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Original Article

MICA polymorphisms and cancer risk: a meta-analysis

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Abstract: The major histocompatibility complex class I chain-related gene A transmembrane (MICA-TM) polymorphism has been implicated in susceptibility to cancer. However, the results are inconsistent. The aim of this meta-analysis is to evaluate the association between the MICA-TM polymorphisms and cancer risk. All eligible case-control studies published up to August 20, 2014 were identified by searching PubMed, Web of Science, CNKI and Wanfang databases. The cancer risk associated with the MICA polymorphism was estimated for each study by odds ratios (OR) together with its 95% confidence interval (CI), respectively. 21 studies from 19 publications with 3620 cases and 4903 controls were included. Overall, no significant associations between the MICA-TM polymorphism and cancer risk were found (A4 allele: OR = 0.97, 95% CI: 0.88-1.07; A5 allele: OR = 0.91, 95% CI: 0.81-1.04; A5.1 allele: OR = 1.03, 95% CI: 0.89-1.18; A6 allele: OR = 1.05, 95% CI: 0.95-1.15; A9 allele: OR = 0.96, 95% CI: 0.80-1.14; A10 allele: OR = 0.88, 95% CI: 0.43-1.79; del: OR = 2.50, 95% CI: 0.73-8.58; A7 allele: OR = 0.93, 95% CI: 0.43-2.00). When stratified by ethnicity, similar results were observed among Asians; however, there were significant association in Caucasian population for A5 (OR = 0.77, 95% CI: 0.68-0.87) and A9 allele (OR = 0.75, 95% CI: 0.66-0.85). This meta-analysis suggests that the MICA-TM A5 and A9 alleles may be an important protective factor for cancer in Caucasian populations.

Keywords: MICA, polymorphism, cancer, meta-analysis

Introduction

Cancer has become a major public health burden. Due to the aging of the world, the global burden of cancer continues to increase [1]. However, cancer is a multifactorial disease. The mechanism of carcinogenesis is complicated and remains largely unknown. It has been suggested that the complex interactions between environmental factors and genetics play a vital role in the process of carcinogenesis [2]. In addition, various genetic variations have been identified to affect cancer risk [3].

The major histocompatibility complex class I chain-related gene A (MICA) gene locus is located on the short (p) arm of chromosome 6 (6p21.33) and belongs to one of the members of the MIC family. The MIC family comprises of functional MICA, MICB genes and five pseudogenes MICC to MICG [4]. MICA is a membrane protein which is up-regulated in various tumor cells and also induced in response to various cellular stresses such as infection, hypoxia, and heat shock [5]. Different MICA molecules were reported to vary in their affinities to soluble NKG2D receptors, which may influence antitumor immune responses [6, 7]. Recent studies have shown increased serum levels of soluble MICA molecules in patients with various malignancies with a correlation to advanced tumor stages [8]. Circulating tumor-derived soluble MICA molecules induce down-regulation of NKG2D receptors on natural killer cells and thereby decrease responsiveness of tumor-antigen-specific effector T cells [9]. Exons 2-4 of MICA encode three extracellular domains and exon 5 encodes the trans-membrane (TM) portion. Similar to human leukocyte antigen (HLA) genes, MICA is highly polymorphic. Exons 2-4 of MICA have microsatellite polymorphisms, whereas exon 5 shows a variable number of GCT repeats. To date, 65 alleles have been identified in human MICA gene. Of those, the MICA-TM polymorphism was most commonly studied one. It consists of eight alleles, with 4, 5, 6, 7, 8, 9 and 10 repetitions of GCT or 5 repetitions of GCT with 1 additional nucleotide

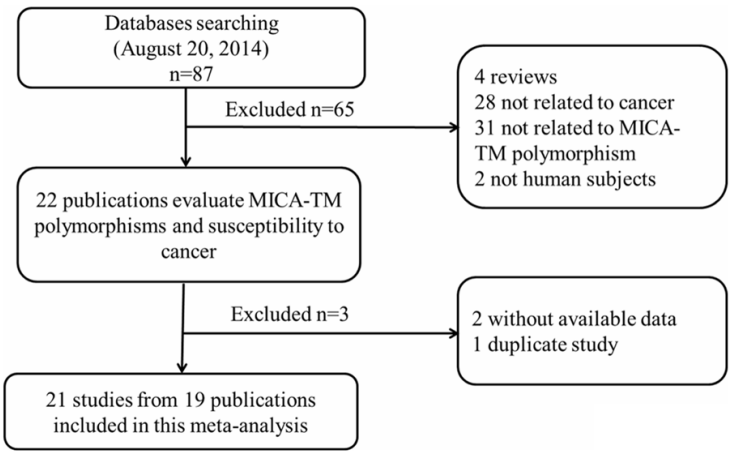

Figure 1. Flow chart showing study selection procedure.

insertion (G), designated as A4, A5, A6, A7, A8, A9, A10 and A5.1, respectively [10-13]. Recently, several studies have investigated the association between the polymorphism and cancer risk [14-33]. However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the associations of the MICA-TM polymorphism with cancer susceptibility in diverse populations.

Materials and methods

Search strategy

We searched for relevant studies before August 20, 2014 by using electronic PubMed, Web of Science, CNKI and Wanfang databases with the following terms: "major histocompatibility complex class I chain-related gene A or MICA", "genetic polymorphism or polymorphism or variant", "cancer or carcinoma or tumor". The search was restricted to humans and without language restrictions. Additional studies were identified by a hand search of references of original or review articles on this topic. If more than one geographic or ethnic heterogeneous group was reported in one report, each was extracted separately. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) studies that evaluated the association between the MICA-TM polymorphism and cancer, (2) in a case-control study design, and (3) had detailed allele frequency of cases and controls or could be calculated from the article text. While the exclusion criteria were: (1) case-only study, case reports, and review articles, (2) studies without the raw data of the MICA alleles, and (3) repetitive publications.

Data extraction

The following information was extracted from each eligible publication: the first author's name, year of publication, country of origin, ethnicity, cancer type, genotyping methods, number of cases and controls and association alleles. All data were extracted by two investigators independently, using the same standard. The results were compared and disagreements were resolved by consensus.

Statistical analysis

The risk of cancer associated with the MICA-TM polymorphism was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). A X^2-test-based Q statistic test was performed to assess the between-study heterogeneity [34]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P < 0.05$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used [35], or else the fixed effects model was chosen [36]. We performed stratification analyses on ethnicity. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg' funnel plot and Egger's regression test [37, 38]. $P < 0.05$ was considered statistically significant.

All analyses were performed by the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

The search strategy retrieved 87 potentially relevant studies. According to the inclusion criteria, 20 studies [14-33] with full-text were included in this meta-analysis and 67 studies were excluded. Because the studies [19] included three tumor types, we treated them sepa-

Table 1. Characteristics of studies included in the meta-analysis

Study	Year	Country	Ethnicity	Tumor type	Genotype methods	Number		alleles
						case	control	
Chen	2005	China Taiwan	Asian	Cervical	PCR-based	110	82	A4, A5, A5.1, A6, A9
Chen	2013	Sweden	Caucasian	Cervical	PCR	1140	1058	A4, A5, A5.1, A6, A9
Ghaderi	2001	Sweden	Caucasian	Cervical	PCR	85	120	A4, A5, A5.1, A6, A9
Gong	2010	China	Asian	Colorectal	PCR-SSP	117	113	A4, A5, A5.1, A6, A9, A10, del
Jiang	2010	China	Asian	Hepatocellular	PCR	141	141	A4, A5, A5.1, A6, A9
Kennedy	2002a	Nertherlands	Caucasian	Squamous cell carcinoma	PCR	153	247	A4, A5, A5.1, A6, A9
Kennedy	2002b	Nertherlands	Caucasian	Basal cell carcinoma	PCR	261	247	A4, A5, A5.1, A6, A9
Kennedy	2002c	Nertherlands	Caucasian	Malignant melanoma	PCR	111	247	A4, A5, A5.1, A6, A9
Kopp	2009	Germany	Caucasian	Colorectal	PCR	79	306	A4, A5, A5.1, A6, A9
Lavado-Valenzuela	2009	Spain	Caucasian	Breast	PCR-based	110	121	A4, A5, A5.1, A6, A9
Lin	2002	China Taiwan	Asian	Oral	PCR-based	67	351	A4, A5, A5.1, A6, A9
Lo	2004	China Taiwan	Asian	Gastric	PCR-based	107	351	A4, A5, A5.1, A6, A9
Lopez-Vazquez	2004	Spain	Caucasian	Hepatocellular	PCR	46	48	A4
Luo	2011	China	Asian	leukemia	PCR-SSP	107	162	A4, A5, A5.1, A6, A9
Metzelaar-Blok	2005	Nertherlands	Caucasian	Uveal melanoma	PCR	168	247	A4, A5, A5.1, A6, A9
Reinders	2006	France	Caucasian	Head and Neck	PCR	139	106	A4, A5, A5.1, A6, A9
Tamaki	2007	Japan	Asian	Oral	PCR	123	188	A4, A5, A5.1, A6, A9
Tamaki	2009	Japan	Asian	Oral	PCR	80	70	A4, A5, A5.1, A6, A7, A9, A10
Tian	2006	China	Asian	Nasopharyngeal	PCR/size-sequencing	218	196	A4, A5, A5.1, A6, A9, del
Tong	2013	Vietnam	Asian	Hepatocellular	PCR	171	416	A4, A5, A5.1, A6, A9
Vallian	2012	Iran	Asian	Breast	PCR	110	110	A4, A5, A5.1, A6, A9

PCR-SSP, polymerase chain reaction sequence-specific priming.

rately in this meta-analysis. We excluded one study [33] because it included the overlapped data with those included in the analysis [30]. The flow chart of study selection in summarized in **Figure 1**. As shown in **Table 1**, there were 21 case-control studies concerning MICA-TM polymorphism. Of those, 21 case-control studies [14-32] with 3620 cases and 4903 controls on A4 allele, 20 studies [14-23, 25-32] with 3574 cases and 4855 controls on A5, A5.1, A6, A9 alleles, respectively, 2 studies on del [17, 30] and A10 allele [17, 28] respectively, and one study [28] on A7 allele. Two ethnicities were addressed: eleven studies focused on Asian populations [14, 17, 18, 22, 23, 25, 28-32], ten studies on Caucasians [15, 16, 19, 20, 21, 24, 26, 27].

Quantitative data synthesis

The results of this meta-analysis are listed in **Table 2**. For the MICA-TM A4 allele, there was no heterogeneity (I^2 = 49%, P = 0.0006). A fixed-effect model was used in the OR calculation. Overall, no evidence of associations between MICA-TM A4 allele and susceptibility of cancer were found (OR = 0.97, 95% CI: 0.88-1.07). Similarly, in subgroup analysis by ethnicity, there was no significantly association between them in Asian (OR = 0.88, 95% CI: 0.77-1.02) or Caucasian population (OR = 1.22, 95% CI: 0.96-1.56).

For the MICA-TM A5 allele, significant heterogeneity between studies was observed (I^2 = 58%, P = 0.0007). A random-effect model was used in the OR calculation. Overall, no significant associations between the MICA-TM A5 allele and cancer risk were found (OR = 0.91, 95% CI: 0.81-1.04). In the subgroup analysis by ethnicity, similar results were observed in Asian populations (OR = 1.03, 95% CI: 0.86-1.24); while, the MICA-TM A5 allele was associated with a decreased risk of cancer in Caucasian populations (OR = 0.77, 95% CI: 0.68-0.87) (**Figure 2**).

For the MICA-TM A5.1 allele, significant heterogeneity between studies was observed (I^2 = 73%, P < 0.00001). A random-effect model was used. The pooled results showed that no significant association was found both in overall and ethnicity subgroup analysis.

For the MICA-TM A6 allele, there was no heterogeneity (I^2 = 9%, P = 0.34). A fixed-effect model was used. The results also showed that no sig-

Table 2. Overall and group-specific statistics for association between MICA-TM and cancer

Allele	Subgroup	No. of study	Test of heterogeneity		Model	Test of association		Publication bias
			I^2	P		OR (95% CI)	P	Egger's
A4	Overall	21	49	0.0006	F	0.97 (0.88, 1.07)	0.53	0.291
	Asian	11	23	0.22	F	0.88 (0.77, 1.02)	0.09	0.654
	Caucasian	10	62	0.005	R	1.22 (0.96, 1.56)	0.11	0.180
A5	Overall	20	58	0.0007	R	0.91 (0.81, 1.04)	0.18	0.984
	Asian	11	61	0.004	R	1.03 (0.86, 1.24)	0.74	0.976
	Caucasian	9	0	0.50	F	0.77 (0.68, 0.87)	< 0.0001	0.797
A5.1	Overall	20	73	< 0.00001	R	1.03 (0.89, 1.18)	0.72	0.056
	Asian	11	72	0.0001	R	0.95 (0.75, 1.20)	0.65	0.191
	Caucasian	9	53	0.03	R	1.14 (0.99, 1.30)	0.07	0.835
A6	Overall	20	9	0.34	F	1.05 (0.95, 1.15)	0.33	0.399
	Asian	11	44	0.06	F	1.10 (0.94, 1.29)	0.22	0.859
	Caucasian	9	0	0.98	F	1.02 (0.91, 1.14)	0.75	0.492
A9	Overall	20	69	< 0.00001	R	0.96 (0.80, 1.14)	0.64	0.180
	Asian	11	67	0.0009	R	1.15 (0.90, 1.46)	0.26	0.719
	Caucasian	9	41	0.09	F	0.75 (0.66, 0.85)	< 0.00001	0.560
A10	Overall	2	45	0.18	F	0.88 (0.43,1.79)	0.71	-
del	Overall	2	49	0.16	F	2.50 (0.73, 8.58)	0.15	-
A7	Overall	1	NA	NA	-	0.93 (0.43, 2.00)	0.86	-

F, fixed-effects model; R, random-effects model.

nificant association was found both in overall and ethnicity subgroup analysis.

For the MICA-TM A9 allele, significant heterogeneity between studies was observed (I^2 = 69%, P < 0.00001). A random-effect model was used. There was no significant association in the overall comparison and Asians. However, significant association was observed among Caucasian population (OR = 0.75, 95% CI: 0.66-0.85) (**Figure 3**).

For the MICA-TM A10, del, A7 alleles, there was no heterogeneity (I^2 = 45%, P = 0.18, I^2 = 49%, P = 0.16). A fixed-effect model was used. No significant association between these alleles and cancer risk was detected.

Sensitivity analysis

Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the results. We found that the estimated pooled odd ratio changed quite little, indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Figure not shown). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (A4 allele: P = 0.291, A5 allele: P = 0.984, A5.1 allele: P = 0.056, A6 allele: P = 0.399; A9 allele: P = 0.180) (**Table 2**).

Discussion

To our knowledge, this is the first meta-analysis which comprehensively assessed the associations between MICA-TM polymorphism and cancer risk. In this study, we found there were no significant associations between the MICA-TM polymorphism and cancer risk in the overall comparison. Moreover, in the stratified analysis by ethnicity, we also failed to detect any association between them in Asian populations; while we observed a significant association in Caucasian population for A5 and A9 alleles.

MICA is one of the genes in the HLA class I region. Unlike HLA classical class I gene products, MICA does not present any antigen but acts as a ligand for several immune cells including natural killer (NK) cells bearing NKG2D receptors [39, 40]. MICA is the member of the

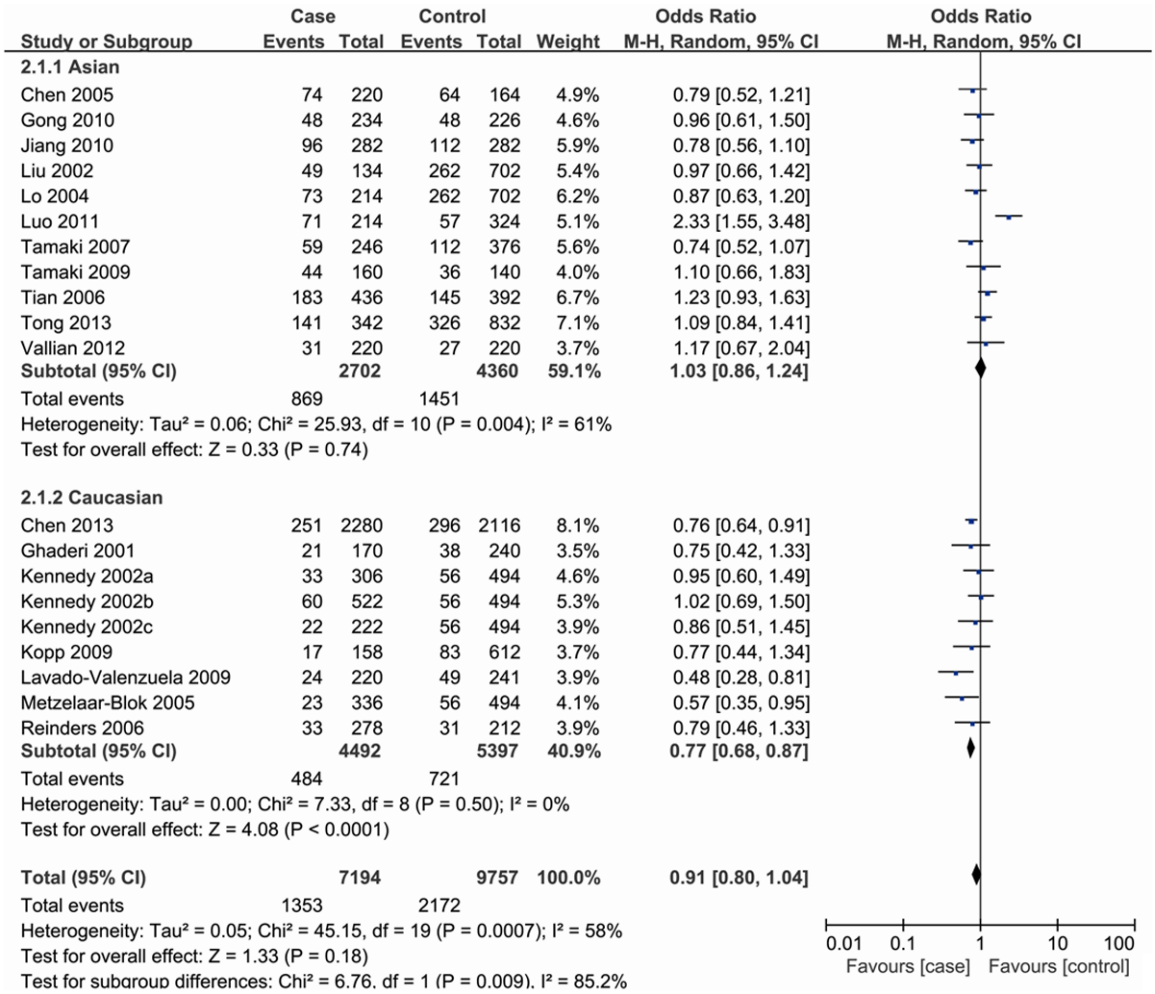

Figure 2. Subgroup analysis by ethnicity of odds ratios for association of MICA-TM gene A5 polymorphism and cancer risk.

non-classical class I family that displays the greatest degree of polymorphism. MICA polymorphisms are associated with a number of diseases related to NK activity, such as cancer [4]. Some investigations demonstrated that genetic alteration of the MICA can modulate cancer susceptibility and that the frequency of the variant genotype was significantly higher in patients when compared with controls [18, 22, 23, 25, 29, 32, 33]. In a study from South China, Jiang et al [18] suggested MICA-A5.1 polymorphism is associated with HCC patients in Han population and the MICA-A5.1 polymorphism may contribute to the development of HCC by promoting the release of sMICA to evade tumor immunosurveillance. However, the association of allele variants and cancer risk was not validated by others [14, 16, 17, 19, 26]. For example, Chen et al [14] found no association between MICA gene polymorphism and cervical cancer in Taiwan; similarly, Ghaderi et al [16] reported it was not associated with cervical carcinoma in Sweden; Gong et al [17] reported there was no genetic susceptibility attributed to MICA gene polymorphism with regard to development of colorectal cancer. Additionally, Reinders et al [27] reported the MICA-A9 frequency was significantly decreased in the total patient group compared with that in the control group, indicating that there were fewer patients with a nine alanine repeat in their transmembrane region compared with the controls. Lavado-Valenzuela et al [21] suggest that the MICA-A5 allele appears to confer protection against human breast cancer.

In this study, we found that the MICA-TM allele distribution between cancer and control group

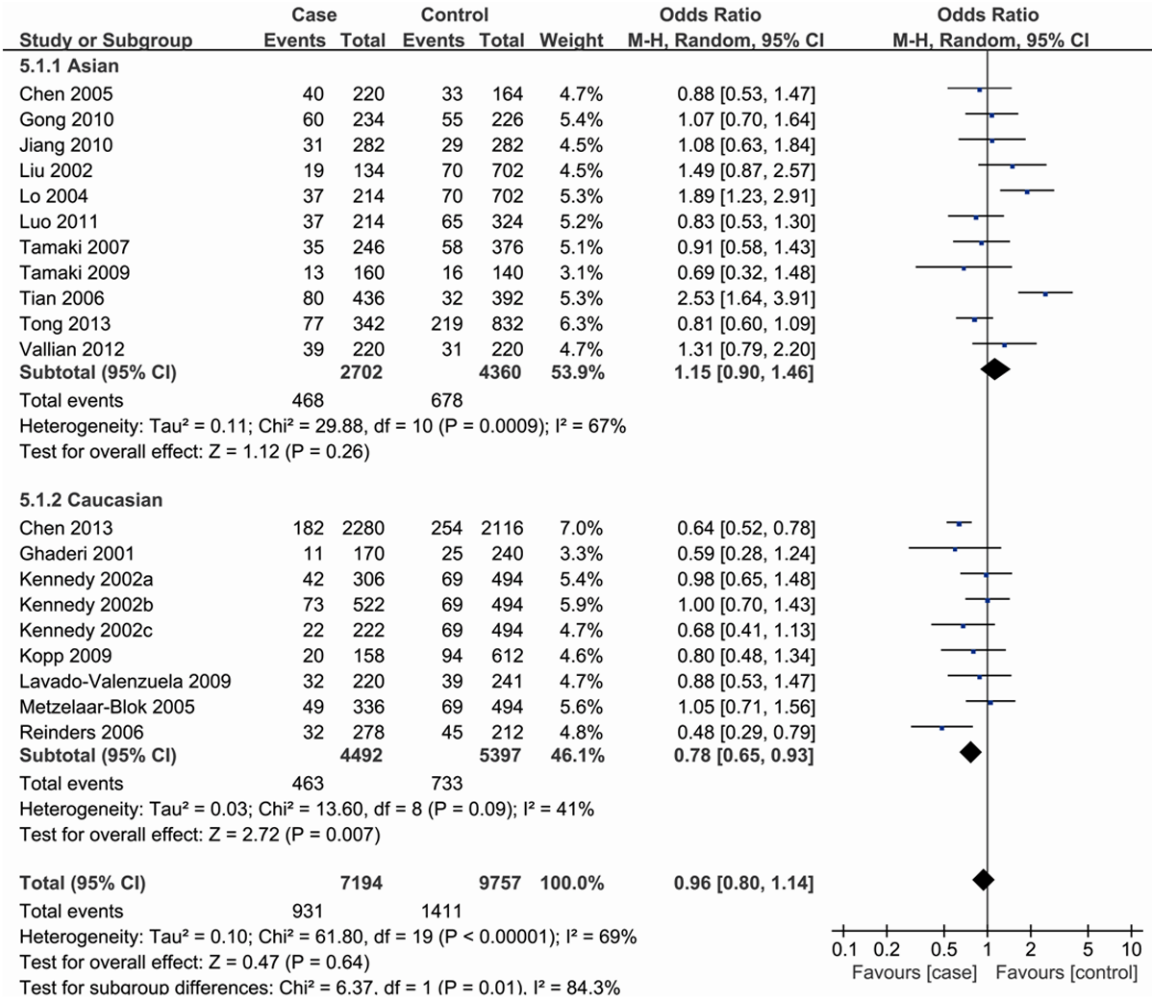

Figure 3. Subgroup analysis by ethnicity of odds ratios for association of MICA-TM gene A9 polymorphism and cancer risk.

was no significant difference. However, in the stratified analysis by ethnicity, we observed individuals with A5 and A9 alleles had a decreased risk of developing cancer in Caucasian populations. The inconsistent results may be attributed to differences in genetic backgrounds, environmental factors, and other factors, such as small sample size or inadequate adjustment for confounding factors. For example, the frequencies for MICA repeats in different populations were different. In addition, Given that MICA is expressed on the surface of transformed cells, the MICA molecule in carriers of the A5 or A9 allele might bind more efficiently to the NKG2D receptor, producing a more effective attack by the NK cells against the tumor cells. Furthermore, the interaction among some other genes might affect the relationship of each polymorphism included with the development of cancer. As we known, MICA is at the centromeric end of the classical class I region approximately 46.4 Kb from HLA-B [41]. Some alleles of the MICA-TM region exhibit strong linkage disequilibrium with alleles of the HLA-B locus [42], including an association between HLA-B7 and MICA-A5.1 [43].

Two significant issues should be addressed in this study, that is, heterogeneity and publication bias, which may influence the results of meta-analysis. We don't detect a significant publication bias in this meta-analysis, suggesting the reliability of our results. With regard to heterogeneity, in this study, heterogeneity was found in MICA-TM A5, A5.1 and A9 alleles. When stratified analysis by ethnicity, we found that heterogeneity still exists in Asian population, however, heterogeneity disappear in Cau-

casian population for MICA-TM A5 allele. Then sensitivity analyses were conducted by successively excluding one study, when excluded the study by Luo et al, the heterogeneity disappear in A5 allele. The results above suggest that the ethnic difference and particular study may be the source of heterogeneity.

Some limitations of this meta-analysis should be addressed. First, our results were based on unadjusted estimates, while lacking of the information (such as age, gender, family history) for the date analysis may cause serious confounding bias. Second, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Third, the number of published studies was not sufficiently large for a comprehensive analysis, and some studies with small size (e.g. the study by Lopez-Vazquez et al.) may not have enough statistical power to explore the real association.

Conclusion

In summary, this meta-analysis suggested that the MICA-TM A5 and A9 alleles may be an important protective factor for cancer in Caucasian populations. However, large and well-designed studies are warranted to validate our findings. Moreover, more gene-gene and gene-environment interactions should also be considered in the future.

Disclosure of conflict of interest

None.

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