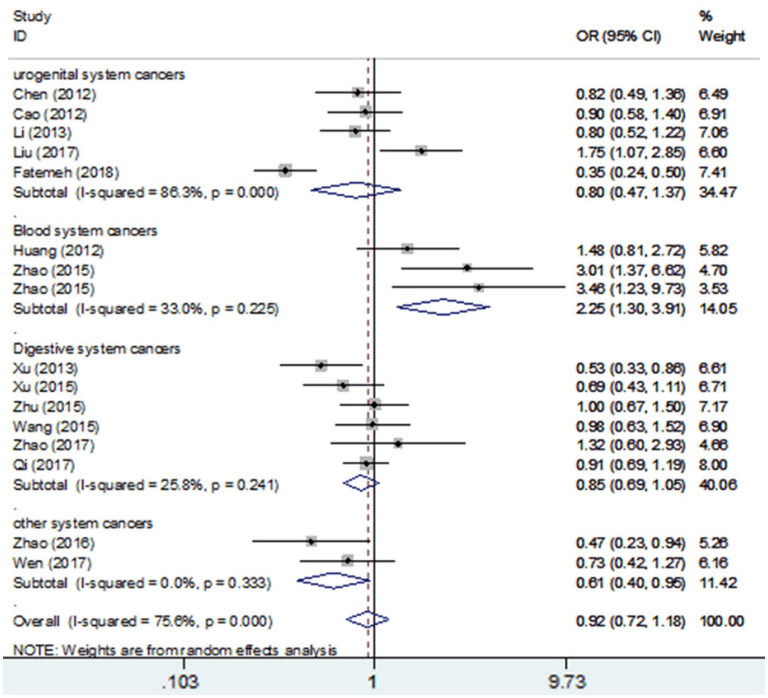

Figure 3. Overall and individual systemic meta-analysis of the mTOR rs0095080 polymorphism and cancer risk in the recessive-model.

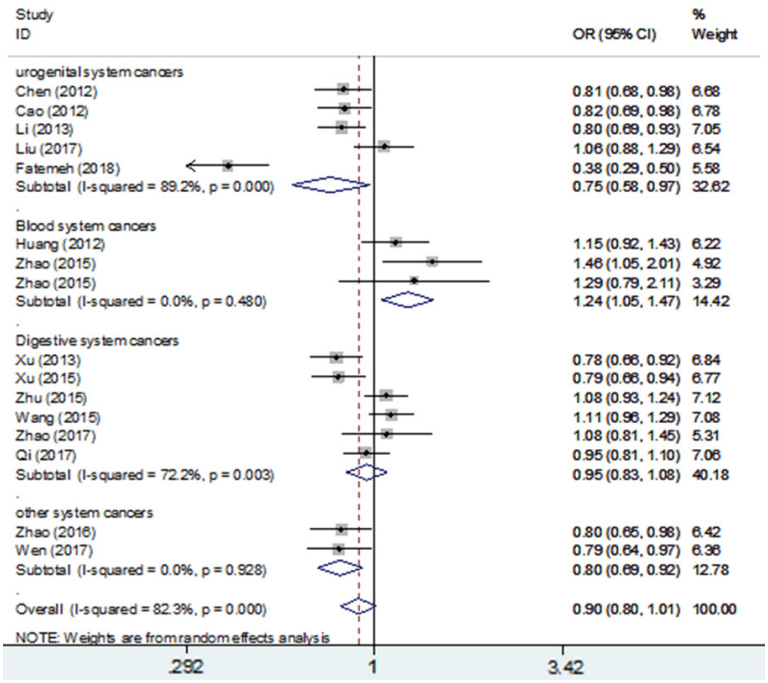

Figure 4. Overall and individual systemic meta-analysis of the mTOR rs0095080 polymorphism and cancer risk in the additive-model.

+ GG versus TT: OR = 0.88, 95% CI 0.79-0.99 P = 0.035; TG versus TT: OR = 0.89, 95% CI 0.81-0.98 P = 0.021).

A subgroup analysis showed that the rs2295080 gene polymorphism reduced the risk of urogenital system cancers (TG + GG versus TT: OR = 0.72, 95% CI 0.58-0.90 P = 0.004; G versus T: OR = 0.75, 95% CI 0.58-0.97 P = 0.026; TG versus TT: OR = 0.77, 95% CI 0.69-0.86 P = 0.000). But, it is noteworthy that we found the rs2295080 polymorphism significantly increased the cancer risk in blood system cancers (GG versus TG + TT: OR = 2.25, 95% CI 1.30-3.91 P = 0.004; G versus T: OR = 1.24, 95% CI 1.05-1.47 P = 0.013; GG versus TT: OR = 2.25, 95% CI 1.33-3.82 P = 0.003). However, we didn't observe any connection between SNP rs2295080 and cancer risk in the digestive system in any of the models.

Evaluation of heterogeneity

The *P* value is Cochran's Q test for between-study heterogeneity in every genetic comparison model. As shown in **Tables 1**, **2** and **Figures 2**-**6**, obvious heterogeneities existed in the overall meta-analysis model. The random effects model was selected. Another analysis we performed was the further sub-group analysis.

Publication bias

Begg's funnel plots were used for evaluating publication bias in different models. As displayed in **Table 2** and **Figures 7**-**11**, these studies have no significant publication bias.

Discussion

MTOR is a key part of the P13K/AKT/mTOR signaling pathway. By altering gene expression widely distributed in mTOM, protein function

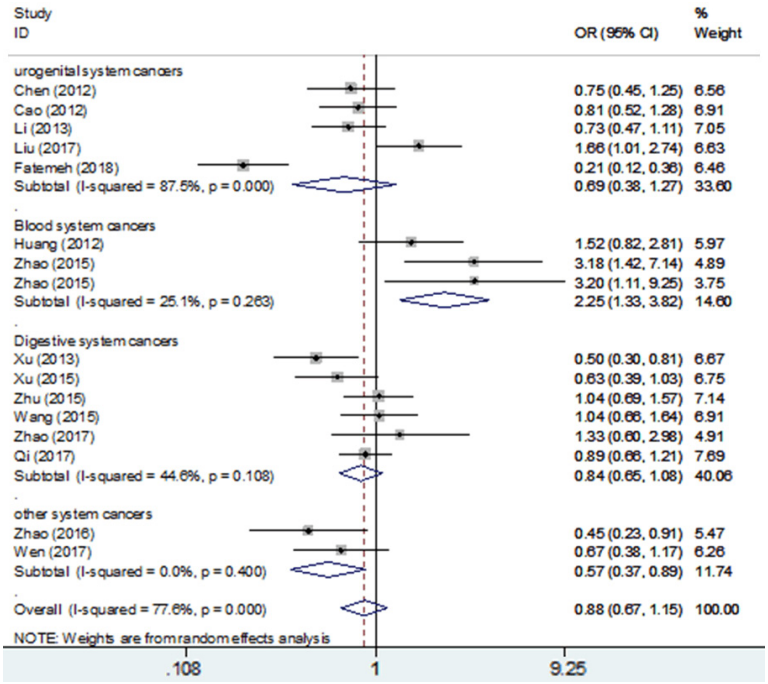

Figure 5. Overall and individual systemic meta-analysis of the mTOR rs0095080 polymorphism and cancer risk in the homozygous-model.

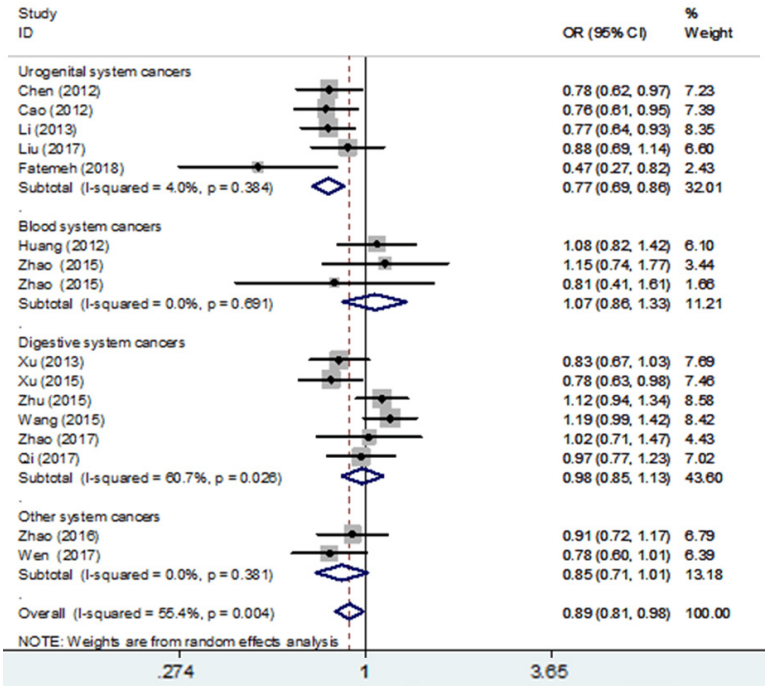

Figure 6. Overall and individual systemic meta-analysis of the mTOR rs0095080 polymorphism and cancer risk in the heterozygous-model.

was affected. The mutated mTOR protein in mTOR's kinase domain has been shown to involve constitutive activation [31-33], which has been shown to influence the cell size and cycle progression of human tumor cells [31]. Studies have shown that SNP can be applied to different organs' tumor cellular physiological processes, that rs2295080 in the promoter region of the mTOR gene is associated with tumors [3, 12, 13]. XU et al. showed that the mTOR rs2295080 promoter region polymorphism is connected with a significant risk for gastric cancer. Meanwhile, the single nucleotide site effectively influenced the expression of mTOR and the change of the G allele loci through the combination of some transcription factors that may affect or significantly change the mTOR gene transcription activity, and the T allele and body mTOR mRNA expression level is higher [12].

In the previous three meta-analyses, first a meta-analysis only contained 5 studies presented that the rs2295080 G allele is related to a decreased cancer risk [15], and the other one included eight studies suggesting that rs2295080 G allele increased the risk of acute leukemia and decreased the risk of genitourinary cancers [16], and the final meta-analysis results showed a substantial reduction risk between rs2295080 TG, GG genotype, and the GG/TG genotypes and whole cancer and the subgroup of urinary system tumors and digestive system tumors [17]. The above results of the three articles is not consistent; meanwhile, there were 6 studies on the correlation between rs2295080 and tumors. For example, Liu et al. found that the GT genotype of mTOR rs2295080 G > T was more of a safeguard than the TT genotypes to prostate cancer [18], and Wen et al. showed that the G allele may be a protective gene in the

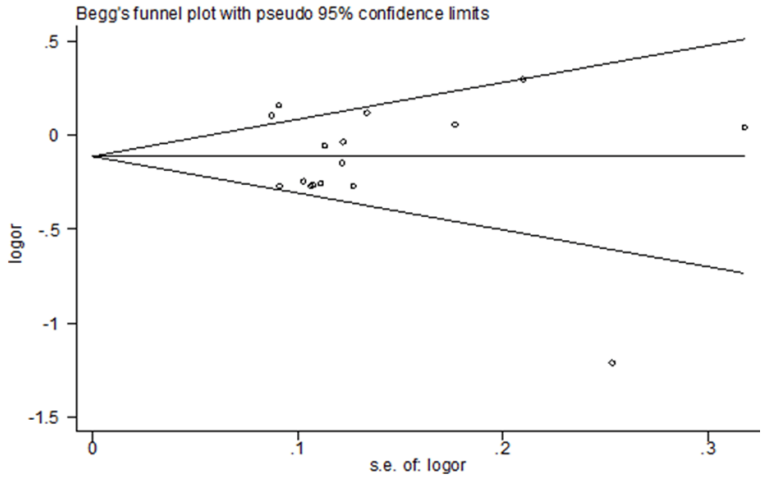

Figure 7. Funnel plot analysis to detect publication bias for rs2995080 (TG + GG/TT) polymorphism associated with cancer risk.

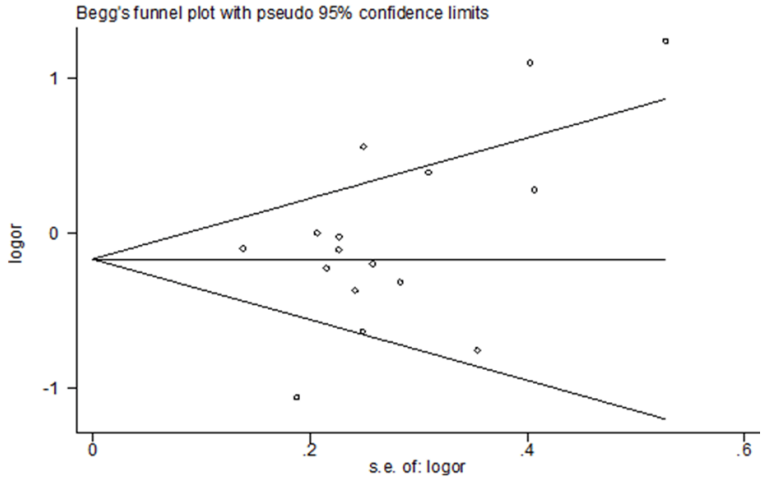

Figure 8. Funnel plot analysis to detect publication bias for rs2995080 (GG/TG + TT) polymorphism associated with cancer risk.

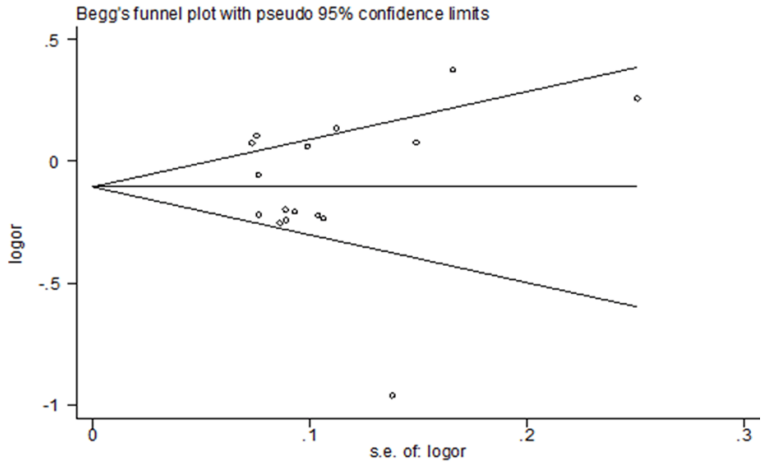

Figure 9. Funnel plot analysis to detect publication bias for rs2995080 (GG/TT) polymorphism associated with cancer risk.

pathogenesis of thyroid cancer [20]. Zhao et al. suggested that SNP rs2295080 was not relevant with the risk of noncardia gastric cancer [21], whereas Qi et al. confirmed that the rs2295080 polymorphisms were associated with gastric cancer risk [22]. Bizhani et al. observed that the mTOR rs2295080 (G/T) variant notably increased bladder tumor risk in the Iranian population [23].

The results of our research had the same and different findings as other studies. According to 16 studies with 9207 cases and 10739 controls about the correlation of the mTOR rs2295080 polymorphism with cancer risk, this meta-analysis offered strong evidence of the association that rs2295080 (TG, GG genotype, G allele and TG/GG genotypes) was a protective factor for overall cancer. It is the same point with the previous meta-analysis [15, 17]. Another example, in the subgroup analysis, the results of our research show that the rs2295080 polymorphism is able to decrease the risk of urogenital system cancers. But significantly, it increases the risk of cancers in the blood system. This could be attributed to the cancer-specific characteristics. The difference was that the conclusion of this meta-analysis was the opposite of the previous meta-analysis between rs2295080 and digestive system tumor risk, and we did not observe that rs2295080 is a protective or risk factor for digestive system tumors, but rs2295080 was correlated with decreasing the risk of digestive system tumor in a previous meta-analysis [17]. That is to

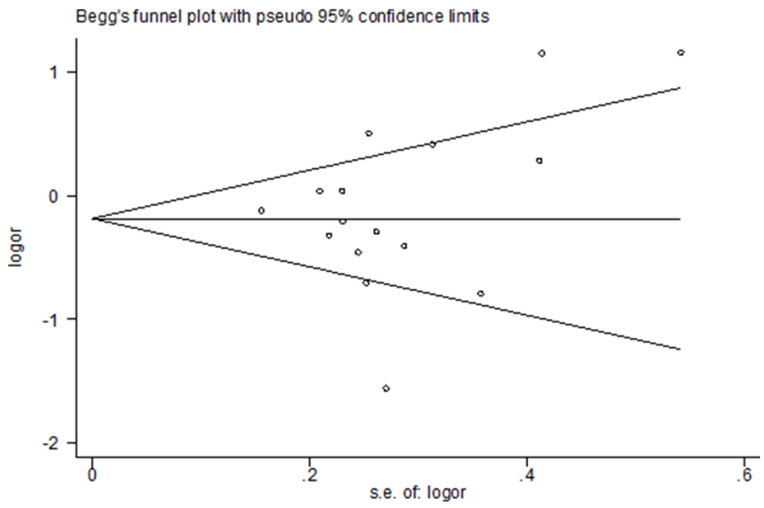

Figure 10. Funnel plot analysis to detect publication bias for rs2995080 (TG/TT) polymorphism associated with cancer risk.

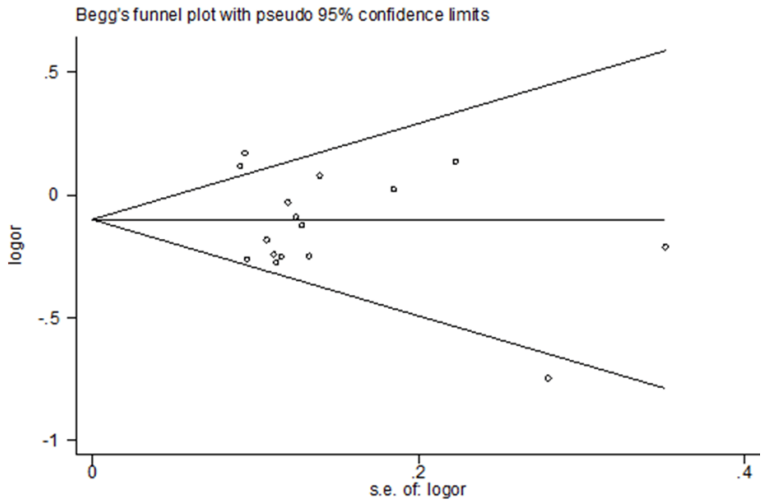

Figure 11. Funnel plot analysis to detect publication bias for rs2995080 (G/T) polymorphism associated with cancer risk.

say, there were different conclusions among different studies on the same topic. On the one hand, country, gender and ethnic differences in the study population may influence the results of the study. On the other hand, usually for a study, a sufficient sample size is an important guarantee of the accuracy of the results. The larger the sample size, the more convincing the results, and different sample sizes will lead to different results in different studies. In addition, cancer diagnostic methods, genotyping methods, and statistical analysis methods can play an important role in the results of each study. Using different research methods, the final result may be different.

There is prominent heterogeneity in the meta-analysis. Heterogeneity covers many sides, such as tumor type, sample size, race, lifestyle, environment, etc. Thus, a subgroup analysis was performed according to the tumor type to find the source of heterogeneity. In addition, there are some limitations of meta-analyses. First, the number of tumor samples is not large enough to affect the effectiveness and reliability of the results. Second, a subgroup analysis is based only on systemic cancer types. Third, ethnicity, lifestyle, dietary habits, and environment may affect gene expression, causing differing results. Therefore, to get more precise results, additional studies on the association of mTOR rs2295080 with cancer risk are needed about different ethnicities, cancer types, life-style, diet and environment.

In conclusion, our results indicate that rs2295080 is connected with a decrease in the whole cancer risk in the dominant-model and heterozygous-model, A subgroup analysis was performed by cancer systemic type, and we observed that the rs2295080 polymorphism decreased the cancer risk in urogenital system cancers, but it increased the risk in blood system cancers, Therefore, our conclusion is that the biological effects of rs2295080 may be cancer-specific. It is worth noting that the significant differences regarding rs2295080 in the cancer of the digestive system. Some studies have shown that SNP rs2295090 can reduce cancer risk, but others have shown the opposite. Maybe a more detailed classification on the basis of region, age, upper and lower alimentary canal cancer, pathological, histological, and molecular characteristics are helpful to illuminate the connection between rs2295080 and gastrointestinal tumors and other tumors.

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Disclosure of conflict of interest

None.

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