RESEARCH ARTICLE

Association of mir-499 and mir-149 Polymorphisms with Cancer Risk in the Chinese Population: Evidence from Published Studies

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Abstract

Meta-analyses have shown that microRNA polymorphisms have variable effects in different population. Yet, no meta-analysis investigated the association of two common polymorphisms of miRNA, mir-499 rs3746444 polymorphism and mir-149 rs2292832 polymorphism, with cancer risk in the Chinese population. We searched the PubMed, Web of Knowledge, MEDLINE, CNKI databases, as well as Cochrane library, updated on December 31, 2012 for assays regarding cancer risk association with these two common polymorphisms in the present meta-analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to explore the strength of associations. The results showed that rs3746444 polymorphism was associated with increased cancer risk (dominant model: GG/AG vs. AA: OR = 1.43, 95% CI: 1.14-1.80; recessive model: GG vs. AG/AA: OR = 1.54, 95% CI: 1.04-2.30; homozygote model: GG vs. AA: OR = 1.69, 95% CI: 1.10-2.60; heterozygote model: AG vs. AA: OR = 1. 35, 95% CI: 1.09-1.67), and rs3746444 was associated with liver cancer in the subgroup of cancer types. For the rs2292832 polymorphism, the results showed no significant risk association in both overall pooled analysis and subgroup of cancer types, smoking status, gender and tea drinking status in the Chinese population. This meta-analysis suggested that the rs3746444 GG genotype is associated with increased cancer risk, especially liver cancer, while the rs2292832 polymorphism showed no association with cancer risk in Chinese.

Keywords: Cancer - microRNA (miRNA) - polymorphisms - Chinese population - meta-analysis

Asian Pacific J Cancer Prev, **14 (4)**, 2337-2342

Introduction

MicroRNAs (miRNA), encoded by eukaryotic nuclear DNA, is a small nonprotein-coding single-stranded RNA molecules of 18 to 24 nucleotides in length, with gene regulatory functions. By December 31, 2012, approximately 2042 mature human miRNAs have been described in the latest version of miRBase (a public database of published miRNA sequences and annotation, www.mirbase.org). Most miRNA located at cancer-associated genomic regions or fragile sites (Calin et al., 2004). Each miRNA has hundreds or thousands of target genes, almost all the coding genome is under the control of miRNAs (Fabbri et al., 2013). Mature miRNAs, stably associated with RISC (RNA-induced silencing complex), regulate target messenger RNAs (mRNAs) (Bartel, 2004), causing a suppression in gene expression levels (Filipowicz et al., 2008), while others can promote gene expression (Vasudevan et al., 2007). In this way, some miRNAs perform mainly as tumor suppressor genes, while others function as oncogene.

MiRNAs recognize their target mRNAs mainly by base-pairing 2 ~ 8 nucleotides with target mRNAs (Lewis et al., 2005), a SNP in microRNA may create a mismatch, leading to gene expression disorder and diseases. Several studies have investigated the association of mir-499 rs3746444 polymorphism and mir-149 rs2292832 polymorphism with cancer risk, but the results remain conflicting. One study (Xiang et al., 2012) showed that rs3746444 was associated with hepatocellular cancer (HCC) risk, while another study (Zhou et al., 2012) showed no such association. Previous meta-analyses (Jang et al., 2011; Srivastava et al., 2012) showed that rs3746444 was associated with increased cancer risk in Asian, but not in Caucasian. And when stratified by cancer type, it was associated with breast cancer (Wang et al., 2011). Two studies (Liu et al., 2011; Kim et al., 2012) showed rs2292832 was associated with cancer risk, while other studies did not. A meta-analysis (Zhang et al., 2011) also found no association between rs2292832 and cancer risk.

To further investigate the association of cancer risk with these two polymorphisms in the Chinese population, we conducted the present meta-analysis of published studies.

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Table 1. Characteristics of Studies in the Meta-analysis

	First author	Year	Cancer type	Matching criteria	Source of control*	Genotyping method	HWE of control (*P*)	Cases	Control
rs3746444	Chu YH	2012	Oral cancer	Not refered	HB	PCR-RFLP	0.96	470	425
	Hu ZB	2012	Liver cancer	Not refered	HB	PCR-RFLP	0.28	100	100
	Ling XX	2011	Lung cancer	Age; sex	PB	PCR-RFLP	<0.01	526	526
	Tian T	2011	Liver cancer	Not refered	HB	PCR-RFLP	0.1	186	483
	Xiang Y	2010	Cervical cancer	Not refered	HB	PCR-RFLP	<0.01	226	309
	Zhou B	2009	Lung cancer	Age; sex; area	PB	PCR-RFLP	0.4	1058	1035
	Zhou J	2008	Breast cancer	Age; area	HB	PCR-RFLP	0.06	1009	1093
rs2292832	Chu YH	2012	Oral cancer	Not refered	HB	PCR-RFLP	<0.01	470	425
	Hu ZB	2008	Breast cancer	Age; area	HB	PCR-RFLP	0.16	1009	1093
	Tian T	2009	Lung cancer	Age; sex; area	PB	PCR-RFLP	0.86	1058	1035
	Tu HF	2012	Head & neck cancer	Not refered	HB	PCR-RFLP	0.27	273	122
	Zhang M	2011	Breast cancer	Age; sex; area	PB	PCR-RFLP	0.21	274	269
	Zhang MW	2011	Colorectal cancer	Age; sex; area	PB	PCR-RFLP	0.43	245	229
	Zhang MW	2011	Gastric cancer	Age; sex; area	PB	PCR-RFLP	0.7	443	435
	Zhang MW	2011	Lung cancer	Age; sex; area	PB	PCR-RFLP	0.12	232	231

*HB is short for hospital-based, and PB is short for population-based

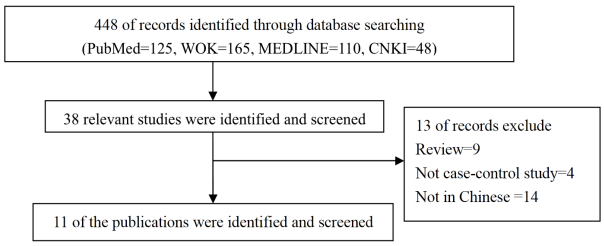

Figure 1. Flow Diagram of the Study Selection Process

Materials and Methods

Publication Search

We searched the PubMed, Web of Knowledge, MEDLINE, CNKI databases, as well as Cochrane library, updated on December 31, 2012, using the searching terms 'rs2292832/rs3746444' or 'mir-149/499' or 'mirna149/499' or 'microrna149/499' or 'mir149/499', 'cancer', 'tumor', 'carcinoma' and 'neoplasm' to get the publications about the association of the two polymorphisms with cancer risk. Searching language was limited to English and Chinese, but was not limited to publication years. This task was completed by two independent investigators, Yougai Zhang, Jianxiang Shi. We evaluated potentially relevant publications by examining their titles and abstracts, thereafter all studies matching the eligible inclusion criteria were retrieved. In addition, studies were identified by a manual search of the references listed in the reviews involved. A total of 11 published papers were included in this analysis. All the steps were carried out as shown in Figure 1.

Inclusion and Exclusion Criteria

All studies we included in the present meta-analysis met the following criteria: 1) evaluation of rs2292832/rs3746444 and cancer risks; 2) case-control study; 3) outcome cancer (histologically/pathologically proven); 4) genotype frequencies available; 5) published on the journal; 6) study subjects are Chinese. The major exclusion criteria were as follows: 1) duplicate data; 2) case reports, series, abstract, comment, review and editorial; 3) insufficient data.

Data Extraction

Information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion and exclusion criteria listed above. For these studies, the following information were extracted: the first author's name, year of publication, the numbers of genotyped cases and controls, source of control groups (population-based or hospital-based controls), genotyping methods and cancer type. A polymorphism in one type of cancer was treated as one independent study. Information was carefully extracted independently by two of the authors; disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, then a third author was consulted to resolve the dispute.

Statistical analysis

In this meta-analysis, OR and 95% CI were calculated to estimate the association between the two miRNA SNPs and cancer risk based on reported frequencies of alleles and genotypes in cases and controls. We investigated the associations of the two SNPs and cancer susceptibility with different genetic models: allelic comparison (G versus A), dominant model (GG/AG versus AA), recessive model (GG versus AG/AA), homozygote model (GG versus AA) and heterozygote model (AG versus AA), respectively.

The statistical significance of the pooled OR was determined with the Z test, and it was considered significant when $P < 0.05$. The heterogeneity between studies was evaluated by the Chi-square based Q statistical test (Handoll et al., 2006), with heterogeneity (*Ph*), and $P < 0.05$ being considered significant. Fixed-effect model using the Mantel–Haenszel method and random-effect model using the DerSimonian and Laird method were used in this meta-analysis (Midgette et al., 1994). Random-effects model was used when heterogeneity was significant; otherwise fixed-effect model was used.

Funnel plots and Egger's linear regression tests were applied to determine whether there was a publication bias (Egger et al., 1998). Funnel plots, the standard error of logarithm for OR was plotted against its OR,

Table 2. Stratification Analyses of Genetic Susceptibility to Cancer Risk

Comparisons			Test of association				Test of heterogeneity		
			OR (95%CI)	Z	*P*-value	Model*	χ^2	*P*-value	I^2(%)
rs3746444	Total	G vs A	1.12(0.81,1.5)	0.69	0.49	R	74.5	<0.01	92
		GG+AG vs AA	1.43(1.14,1.8)	3.08	<0.01	R	26.28	<0.01	77
		GG vs AG+AA	1.54(1.04,2.3)	2.13	0.03	R	14.88	0.02	60
		GG vs AA	1.69(1.10,2.6)	2.39	0.02	R	16.65	0.01	64
		AG vs AA	1.35(1.09,1.6)	2.79	<0.01	R	19.52	<0.01	69
	Lung cancer	G vs A	1.29(072,2.3)	0.84	0.4	R	20.39	<0.01	95
		GG+AG vs AA	1.25(0.73,2.1)	0.81	0.42	R	11.38	<0.01	91
		GG vs AG+AA	1.44(0.61,3.4)	0.83	0.41	R	6.83	<0.01	85
		GG vs AA	1.50(0.57,3.9)	0.82	0.41	R	8.41	<0.01	88
		AG vs AA	1.07(0.91,1.2)	0.81	0.42	F	3.35	0.07	70
	Liver cancer	G vs A	0.56(0.17,1.8)	0.94	0.36	R	18.97	<0.01	95
		GG+AG vs AA	1.32(0.96,1.8)	1.72	0.09	F	3.71	0.05	73
		GG vs AG+AA	1.93(1.04,3.5)	2.08	0.04	F	2.8	0.09	64
		GG vs AA	2.17(1.15,4.1)	2.39	0.02	F	3.75	0.05	73
		AG vs AA	1.23(0.88,1.7)	1.22	0.22	F	1.32	0.25	24
rs2292832	Total	T vs C	1.01(0.94,1.08)	0.27	0.78	F	9.32	0.23	25
		TT+TC vs CC	0.97(0.86,1.09)	0.54	0.59	F	11.48	0.12	39
		TT vs TC+CC	1.04(0.94,1.15)	0.85	0.4	F	7.23	0.41	3
		TT vs CC	0.99(0.85,1.15)	0.19	0.85	F	11.1	0.13	37
		TC vs CC	0.95(0.84,1.08)	0.78	0.43	F	11.09	0.13	37
	Lung cancer	T vs C	1.14(0.96,1.35)	1.5	0.13	F	2.28	0.13	56
		TT+TC vs CC	0.88(0.69,1.13)	0.97	0.33	F	0.61	0.43	0
		TT vs TC+CC	0.94(0.80,1.09)	0.82	0.41	F	0	0.98	0
		TT vs CC	0.86(0.66,1.12)	1.1	0.27	F	0.46	0.5	0
		TC vs CC	0.90(0.70,1.18)	0.75	0.45	F	0.68	0.41	0
	Breast cancer	T vs C	1.00(0.83,1.20)	<0.01	1	F	0.97	0.32	0
		TT+TC vs CC	0.99(0.84,1.17)	0.11	0.91	F	0.2	0.66	0
		TT vs TC+CC	1.14(0.91,1.43)	1.15	0.25	F	2.38	0.12	58
		TT vs CC	1.04(0.79,1.37)	0.3	0.76	F	0.83	0.36	0
		TC vs CC	0.98(0.82,1.16)	0.27	0.49	F	0.01	0.91	0
	smoke	T vs C	0.89(0.67,1.17)	0.84	0.4	R	4.09	0.04	76
		TT+TC vs CC	0.86(0.49,1.52)	0.53	0.6	F	0.03	0.87	0
		TT vs TC+CC#	0.89(0.32,2.46)	0.23	0.82	R	7.16	<0.05	86
		TT vs CC	0.80(044,1.46)	0.73	0.47	F	1.22	0.27	18
		TC vs CC	0.88(0.48,1.61)	0.41	0.68	F	0.58	0.45	0
	No smoke	T vs C	1.15(0.74,1.79)	0.364	0.52	F	0.1	0.75	0
		TT+TC vs CC	0.84(0.39,1.83)	0.43	0.67	F	1.06	0.3	6
		TT vs TC+CC#	1.50(0.80,2.80)	1.26	0.21	F	0.25	0.62	0
		TT vs CC	1.19(0.50,2.82)	0.39	0.69	F	0.25	0.62	0
		TC vs CC	0.63(0.27,1.49)	1.05	0.29	F	2	0.16	50
	Male	T vs C	0.99(0.81,1.21)	0.13	0.29	F	1.91	0.17	48
		TT+TC vs CC	0.91(0.61,1.36)	0.47	0.64	F	0.33	0.56	0
		TT vs TC+CC#	1.09(0.54,2.21)	0.24	0.81	R	6.53	0.01	85
		TT vs CC	0.95(0.62,1.45)	0.25	0.8	F	0.14	0.71	0
		TC vs CC	0.87(0.57,1.33)	0.66	0.51	F	2.25	0.13	56
	Female	T vs C	1.03(0.81,1.31)	0.23	0.81	F	0.14	0.71	0
		TT+TC vs CC	1.10(0.64,1.86)	0.34	0.74	F	0.07	0.79	0
		TT vs TC+CC#	1.02(0.74,1.41)	0.11	0.92	F	0.12	0.73	0
		TT vs CC	1.09(0.63,1.91)	0.32	0.75	F	0.12	0.73	0
		TC vs CC	1.10(0.63,1.92)	0.33	0.74	F	0.03	0.87	0
	Drinking tea	T vs C	1.16(0.78,1.73)	0.73	0.46	R	3.24	0.07	69
		TT+TC vs CC	1.03(0.66,1.59)	0.13	0.9	F	0.52	0.47	0
		TT vs TC+CC#	1.34(0.55,3.27)	0.64	0.52	F	8.67	0.003	88
		TT vs CC	1.22(0.76,1.95)	0.83	0.4	F	0.23	0.63	0
		TC vs CC	0.85(0.34,2.10)	0.36	0.72	F	3.72	0.05	73
	No drinking tea	T vs C	0.87(0.70,1.09)	1.18	0.24	F	0.98	0.32	0
		TT+TC vs CC	0.89(0.56,1.43)	0.46	0.64	F	0.26	0.61	0
		TT vs TC+CC#	0.82(0.61,1.11)	1.28	0.2	F	0.96	0.33	0
		TT vs CC	0.82(0.50,1.34)	0.8	0.42	F	0.55	0.46	0
		TC vs CC	0.99(0.60,1.63)	0.05	0.96	F	0.04	0.85	0

*R is short for Random model, F is short for Fixed model

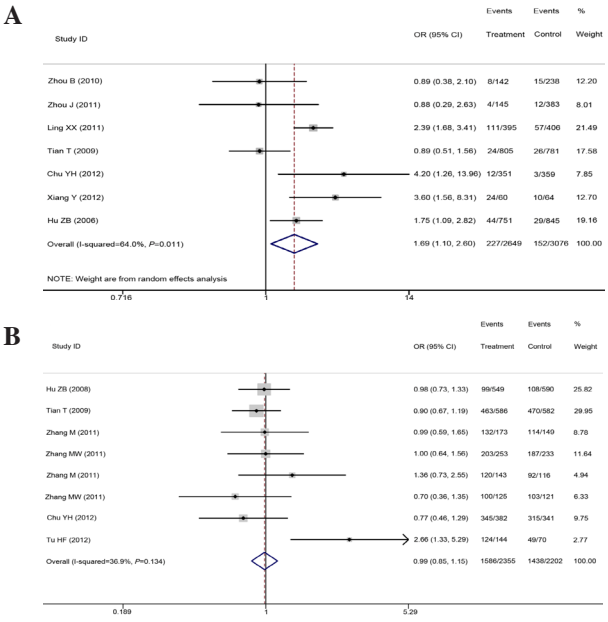

Figure 2. Forest Plots of Cancer Risk Associated with the Two miRNA Polymorphisms in Homozygote Model. For each study, the estimate of OR and its 95 % CI is plotted with a box and a horizontal line. The diamond represents the pooled OR and 95% CI. A: rs3746444 (GG vs. AA), B: rs2292832 (TT vs. CC)

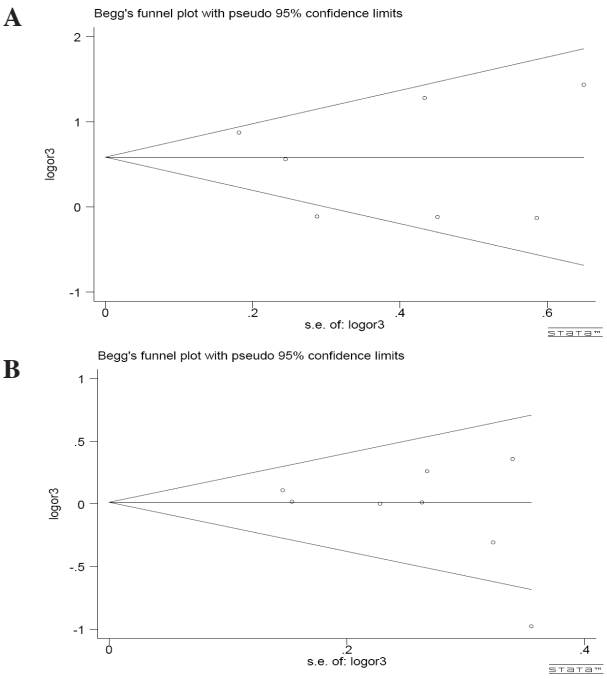

Figure 3. Begg's Funnel Plots for Publication Bias Test. Each point represents a separate study for the indicated association. Log (or), natural logarithm of OR. Horizontal line means effect size. A: rs3746444 (GG vs. AA), B: rs2292832 (TT vs. CC)

would display the bias graphically. In the Egger's linear regression test, an asymmetric plot stands for a possible publication bias (Egger et al., 1998). The significance of the intercept was determined by the t-test ($P < 0.05$ was considered representative of statistically significant publication bias).

All statistical tests were performed using RevMan 5.2 software (Cochrane Collaboration, http://ims.cochrane.org/revman), Funnel plots and Egger's linear regression tests were accomplished by Stata software 12.0 (Stata Corporation, College Station, Texas). Two-sided *P* value less than 0.05 were considered statistically significant.

Results

Characteristics of the studies

A total of 11 publications, including 5048 cancer cases and 5257 controls, met the inclusion criteria, among which we extracted 7 studies for rs3746444 and 8 studies for rs2292832 respectively as shown in Table 1. To determine the SNPs, genotyping by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were performed in all the 15 studies. 8 of the control groups were hospital-based; other 7 studies were population-based. 6 studies matched cases and controls by sex, area and age, 3 studies matched cases and controls by area and age, while other 6 studies did not mention it.

Quantitative synthesis

Figures 2 showed the results of the pooling of data, illustrating two forest plots of ORs (95 % CIs) for the risk of developing cancer associated with the variant homozygotes of rs3746444 and rs2292832 polymorphisms in 15 case–control studies.

As shown in Table 2, we observed that rs3746444 polymorphism was associated with increased cancer risk in Chinese population (dominant model: GG/AG vs. AA: OR = 1.43, 95% CI: 1.14-1.80; recessive model: GG vs. AG/AA: OR = 1.54, 95% CI: 1.04-2.30; homozygote model: GG vs. AA: OR = 1.69, 95% CI: 1.10-2.60; heterozygote model :AG vs. AA: OR = 1. 35, 95% CI: 1.09-1.67). No association was observed in allele contrast (G vs. A: OR = 1.12, 95% CI: 0.81-1.55). When stratified by cancer type, rs3746444 polymorphism was associated with liver cancer (GG vs. AG/AA: OR = 1.93, 95% CI: 1.04-3.58; GG vs. AA: OR = 2.17, 95% CI: 1.15-4.10), while rs3746444 polymorphism was not associated with lung cancer. For rs2292832 polymorphism, there was no significant heterogeneity between the 8 studies and fixed-effect model was applied. The results, as listed in Table 2, showed no significant risk association in overall pooled analysis. The gene frequency of TT and TC/CC in different smoking status and gender can be extract in one publication (Zhang et al., 2011), and the gene frequency of TT, TC and CC in different smoking status, tea drinking status and gender can be extract in one publication (Zhang et al., 2012).When stratified by these factors, no significant association was observed between these models and cancer risk (Table 2).

Table 3. the Results of Meta-regression of rs3746444 (*P*)

Factors	G vs A	GG+AG vs AA	GG vs AG+AA	GG vs AA	AG vs AA
HWE	0.52	0.357	0.834	0.905	0.377
Cancer type	0.609	0.772	0.408	0.459	0.969
match	0.463	0.268	0.97	0.806	0.093
Source of control	0.631	0.46	0.871	0.76	0.246
Size	0.463	0.268	0.97	0.806	0.093
Language	0.13	0.095	0.253	0.198	0.135

Test of heterogeneity

There was significant heterogeneity in the studies of the rs3746444. To detect the source of the heterogeneity, meta-regression was used in our study. As shown in Table 3, all the factors extracted from the publications, including cancer type (oral cancer, breast cancer, lung cancer, cervical cancer and liver cancer), match (by age or not referred), source of control (hospital based or population based), size (with more than 500 hundred controls or else, publication language (English or Chinese) were not the source of the heterogeneity.

Then sensitivity analysis was performed and showed one study (Hu et al., 2009) was the main cause of the heterogeneity for rs3746444. When this study was removed, the heterogeneity decreased significantly (GG vs. AA: Ph increased from 0.01 to 0.09, AG vs. AA: Ph increased from 0.003 to 0.07).

Publication bias

Begg's funnel plot and Egger's test were performed to detect potential publication bias in this meta-analysis. No obvious asymmetry was observed in Begg's funnel plots (Figure 3). The Egger's test also showed no potential publication bias (rs37464444: t = -0.42, P = 0.689 (GG vs. AA), and rs2292832: t = -1.04, P = 0.338 for dominant model).

Discussion

MiRNA can be involved in malignant biological behaviors such as cell proliferation, differentiation, apoptosis, migration and invasion (Chen et al., 2012; Ivanovska et al., 2012; Lu et al., 2012; Wang et al., 2012). SNPs in miRNAs can affect miRNA function by modulating the transcription of the primary transcript, pri-miRNA and pre-miRNA processing and maturation, or miRNA-mRNA interactions, which could possibly contribute to cancer susceptibility (Ryan et al., 2010). Mir-499 directly targets on both α-and β-isoforms of calcineurin A, which provokes apoptosis by mediating dephosphorylation of dynamin-related protein-1 (Drp1) (Wang et al., 2010). The variantion of mir-149 might affect its mediation function in cancer development. Mir-149 can inhibit proliferation and invasion of glioma cells via blockade of AKT1 signaling (Pan et al., 2010), targeting on SP1, mir-149 can suppress colorectal cancer (Wang et al., 2010).

Two common SNPs, mir-499 rs3746444 and mir-149 rs2292382, were found to be associated with increased risk of cancer risk, but the results remain debatable. Several meta-analyses have evaluated the association of the two common miRNA polymorphisms and cancer risk, however, no one have evaluated the association of these two miRNA SNPs and cancer risk in Chinese population. Hence, we performed this meta-analysis in the hope of obtaining a precise conclusion. This meta-analysis evaluated association between the two common SNPs in miRNAs (rs3746444 and rs2292832) and cancer risk in Chinese population. The results demonstrated that the rs3746444 GG genotype was associated with an increased cancer risk in Chinese population.

Three precious meta-analyses (He et al., 2012; Qiu et al., 2012; Srivastava et al., 2012) showed that rs3746444 GG and GA genotypes were associated with increased cancer risk in Asian population, but, they showed no association with cancer risk in Caucasian, suggesting a possible ethnic difference in genetic and environmental background. However, they did not display the association in Chinese population. The results of this meta-analysis demonstrated that the rs3746444 GG genotype was associated with an increased cancer risk in Chinese population. Previous meta-analyses showed no association between rs3746444 and liver cancer, while in this meta-analysis we found rs3746444 GG genotype was a risk factor of liver cancer in Chinese population. This might be that the gene susceptibility was variable in different ethnics.

For rs2292832, no association with cancer risk in Chinese population was observed in this meta-analysis, which was the same with two precious meta-analyses (He et al., 2012; Srivastava et al., 2012) in which rs2292832 was not associated with cancer risk in Asian population. When stratified by cancer type, smoking status, tea drinking status and gender, no association was observed between rs2292832 and cancer risk in Chinese population, this might mean that rs2292832 had no interference with cancer risk. As the number of studies included was limited, we should further explore the association in the future.

We have searched as many publications as we could in this meta-analysis. And we carried out test of heterogeneity and tried to find some clues leading to the source of heterogeneity. However, as eligible studies were limited, the intention of assessing association between SNPs by different type of cancer was not allowed. And potential gene-gene interaction and gene-environment interaction were not evaluated in this meta-analysis, as no sufficient data could be extracted from the included studies.

To sum up, this meta-analysis suggested that rs3746444 GG genotype was associated with increased cancer risk in Chinese population, notably liver cancer, while the rs2292832 was not.

Acknowledgements

The research is supported by grants from the General Program (No. 81202278) of National Natural Science Foundation of China. The author(s) declare that they have no competing interests.

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