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Functional Foxp3 polymorphisms and the susceptibility to cancer

An update meta-analysis

ZhenYun Cheng, PhD, Yan Guo, PhD, Liang Ming, PhD*

Abstract

Background: Forkhead box P3 (Foxp3) plays important roles in the development and pathogensis of cancer. To investigate the association of 3 polymorphisms of Foxp3 (rs3761548, rs 3761549 and rs2280883) and cancer risk, an updated meta-analysis was performed.

Methods: Around 11 studies including 4344 cancer patients and 4665 healthy controls were selected for this meta-analysis. There were nine studies with 3783 cases and 4096 controls for rs3761548, 4 studies with 1669 cases and 1613 controls for rs3761549 and 4 studies with 1821 cases and 1799 controls for rs2280883. Odds radios (ORs) and 95% confidence intervals (CIs) were used to evaluate the cancer risk.

Results: Meta-analysis showed that rs3761548 was associated with an increased cancer risk in the overall population under the recessive model (AA vs CA+CC: OR=1.45, 95%CI=1.03–2.02, P=.03). No association was found between rs3761549, rs2280883 polymorphisms, and cancer susceptibility in the overall population. Nonetheless, in the genotyping methods subgroup analysis of rs2280883, a lower risk of cancer was found in studies using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) under the allelic model (C vs T: OR=0.70, 95%CI=0.52–0.95, P=.02), heterozygote model (TC vs TT: OR=0.60, 95%CI=0.41–0.87, P=.008) and dominant model (CC+TC vs TT: OR=0.63, 95%CI=0.45–0.90, P=.01). In the subgroup analysis by cancer types showed C allele or TC carriers were insusceptible to cancer under 3 genetic models (C vs T: OR=0.78, 95%CI=0.64–0.95, P=.01; TC vs TT: OR=0.50, 95%CI=0.32–0.79, P=.003; CC+TC vs TT: OR=0.64, 95%CI=0.51–0.82, P<.001).

Conclusion: Our results suggest that rs3761548 polymorphism is associated with cancer risk.

Abbreviations: AS-PCR = allele specific-polymerase chain reaction, CI = confidence interval, CNS2 = conserved noncoding sequence 2, DTC = differentiated thyroid cancer, Foxp3 = Forkhead box P3, MALDI-TOF = matrix assisted laser desorption/ionization-time-of-flight mass spectrometry, NOS = Newcastle–Ottawa Scale, OR = odds radio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PRISMA = Preferred Reporting Items for Systemic Reviews and Meta-Analysis, SNP = single nucleotide polymorphism, Treg = regulatory T cell.

Keywords: cancer, Foxp3, meta-analysis, polymorphism

1. Introduction

Cancer is a global public health problem, and the number of affected people is much more in recent years. Since the high rate of recurrence and metastasis, the prognosis of cancer is still poor. The genesis of cancers resulted from alterations of multiple environmental factors and genes.[1] There are a lot of reports that single nucleotide polymorphisms (SNPs) are associated with cancer risk. Several studies have showed that polymorphic genes play vital roles in the development and pathogensis of cancer.[2–4] However, the specific mechanism of numerous polymorphic genes remain to be unknown.

Regulatory T cells (Tregs), aid in the immune response and autotolerance, are characterized by CD4+Foxp3+expression.[5,6] Foxp3, as a transcription factor, is predominantly expressed on Tregs and involved in the regulation, activation and differentiation of T cells.[7] Foxp3 expression is crucial for Tregs which may cause an abnormal production of Tregs in several different mechanisms.[8,9] Besides, several studies showed that the lower or loss of Foxp3 expression may contribute to the development of cancers in humans.[10] The polymorphisms of Foxp3 were likely to change its expression level and impair the suppressive function of Tregs. Three polymorphisms of Foxp3, −3279/rs3761548 (C>A), −2383/rs3761549 (C>T) in the promotor and IVS9+459/rs2280883 (T>C) in the intron region, have been reported to be associated with cancer risk.[11,12]

In recent years, several studies have showed the association between these 3 functional polymorphisms and cancer risk.[11,13–15] Nonetheless, the results of these relevant studies remain to be inconsistent, possibly due to ethnicity, genotyping methods, and the sample size. Therefore, this meta-analysis was performed to evaluate the association of these 3 functional polymorphisms with the risk of cancer and heighten the effects of these SNPs.

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2. Materials and methods

2.1. Publication search

A systematic literature search was performed using PubMed, Embase, and Chinese Wanfang database. Eligible studies were identified to investigate the associations between Foxp3 polymorphisms and cancer risk, using the following keywords: Foxp3 or rs3761548/rs3761549/rs2280883, polymorphisms cancer/carcinoma/tumor. This meta-analysis was performed according to the guideline of Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA).[16] Additional eligible studies were manually searched from the reference of reviews and original articles.

2.2. Criteria for study selection

All the included studies for further meta-analysis were required to meet the following criteria: case–control study design; studies that investigated the association between the Foxp3 polymorphisms and cancer risk; all cases were cancer patients confirmed by histology or pathology; detailed allele and genotype frequencies of rs3761548 and/or rs3761549 and/or rs2280883 for estimating odds ratio (OR) and 95% confidence interval (CI). The reviews or case-only studies were excluded. If 2 or more studies included overlapping subjects, the study with the largest sample size was included in this meta-analysis.

2.3. Data extraction

All of the selected articles were independently reviewed by 2 authors. The discrepancies of data were discussed to reach an agreement by all the authors. The following information were extracted from each eligible study: first author, the year of publication, country of origin, ethnicity, genotyping methods, cancer types, number of cases and controls as well as the genotype frequencies in cases and controls. The ethnicities were classified as Caucasian, Chinese, and others. Genotyping methods were categorized as polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) and others. Additionally, selected studies were sorted as breast cancer and others by cancer types. The study was approved by the Ethics Committee of First Affiliated Hospital of Zhengzhou University.

2.4. Quality assessment

The quality of eligible case–control studies was assessed by 2 reviewers using Newcastle–Ottawa scale (NOS). The selected studies were judged on 3 broad perspectives, including the selection of study subjects (4 scores in total); the comparability of groups (2 scores in total); exposure factors or outcomes (3 scores in total). Low-quality studies: 0 to 4 points; high-quality studies: 5 to 9 points.

2.5. Statistical analysis

The association between Foxp3 polymorphisms and cancer risk was assessed by ORs and 95% CI. The significance of the pooled ORs was measured by the Z test with $P < .05$. This meta-analysis evaluated the association by using 5 different genetic models: homozygous model (aa vs AA), heterozygote model (Aa vs AA), dominant model (aa + Aa vs AA), recessive model (aa vs Aa + AA), and allelic model (a vs A; "a": variant allele; "A": wild-type allele). In addition, the stratified analysis was performed by ethnicity, genotyping methods, and cancer types. The statistical heterogeneity among studies was assessed by Cochran Q test and I^2 test. If the P value of heterogeneity test was $> .1$ ($P \geq .10$) or I^2 was $<50\%$, the fixed effects model was employed to estimate the pooled OR of the study. Otherwise, a random effects model was applied.[17] Funnel plot, egger's linear regression asymmetry test, and sensitivity analysis were performed to estimate the publication bias. All of the statistical tests were performed by review manager version 5.0 software (RevMan; The Cochrane Collaboration, Oxford, UK) and STATA 12.0.

3. Results

3.1. Characteristics of studies

By the combinations of the keywords, a total of 69 relevant studies were identified. As shown in Figure 1, 11 studies were included in this meta-analysis according to the inclusion criteria.[12–15,18–24] Among the eligible 11 studies, 4 were performed in Caucasians; 5 were carried out in Chinese and 2 were from other countries in Asia. In Haghighi's and Ozawa's studies, the men of cases and controls without detailed genotypes were excluded.

These studies included 4344 cancer patients and 4665 controls. In general, 9, 4, and 4 studies were pooled for this meta analysis of rs3761548, rs3761549, and rs2280883. In the view of genotyping methods, 6 studies were PCR-RFLP methods, the others were matrix assisted laser desorption/ionization-time of-flight mass spectrometry (MALDI-TOF), allele specific-polymerase chain reaction (AS-PCR), TaqMan assay, and direct sequencing. Besides, there were 5 studies about breast cancer, the others contained thyroid cancer, hepatocellular carcinoma, lung cancer, colorectal cancer, etc. Characteristics were summarized in Table 1. On the basis of NOS, each study received no <5 stars for methodological quality assessment.

3.2. Associations between Foxp3 polymorphisms and cancer risk

The genotypes and allele frequencies of eligible studies in this meta-analysis were shown in Table 2. The frequencies of minor allele for rs3761548, rs3761549 and rs2280883 varied widely from 0.20 to 0.53, 0.10 to 0.49, and 0.11 to 0.27 in cases, respectively; and 0.16 to 0.56, 0.05 to 0.49 and 0.15 to 0.35 in controls, respectively.

The association of rs3761548 polymorphism and cancer risk was carried out in nine studies with 3783 cases and 4096 controls. As shown in Table 3 and Figure 2, rs3761548 was associated with an increased cancer risk in the overall population under the recessive model (AA vs CA + CC: OR = 1.45, 95%CI = 1.03–2.02, $P = .03$). In the ethnic subgroup analysis, an increased cancer risk associated with rs3761548 polymorphism was found in Chinese under all genetic models (A vs C: OR = 1.58, 95%CI = 1.12–2.23, $P = .009$; AA vs CC: OR = 2.31, 95%CI = 1.37–3.90, $P = .002$; CA vs CC: OR = 1.46, 95%CI = 1.08–1.99, $P = .02$; AA + CA vs CC: OR = 1.62, 95%CI = 1.12–2.36, $P = .01$; AA vs CA + CC: OR = 2.00, 95%CI = 1.34–2.99, $P < .001$). However, no association was found for Caucasian and others under all genetic models. When stratified analysis was performed by cancer types, no association was observed in Breast cancer. Whereas, a significantly increased risk of other cancers was found in all genetic models (A vs C: OR = 1.73, 95%CI = 1.34–2.23, $P < .001$; AA vs CC: OR = 2.49, 95%CI = 1.48–4.19, $P < .001$; CA vs CC: OR = 1.66, 95%CI = 1.36–2.04, $P < .001$; AA + CA vs CC: OR = 1.85, 95%CI = 1.45–2.36, $P < .001$; AA vs CA + CC:

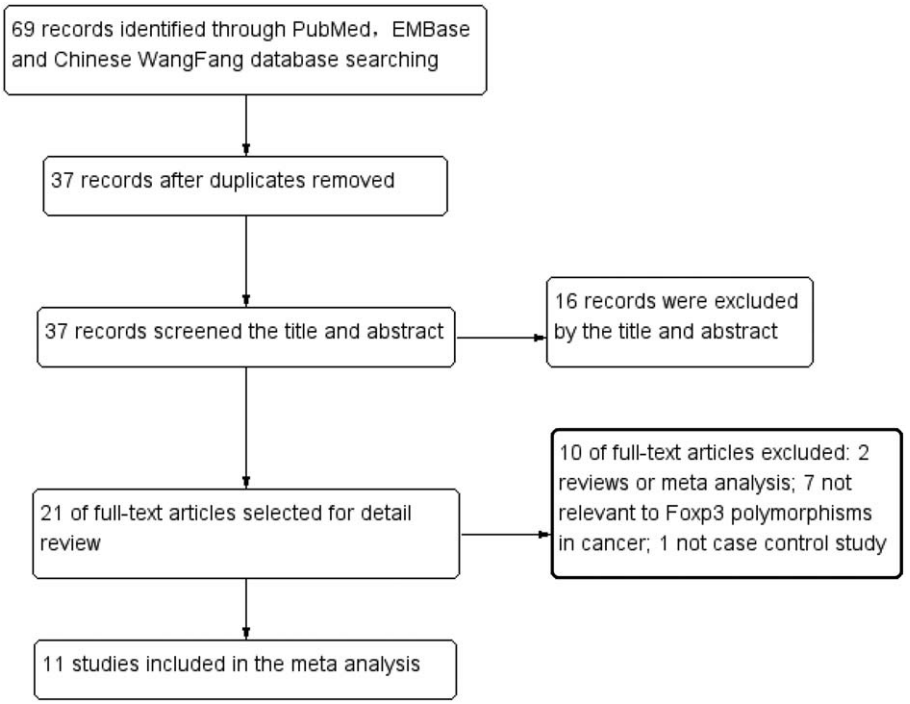

Figure 1. Flow diagram of the studies in this meta-analysis based on the selection criteria.

OR = 2.06, 95%CI = 1.29–3.30, $P = .002$). Negative results were obtained in genotyping method subgroup analysis.

For rs3761549 polymorphism, there were 4 studies based on Asian with 1669 cases and 1613 controls. In the stratified analysis by cancer types, a boardline risk of cancer was found under the allelic model (C vs T: OR = 0.78, 95%CI = 0.61–1.00, $P = .05$). We failed to find any association in other groups and genetic models.

For rs2280883 polymorphism, our meta-analysis included 4 studies with 1821 cases and 1799 controls. No significant association was observed in the overall population. In the genotyping methods subgroup analysis, a lower risk of cancer was found in studies using PCR-RFLP under the allelic model (C vs T: OR = 0.70, 95%CI = 0.52–0.95, $P = .02$), heterozygote model (TC vs TT: OR = 0.60, 95%CI = 0.41–0.87, $P = .008$) and dominant model (CC + TC vs TT: OR = 0.63, 95%CI = 0.45–0.90, $P = .01$; Fig. 3). In addition, subgroup analysis by cancer types showed C allele or TC carriers were insusceptible to cancer under 3 genetic models (C vs T: OR = 0.78, 95%CI = 0.64–0.95, $P = .01$; TC vs TT: OR = 0.50, 95%CI = 0.32–0.79, $P = .003$; Fig. 4; CC + TC vs TT: OR = 0.64, 95%CI = 0.51–0.82, $P < .001$). No correlation was detected in other models.

3.3. Heterogeneity analysis, sensitivity analysis and publication bias

Statistical heterogeneity among studies was tested by Q test and I^2 in all models and subgroup analysis across rs3761548, rs3761549, and rs2280883. Random effects model was performed when P-value of heterogeneity was <.1, otherwise fixed effects model was applied.

Sensitivity analysis showed that the correlation of rs3761548 polymorphism (recessive model: AA vs CA + CC, Fig. 5) with cancer risk remained significant after removing any one study in the meta-analysis.

Table 1

Characteristics of the eligible studies in this meat-analysis.

First author	Year	Country	Ethnicity	genotyping method	Cancer type	Total number (n)		Quality score
						Case	Control	
Raskin et al[13]	2009	Israel	Caucasian	TaqMan	Breast cancer	1444	1458	6
Chen et al[14]	2013	China	Chinese	MALDI-TOF	Hepatocellular carcinoma	392	372	7
Jahan et al[15]	2013	India	Asian	PCR-RFLP	Breast cancer	202	130	6
He et al[18]	2013	China	Chinese	PCR-RFLP	Lung carcinoma	192	259	5
Zheng et al[19]	2013	China	Chinese	MALDI-TOF	Breast cancer	1049	1091	6
Haghighi et al[20]	2014	Iranian	Asian	PCR-RFLP	Lung carcinoma	156	156	5
Chen et al[21]	2014	China	Chinese	PCR-RFLP	Colorectal cancer	360	400	6
Lopes et al[22]	2014	Brazil	Caucasian	AS-PCR	Breast cancer	50	115	5
Ozawa et al[12]	2016	Brazil	Caucasian	Sequencing	Wilms' tumor	32	78	5
Jiang et al[23]	2016	China	Chinese	PCR-RFLP	Thyroid cancer	350	306	6
Banin et al[24]	2017	Brazil	Caucasian	PCR-RFLP	Breast cancer	117	300	5

AS-PCR = allele specific-polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.,

Table 2

Genotype and allele frequency in the eligible studies.

	Genotype (N)								Allele frequency (N)			
	Case				Control				Case		Control	
	aa	Aa	AA	Total	aa	Aa	AA	Total	a	A	a	A
rs3761548												
Raskin 2009[13]	320	722	402	1444	303	763	392	1458	1362	1526	1369	1547
He 2013[18]	37	80	75	192	18	80	161	259	154	230	116	402
Jahan 2013[15]	27	160	15	202	20	106	4	130	214	190	146	114
Zheng 2013[19]	38	338	673	1049	30	342	719	1091	414	1684	402	1780
Chen 2014[21]	57	123	180	360	29	114	257	400	237	483	172	628
Lopes 2014[22]	6	17	27	50	4	66	45	115	29	71	74	156
Jiang 2016[23]	19	109	222	350	11	73	222	306	147	553	95	517
Ozawa 2016[12]	5	5	9	19	12	5	20	37	15	23	29	45
Banin 2017[24]	14	48	55	117	41	132	127	300	76	234	214	600
rs3761549												
Chen 2013[14]	59	28	301	388	41	88	233	362	146	630	170	554
Jahan 2013[15]	0	198	4	202	0	128	2	130	198	206	128	132
Zheng 2013[19]	32	283	734	1049	34	290	767	1091	347	1751	358	1824
Haghighi 2014[20]	1	4	25	30	0	3	27	30	6	54	3	57
rs2280883												
Chen 2013[14]	54	26	312	392	41	64	267	372	134	650	146	598
Zheng 2013[19]	35	365	649	1049	31	349	711	1091	435	1663	411	1771
Haghighi 2014[20]	1	14	15	30	4	13	13	30	16	44	21	39
Jiang 2016[23]	13	49	288	350	10	69	227	306	75	625	89	523

a = variant allele, A = wild-type allele.

Funnel plot and Egger's test were applied to access the potential publication bias. As shown in Figure 6, the funnel plots were all symmetrical in the 3 site of Foxp3 polymorphisms. Furthermore, by Egger's test, no publication bias existed in this meta-analysis.

4. Discussion

Foxp3 gene was thought to be an immunological regulator and repress oncogenes whilst activating additional tumor supressor genes.[25,26] Foxp3 was able to regulate the key target gene activation and supression and alter histione modification by binding to the promotors.[27,28] Recent years, many researchers have reported the associations between rs3761548, rs3761549, rs2280883 polymorphisms and susceptibility to cancer.[19,29] However, the results from these studies are controversy. Consequently, we performed this meta-analysis to systematically analyze the associations of Foxp3 polymorphisms and cancer risk using all the eligible studies.

Table 3

Meta-analysis of Foxp3 polymorphisms and cancer risk.

	a vs A		aa vs AA		Aa vs AA		aa + Aa vs AA		aa vs Aa + AA	
Comparisons	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
rs3761548										
Over all	1.21 (0.98–1.49)	.08	1.48 (0.95–2.30)	.08	1.11 (0.86–1.44)	.41	1.17 (0.89–1.54)	.26	1.45 (1.03–2.02)	**.03**
Caucasian	0.99 (0.90–1.09)	.83	1.02 (0.84–1.25)	.81	0.83 (0.58–1.17)	.29	0.91 (0.78–1.07)	.26	1.09 (0.75–1.59)	.64
Chinese	1.58 (1.12–2.23)	**.009**	2.31 (1.37–3.90)	**.002**	1.46 (1.08–1.99)	**.02**	1.62 (1.12–2.36)	**.01**	2.00 (1.34–2.99)	**<.001**
Others	0.88 (0.64–1.20)	.42	0.36 (0.10–1.25)	.11	0.40 (0.13–1.25)	.11	0.40 (0.13–1.22)	.11	0.85 (0.45–1.59)	.61
PCR-RFLP	1.37 (0.95–1.97)	.09	1.59 (0.75–3.35)	.30	1.30 (0.90–1.89)	.17	1.37 (0.89–2.12)	.15	1.57 (0.92–2.68)	.10
Others	1.03 (0.95–1.12)	.52	1.09 (0.90–1.32)	.38	0.93 (0.71–1.20)	.56	0.98 (0.83–1.16)	.83	1.20 (0.87–1.65)	.26
Breast cancer	1.01 (0.93–1.09)	.85	1.04 (0.75–1.43)	.82	0.87 (0.69–1.09)	.22	0.92 (0.76–1.11)	.38	1.11 (0.87–1.41)	.41
Others	1.73 (1.34–2.23)	**<.001**	2.49 (1.48–4.19)	**<.001**	1.66 (1.36–2.04)	**<.001**	1.85 (1.45–2.36)	**<.001**	2.06 (1.29–3.30)	**.002**
rs3761549										
Over all	0.94 (0.83–1.07)	.35	1.07 (0.77–1.48)	.68	0.66 (0.24–1.84)	.43	0.81 (0.47–1.39)	.45	1.22 (0.88–1.67)	.23
PCR-RFLP	1.03 (0.76–1.39)	.86	3.24 (0.13–83.08)	.48	1.08 (0.34–3.46)	.90	1.24 (0.39–3.87)	.72	3.10 (0.12–79.23)	.49
Others	0.93 (0.81–1.06)	.27	1.06 (0.76–1.46)	.75	0.51 (0.13–2.05)	.34	0.74 (0.38–1.42)	.36	1.20 (0.87–1.66)	.26
Breast cancer	1.01 (0.87–1.16)	.94	0.98 (0.60–1.61)	.95	1.02 (0.84–1.23)	.87	1.01 (0.84–1.22)	.89	0.98 (0.60–1.60)	.93
Others	0.78 (0.61–1.00)	.05	1.14 (0.74–1.75)	0.55	0.50 (0.09–2.74)	0.43	0.77 (0.25–2.35)	.64	1.43 (0.93–2.18)	.10
rs2280883										
Over all	0.88 (0.68–1.14)	.34	1.11 (0.82–1.50)	0.49	0.67 (0.35–1.26)	0.21	0.79 (0.53–1.18)	.25	1.18 (0.87–1.59)	.28
PCR-RFLP	0.70 (0.52–0.95)	**.02**	0.82 (0.38–1.76)	0.61	0.60 (0.41–0.87)	**0.008**	0.63 (0.45–0.90)	**.01**	0.89 (0.42–1.90)	.77
Others	1.00 (0.75–1.32)	.97	1.17 (0.85–1.63)	0.34	0.65 (0.20–2.08)	0.46	0.88 (0.51–1.54)	.66	1.24 (0.90–1.72)	.19
Breast cancer	1.13 (0.97–1.31)	.12	1.24 (0.75–2.03)	0.40	1.15 (0.96–1.37)	0.14	1.15 (0.97–1.38)	.11	1.18 (0.72–1.93)	.51
Others	0.78 (0.64–0.95)	**.01**	1.04 (0.71–1.52)	0.83	0.50 (0.32–0.79)	**0.003**	0.64 (0.51–0.82)	**<.001**	1.18 (0.81–1.71)	.39

a = variant allele, A = wild-type allele, CI = confidence interval, OR = odds ratio.

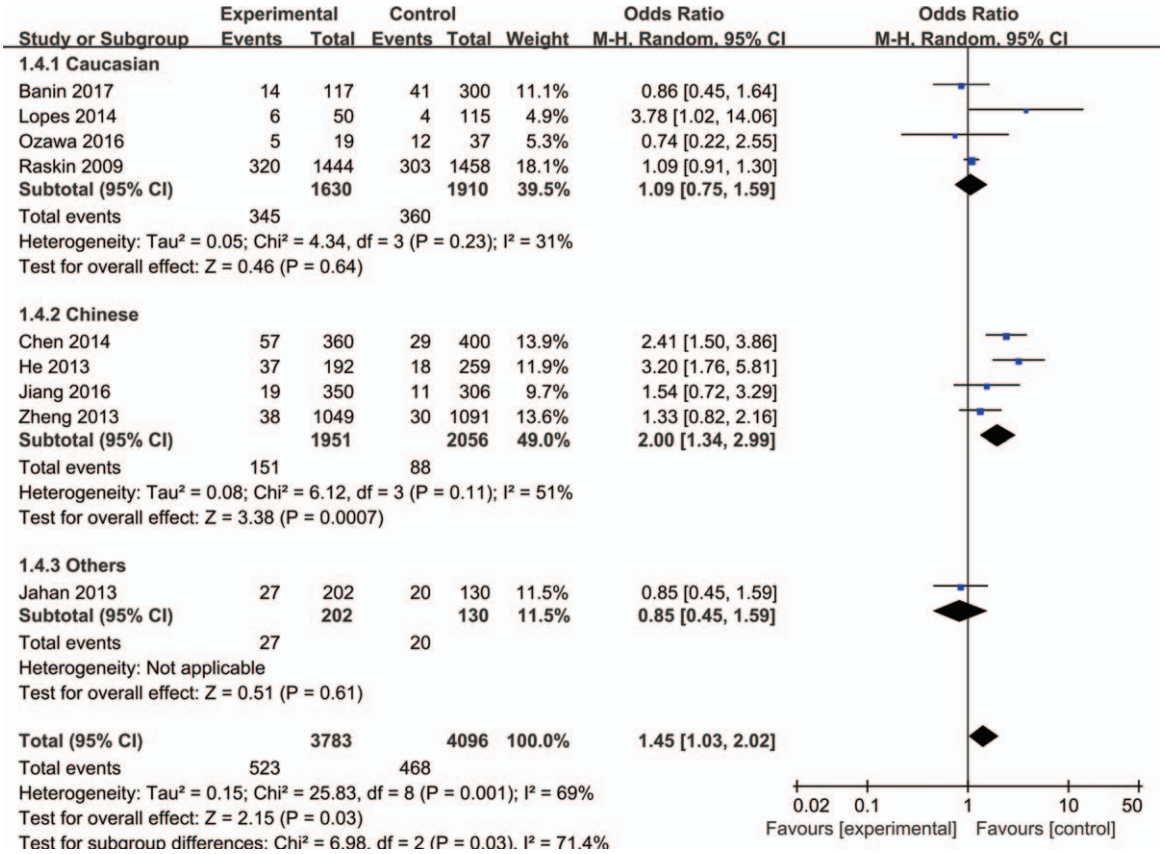

Figure 2. Forest plot of rs3761548 polymorphism and cancer risk (Recessive model: AA vs CA + CC). The squares and horizontal lines represents the study specific OR and 95% CI. CI = confidence interval, OR = odds radio.

Lopes et al[22] showed a high expression of Foxp3 protein in the tumor microenvironment and suggested that Foxp3 transcript factor could be a promising marker of susceptibility and prognosis in human breast cancer pathogenesis. Furthermore, Foxp3 expression in differentiated thyroid cancer (DTC) patients with AA/AC genotype of rs3761548 was increased compared with DTC patients with CC genotype.[23] In the previous meta-analysis of Jiang et al.,[29] no association was found between the rs3761548 polymorphism and cancer risk in any genetic models. However, in our updated meta-analysis, we found that

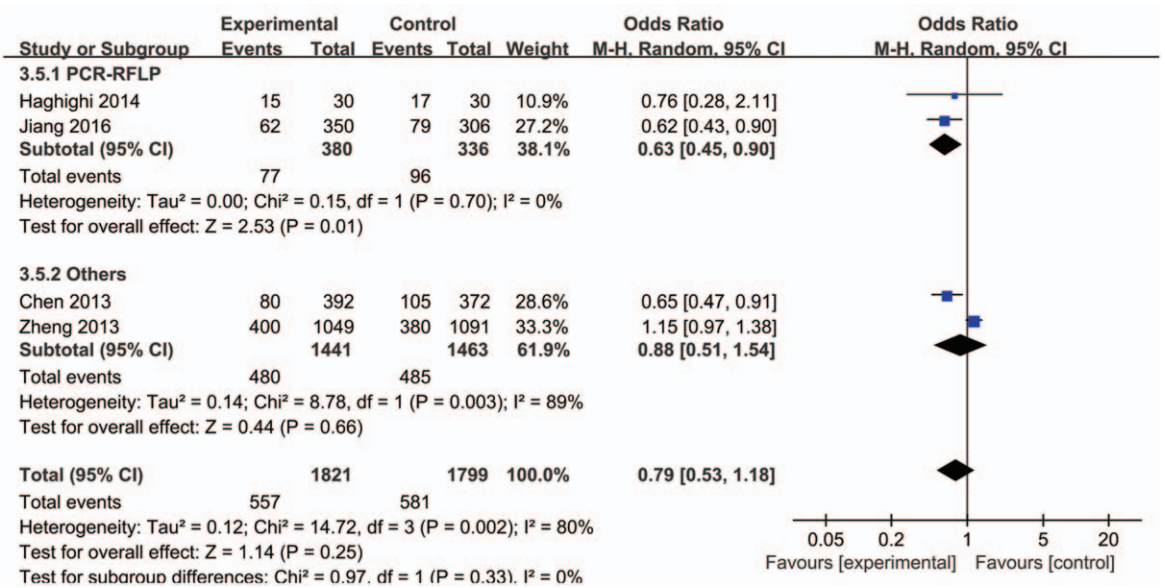

Figure 3. Forest plot of the association between rs2280883 polymorphism and cancer risk in the genotyping methods subgroup (dominant model: CC + TC vs TT). The squares and horizontal lines represent the study specific OR and 95% CI. CI = confidence interval, OR = odds radio.

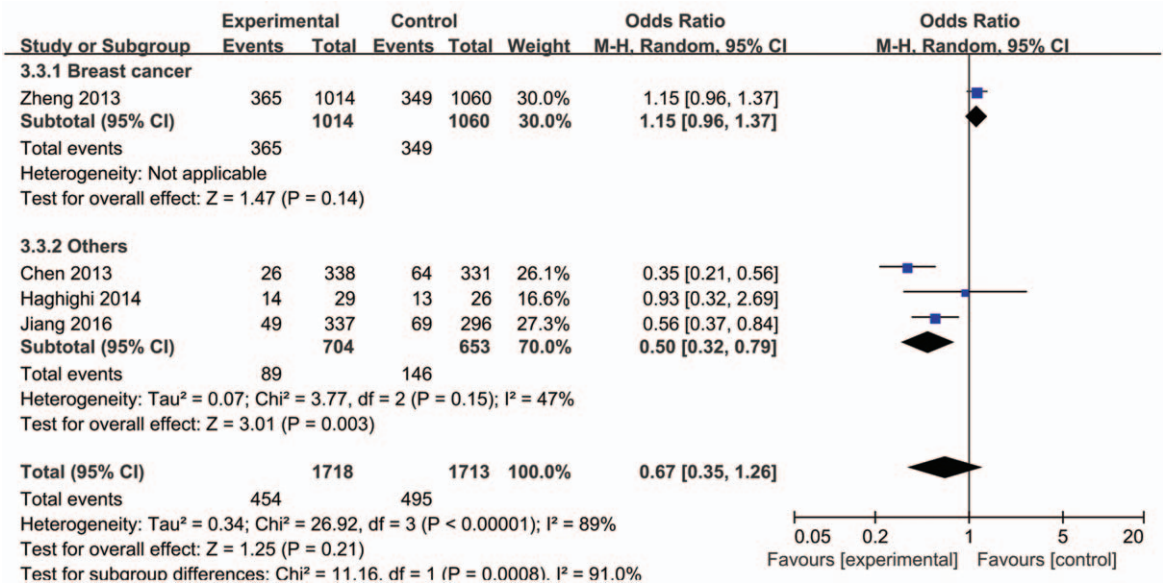

Figure 4. Forest plot of the association between rs2280883 polymorphism and cancer risk in the cancer types subgroup (heterozygote model: TC vs TT). The squares and horizontal lines represent the study specific OR and 95% CI. CI = confidence interval, OR = odds radio.

rs3761548 was associated with an increased cancer risk in the overall population under the recessive model ($P = .03$). At the same time, a significantly increased risk of cancers except breast cancer was found in all genetic models. This difference may result from 5 new articles included in our study. In addition, rs3761548 was located in the promoter of Foxp3. Studies indicated that Foxp3 bound to conserved noncoding sequence 2 (CNS2) in a Runx1 and Cbf-β-dependent manner to ensure the stability of Tregs and CNS2 interacted specifically with Foxp3 promoter in Tregs to promote stable Foxp3 expression.[30,31]

Due to the location in intron 9 near a conserved transcription region of Foxp3, rs2280883 could cause splicing downstream, resulting in the less functional gene. Therefore, for rs2280883 polymorphism of our study, no significant association was observed in the overall population under any genetic models. However, an association was found in the genotyping methods and cancer types subgroup analysis. Additionally, a significantly increased risk of other cancers was found in rs3761548 polymorphism. The results suggested that Foxp3 polymorphisms may have a varying effect on carcinogenesis within different organs. Since studies on thyroid cancer, lung cancer, colorectal cancer and other cancer are rare, further large studies are necessary to substantiate our results.

Some limitations of this meta-analysis should be considered. Firstly, some relatively small number studies and subjects were

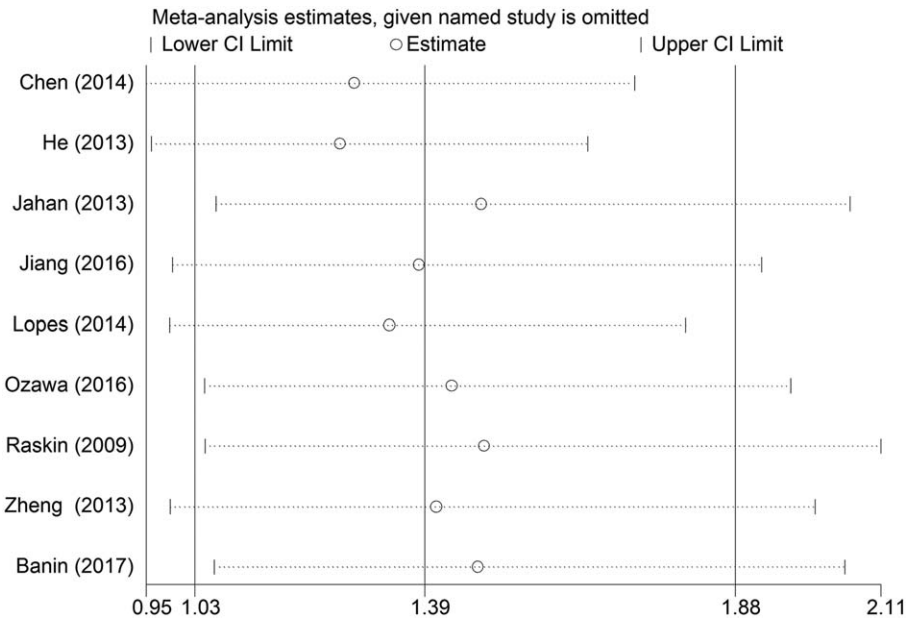

Figure 5. Sensitivity analysis of rs3761548 under the recessive model.

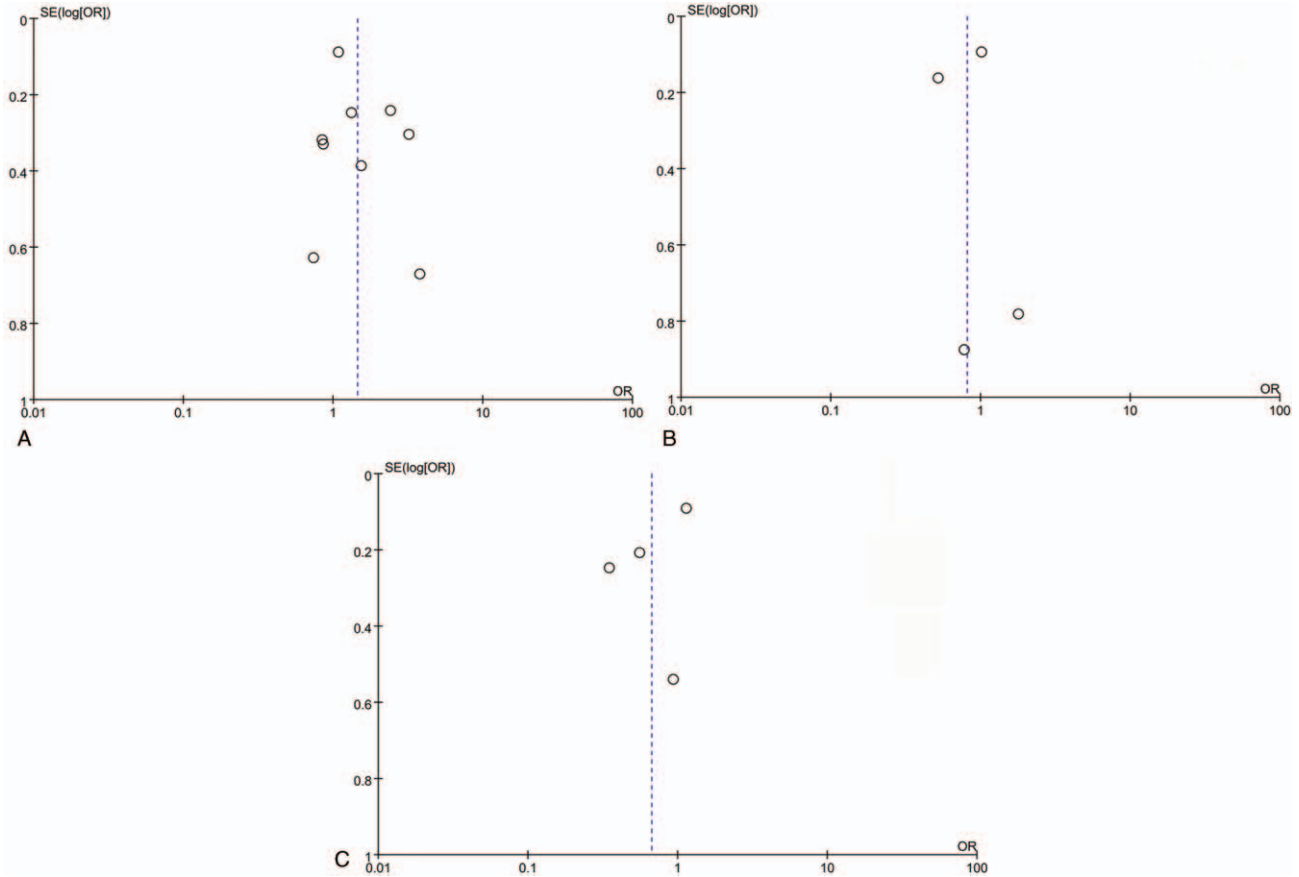

Figure 6. Funnel plots for publication bias. (A) rs3761548 (AA vs CA + CC); (B) rs3761549 (TT + CT vs CC); (C) rs2280883 (TC vs TT).

included, which may reduce the statistical power of our analysis. Secondly, several detailed information, such as gender, age, smoking status and environment factors, was not considered. Thirdly, the results were achieved according to individual unadjusted Ors. Finally, some degree of heterogeneity, which might impact the results, existed in this study.

In conclusion, the present study suggests that rs3761548 polymorphism contributes to an increased risk of cancer in the overall population. In the other cancer types and genotyping methods subgroups, rs2280883 polymorphism was associated with a lower risk of cancer. However, there was no association between rs3761549 polymorphism and cancer susceptibility. Nevertheless, a future study with larger ethnic groups and sample size is required to validate the associations.

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Data curation: Yan Guo.
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