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Original Article

Association of rs6505162 polymorphism in pre-miR-423 with cancer risk: a meta-analysis based on 5,891 cases and 7,622 controls

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Abstract: MicroRNAs (miRNAs) function as negative gene regulators by inhibiting translation or cleaving target mRNAs, for which they are recognized as oncogenes or tumor suppressors. Single nucleotide polymorphisms (SNPs) in miRNAs are closely related with cancer risks. Several studies have evaluated the association of rs6505162 polymorphism in pre-miR-423 with cancer susceptibility. However, the results remain conflicting rather than conclusive. We conducted a meta-analysis of 9 studies that included 5,891 cases and 7,622 controls to identify this association. The meta-analysis showed that the pre-miR-423 rs6505162 polymorphism was not statistically associated with cancer risks in all genetic models. In the stratified analysis of cancer types, the variant AA (CC vs. AA: OR=0.651, 95% CI: 0.482-0.878, *P*=0.005) and CA/AA genotypes (CC vs. CA+AA: OR=0.644, 95% CI: 0.446-0.931, *P*=0.019) were associated with a decreased risk of breast cancer compared with wild-type CC genotype. The same association in the allelic contrast (C vs. A: OR=0.808, 95% CI=0.699-0.934, *P*=0.004) was also observed. However, an increased risk of lung cancer was found in the co-dominant (CC vs. AA: OR=1.850, 95% CI: 1.049-3.263, *P*=0.034) and recessive (CC vs. CA+AA: OR=1.364, 95% CI: 1.074-1.732, *P*=0.011) models. Furthermore, according to the stratified analysis of ethnicity, we found a highly significant association in the Caucasian population (CC vs. AA: OR=0.651, 95% CI: 0.482-0.878, *P*=0.005; CC vs. CA+AA: OR=0.644, 95% CI: 0.446-0.931, *P*=0.019; C vs. A: OR=0.808, 95% CI: 0.699-0.934, *P*=0.004), but no significant association in Asians and other ethnicities. In summary, this meta-analysis suggests a significant association between pre-miR-423 rs6505162 polymorphism and risk of breast cancer and lung cancer. To some extent, this polymorphism is closely related to cancer susceptibility in Caucasians. However, further large-scale case-control studies between this polymorphism and cancer risks are needed in the future.

Keywords: Meta-analysis, miR-423, polymorphism, cancer risk

Introduction

MicroRNAs (miRNAs) are a class of endogenous, small and non-coding RNA molecules (approximately 21-25 nucleotides in length), which negatively regulate gene expression at the post-transcriptional level [1, 2]. Mature miRNAs primarily target the 3' untranslated region (3'UTR) of their target mRNAs, leading to the translation suppression or the target mRNAs degradation [3, 4]. Mounting miRNAs have been discovered in humans [5, 6]. A single miRNA could bind to the mRNAs with about 200 genes [7]. It has been predicted that half of all protein-coding genes in mammals could be regulated by miRNAs [8]. Meantime, massive miRNAs have been considered as key gene regulators in diverse biological pathways, including cell differentiation, proliferation, apoptosis and tumorigenesis [2, 9, 10].

Recent studies have shown that both aberrant expression and genetic variation in miRNAs are closely associated with cancer risk, diagnosis, prognosis, and drug response [11-14]. Single nucleotide polymorphism (SNP) is one of the most common types of genetic variation among the miRNA genes [15]. Previous studies have demonstrated that various SNPs in miRNAs, such as miRNA-146a, miRNA-499 and miRNA-

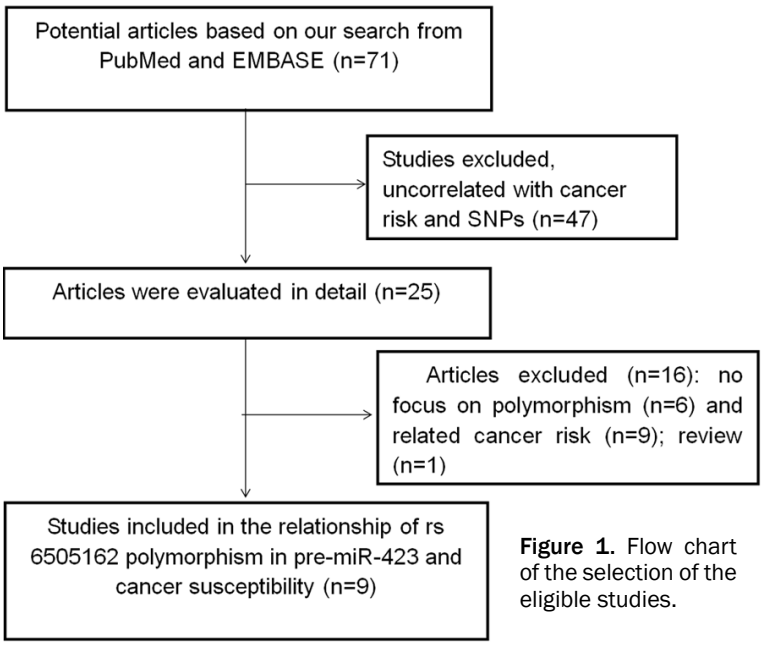


Figure 1. Flow chart of the selection of the eligible studies.

196a2, may contribute to cancer susceptibility [16-18].

Intriguingly, an important polymorphism in the pre-miR-423 with a change of C to A (rs6505162) has been identified [19]. As yet, a number of case-control studies have been conducted to investigate the association between this polymorphism and various cancer risks in diverse populations. However, these results remain controversial and ambiguous. For example, Smith found that the CC genotype of the rs6505162 SNP in pre-miR-423 offered a reduced risk of breast cancer development [20], while Ryan demonstrated that there was no obvious association between rs6505162 polymorphism and esophageal squamous cell carcinoma [21]. Hence, we performed this meta-analysis to combine all the eligible studies to identify whether rs6505162 polymorphism in pre-miR-423 contributes to overall cancer risk, and further evaluate the influence of cancer type and ethnicity.

Materials and methods

Identification of eligible studies

We searched the PubMed and EMBASE databases (last updated on July 14, 2016) for all articles on the association between pre-miR-423 polymorphism and cancer risk. The keywords used for search included "miR-423, pre-miR-423 or rs6505162", "polymorphism or mutation" and "cancer or tumor". This literature retrieval work was performed by two independent investigators Wei Liu and Jinjin Ran. There was no limitation on publication years while the searching work went on. References of related studies and reviews were manually retrieved for additional studies.

Inclusion and exclusion criteria

All the studies must meet all the following criteria: (1) case-control study; (2) the association between pre-miR-423 polymorphism and cancer risks; (3) available genotype frequency; and (4) cancers diagnosed by histopathology. The major exclusion criteria were: (1) duplication of the previous publications; (2) the subjects in control group were high-risk individuals with some gene mutations; and (3) abstracts, letters, reviews or editorial articles. When a study reported the results on different ethnicities, we treated them as separate studies.

Data extraction

The two investigators independently extracted all data of eligible studies with selection criteria. The following items were collected: name of the first author; year of publication; country of origin; ethnicity; cancer types; source of control (population- or hospital-based); number of cases and controls; genotype frequency in cases and controls; Hardy-Weinberg equilibrium (HWE) of control subjects. Discrepancies and differences were resolved by discussion and consensus.

Statistical analysis

To begin with, HWE was assessed by the goodness-of-fit chi-square test in controls of each study. Odds ratio (OR) with 95% confidence intervals (95% CI) was used to assess the strength of association between miR-423 rs6505162 polymorphism and cancer risks. The significance of the pooled OR was determined by the Z-test, and $P<0.05$ was consid-

Table 1. Characteristics of studies in the meta-analysis

Author	Year	Country	Ethnicity	Cancer type	Genotyping	Source of controls	Cases (n)			Controls (n)			*P* value For HWE[e]
							CC	CA	AA	CC	CA	AA	
Smith	2012	Australia	Caucasian	Breast cancer	Taqman	HB[c]	24	95	60	42	80	52	0.3072
Wang[a]	2013	South Africa	Black	Esophageal cancer	Taqman	PB[d]	16	128	207	12	184	376	0.0521
Wang	2013	South Africa	Mixed[b]	Esophageal cancer	Taqman	PB[d]	14	84	89	34	188	198	0.2486
Yin	2013	China	Asian	Esophageal cancer	RT-PCR	HB[c]	425	207	19	374	197	29	0.6419
Ma	2014	China	Asian	Hepatocellular cancer	MassARRAY	HB[c]	643	313	30	652	297	42	0.2710
Zhu	2015	Kazakh	Turks	Esophageal cancer	MassARRAY	PB[d]	99	122	21	109	140	31	0.1592
Shen	2015	China	Asian	Esophageal cancer	SNaPshot	PB[d]	920	421	59	1421	680	84	0.8137
Yin	2016	China	Asian	Lung cancer	Taqman	HB[c]	389	166	20	368	205	35	0.3656
Jiang	2016	China	Asian	Gastric cancer	MassARRAY	HB[c]	593	255	32	656	288	41	0.1915
Morales	2016	Chile	Caucasian	Breast cancer	Taqman	HB[c]	125	229	86	284	385	138	0.7000

[a]The article reported by Wang was regarded as two independent studies according to ethnicity; [b]Mixed: major ancestral components from the indigenous Khoisan, Bantu-speaking Africans, Europeans and Asians; [c]HB: hospital-based; [d]PB: population-based; [e]HWE: Hardy-Weinberg equilibrium.

ered as statistically significant. The pooled ORs were calculated for dominant model (CC vs. AC+AA), recessive model (CA+CC vs. AA), co-dominant model (CC vs. AA), co-dominant model (CA vs. AA) and allele model (C vs. A), respectively. Subgroup analyses were performed by ethnicity and cancer types. Heterogeneity among studies was tested by Chi square-based Q test and I^2 [22]. When heterogeneity exists (based on P>0.05), a random effect model was used for the meta-analysis. Otherwise, a fixed-effects model was employed [23]. In addition, we used Begg's funnel plot and Egger's test to evaluate the publication bias (P<0.05 was considered a significant publication bias) [24]. Sensitivity analysis was conducted by deleting one study at a time to examine the influence of individual data set on the pooled ORs. All statistical analyses were performed with STATA software version 11.0 (STATA Corporation, College Station, TX, USA).

Result

Characteristics of studies

According to the inclusion and exclusion criteria above mentioned, a total of 71 articles were identified from the PubMed and EMBASE databases using different combinations of keywords. After preliminarily screening the title and abstract, 47 studies uncorrelated with cancer risk and SNPs were excluded and 25 articles were evaluated in detail. Finally, a total of 9 case-control studies met our inclusion criteria [20, 21, 25-32], including 5,891 cases and 7,622 controls for assessing the association between rs6505162 polymorphism in pre-miR-423 and cancer risk. The detailed selection process was shown in **Figure 1**. One article of these studies reported by Wang contained two case-control studies, respectively in Black and Mixed Ancestry population. This article was considered as two independent studies according to ethnicity. Cancer cases were diagnosed histologically or pathologically in all studies. Controls in 6 studies were hospital-based and those in the other studies were population-based. A variety of genotyping methods were applied including Taqman, RT-PCR, MassARRAY and SNaPshot. Genotype distribution of controls in all studies was consistent with HWE (**Table 1**).

Meta-analysis results

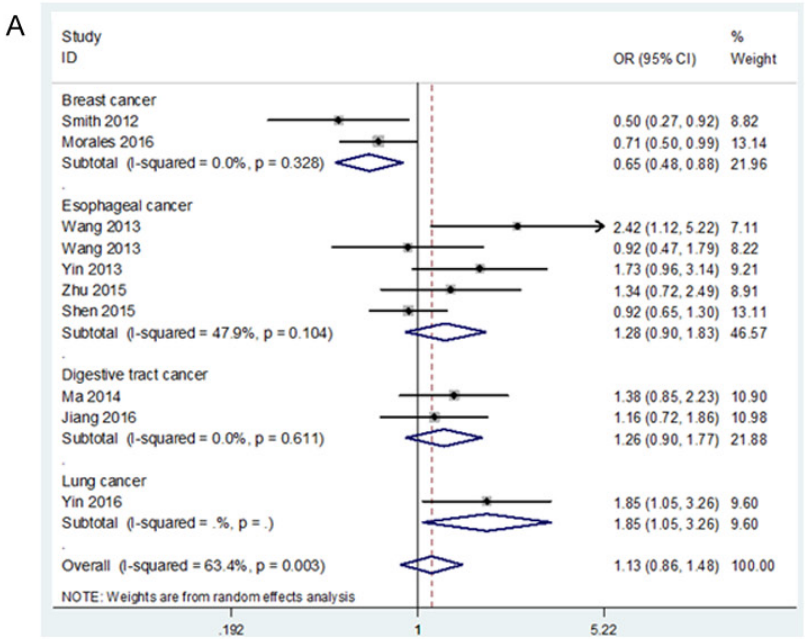
The association between rs6505162 polymorphism and cancer risk was analyzed in the 9 eligible studies. As shown in **Table 2**, no significant association was found in all genetic models. We further performed stratification analysis based on different cancer types and ethnicities.

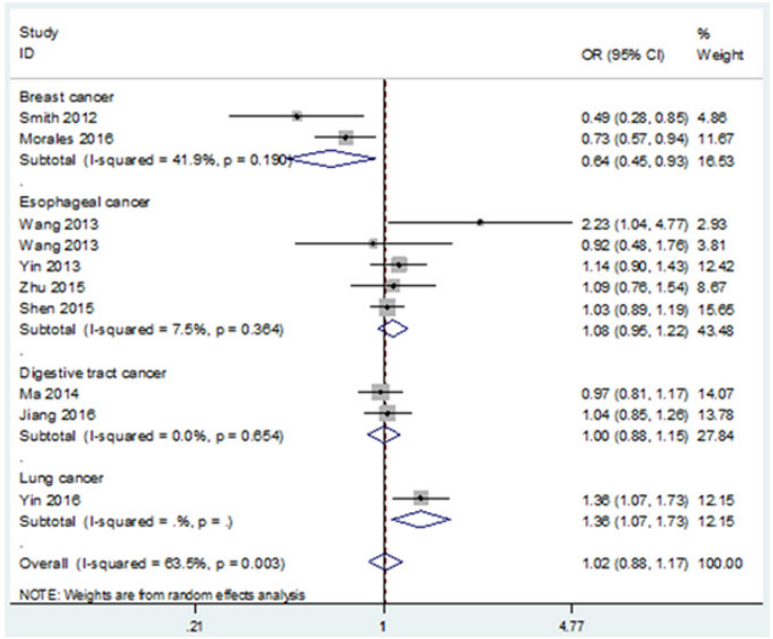
In the stratification analysis of cancer types (**Figure 2**), the results showed that the variant AA (OR=0.651, 95% CI: 0.482-0.878, *P*=0.005) and CA/AA (OR=0.644, 95% CI: 0.446-0.931, *P*=0.019) genotypes were associated with a decreased risk of breast cancer compared with the wild-type CC genotype. We observed the same association in the allelic contrast (C vs. A: OR=0.808, 95% CI=0.699-0.934, *P*=0.004). However, a significantly increased risk of lung cancer was found to be associated with the variant AA (OR=1.850, 95% CI: 1.049-3.263, *P*=0.034) and CA/AA (OR=1.364, 95% CI: 1.074-1.732, *P*=0.011) genotypes compared

Table 2. Pooled ORs and 95% CIs of the overall and stratified meta-analyses

Comparisons	No.	CA vs. AA			CC vs. AA			CC+CA vs. AA			CC vs. CA+AA			C vs. A		
		OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)
Total	10[d]	1.119 (0.983-1.274)	0.088[b]	0.0	1.133 (0.864-1.484)	0.367[c]	63.4	1.105 (0.976-1.252)	0.114[b]	33.3	1.016 (0.881-1.170)	0.831[c]	63.5	1.044 (0.944-1.154)	0.402[c]	62.9
Cancer type																
Esophageal cancer	5	1.122 (0.944-1.333)	0.191[b]	9.3	1.282 (0.899-1.828)	0.170[b]	47.9	1.155 (0.978-1.363)	0.090[b]	28.7	1.080 (0.954-1.223)	0.223[b]	7.5	1.094 (0.986-1.213)	0.090[b]	26.1
Breast cancer	2	0.977 (0.751-1.270)	0.860[b]	0.0	**0.651 (0.482-0.878)**	**0.005[b]**	**0.0**	0.848 (0.661-1.087)	0.193[b]	0.0	**0.644 (0.446-0.931)**	**0.019[b]**	**41.9**	**0.808 (0.699-0.934)**	**0.004[c]**	**0.0**
Digestive tract cancer	2	1.293 (0.913-1.833)	0.148	0.0	1.263 (0.901-1.772)	0.176	0.0	1.273 (0.910-1.780)	0.158	0.0	1.004 (0.878-1.147)	0.957	0.0	1.032 (0.920-1.157)	0.593	0.0
Lung cancer	1	1.417 (0.788-2.547)	0.244	/	**1.850 (1.049-3.263)**	**0.034**	/	1.695 (0.967-2.972)	0.066	/	**1.364 (1.074-1.732)**	**0.011**	/	**1.339 (1.094-1.639)**	**0.005**	/
Ethnicity																
Asian	5	1.172 (0.946-1.451)	0.147[b]	15.8	1.284 (0.982-1.678)	0.067[b]	36.2	1.214 (0.989-1.491)	0.064[b]	30.8	1.077 (0.974-1.192)	0.150[b]	28.4	1.089 (0.990-1.198)	0.081[b]	40.8
Caucasian	2	0.977 (0.751-1.270)	0.860[b]	0.0	**0.651 (0.482-0.878)**	**0.005[b]**	0.0	0.848 (0.661-1.087)	0.193[b]	0.0	**0.644 (0.446-0.931)**	**0.019[b]**	41.9	**0.808 (0.699-0.934)**	**0.004[b]**	0.0
Others	3	1.168 (0.948-1.438)	0.145[b]	0.0	1.398 (0.830-2.354)	0.208[b]	42.9	1.199 (0.981-1.466)	0.077[b]	0.0	1.217 (0.794-1.864)	0.367[b]	42.3	1.136 (0.950-1.359)	0.162[b]	34.9

OR: odds ratio; CI: confidence interval. The results in bold indicated the 95% CI excluded 1 or P<0.05. [a]The statistical significance of the pooled OR was determined by the Z test; [b]No statistical significance was found by the heterogeneity test and the fixed-effects model was adopted here. [c]Confirmatory analysis with a random-effect model was used when significant heterogeneity existed. [d]The article reported by Wang was regarded as two independent studies according to ethnicity.





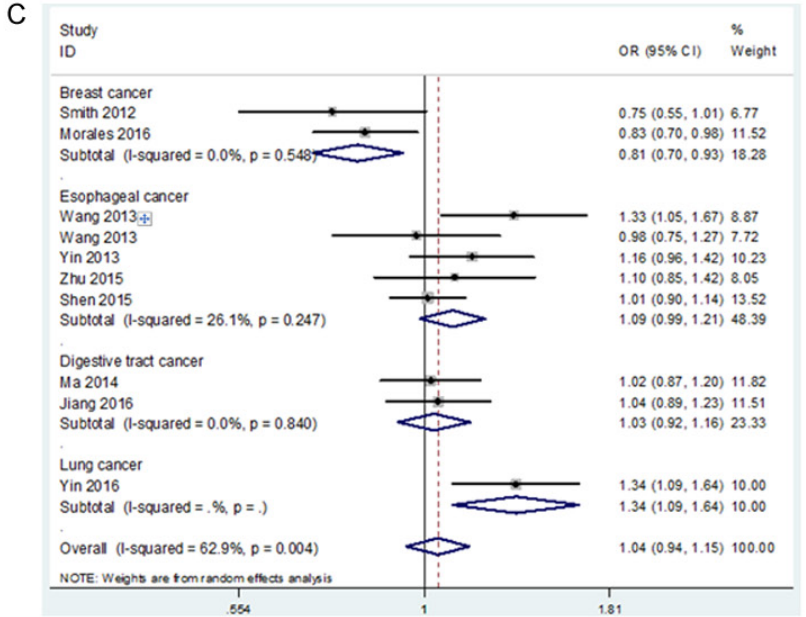


Figure 2. Subgroup analysis of the relationship between miR-608 rs4919510 polymorphism and cancer risk by cancer. A: Co-dominant model (CC vs. AA); B: Dominant model (CC vs. AA+AC); C: Allele model (C vs. A).

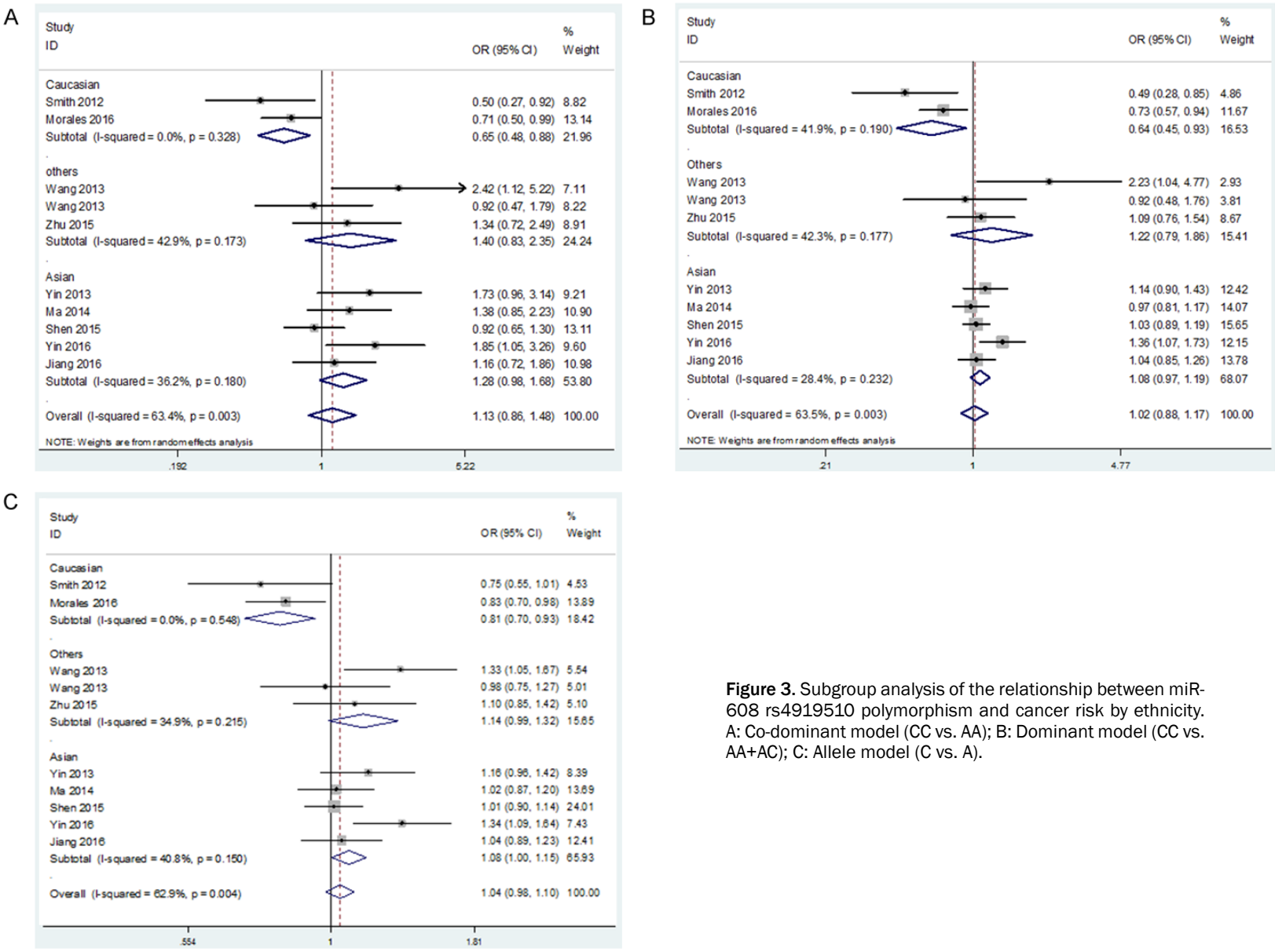


Figure 3. Subgroup analysis of the relationship between miR-608 rs4919510 polymorphism and cancer risk by ethnicity. A: Co-dominant model (CC vs. AA); B: Dominant model (CC vs. AA+AC); C: Allele model (C vs. A).

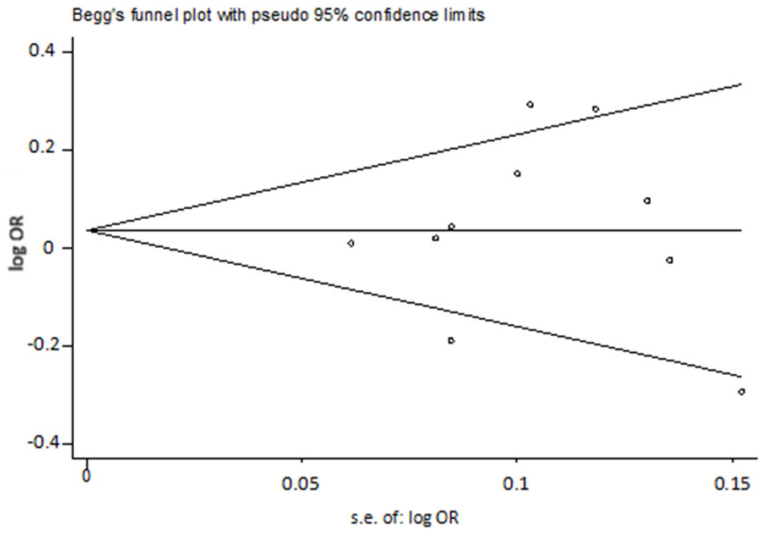


Figure 4. Begg's funnel plot for publication bias test from 9 studies (allele model, C vs. A). Each point represents a separate study for the indicated association. Horizontal line represents size of effect. OR, odds ratio; log OR, nature logarithm of OR.

with the wild-type CC genotype. No significant association was found in esophageal cancer and digestive tract cancer. Furthermore, in the stratification analysis of ethnicity (**Figure 3**), we found a highly significant association in the Caucasian population with co-dominant model (CC vs. AA: OR=0.651, 95% CI: 0.482-0.878, *P*=0.005), dominant model (CC vs. CA+AA: OR=0.644, 95% CI: 0.446-0.931, *P*=0.019) and allele model (C vs. A: OR=0.808, 95% CI: 0.699-0.934, *P*=0.004). No significant association was found in Asians and other ethnicities.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the included studies. There was no evidence of publication bias in Begg's funnel plot for all genetic models (**Figure 4**). In addition, the results of Egger's test did not indicate any evidence of publication bias in our meta-analysis (*P*>0.05).

Heterogeneity and sensitivity analysis

Heterogeneity in all comparisons of the included studies was shown in **Table 2**. A few of comparisons showed slight or moderate heterogeneities among studies. Sensitivity analysis was performed to explore the influence of individual study on the pooled OR by removing one study at a time from eligible analysis. The results suggested that the omission of any study made no significant difference.

Discussion

Polymorphisms in miRNA genes could affect the transcription of miRNA primary transcripts, pre-miRNA maturation or miRNA-mRNA interactions. These mechanisms are involved in the aberrant expression of miRNAs, which have a significant influence on carcinogenesis [32]. MiR-423 is located on chromosome 17 and lies in the first intron of nuclear speckle splicing regulatory protein (NSRP1), which has been confirmed to play an important role in pre-miRNA splicing [33]. Several studies have found different expression patterns of miR-423 in various cancers, such as head and neck cancer [34], breast cancer [35] and hepatocellular cancer [36]. The rs6505162 polymorphism is located in the precursor of pre-miR-423 [20]. Recently, rs6505162 polymorphism in pre-miR-423 has been reported to offer a reduced cancer risk in difference cancer types. For example, Zhao found that the high mutation frequency of the SNP rs6505162 in pre-miR-423 had strong association with the expression of both proliferating cell nuclear antigen (PCNA) and mutant p53, which play an oncogenic role in carcinogenesis [37]. All these studies provoked us to focus on the association of rs6505162 polymorphism and cancer susceptibility.

In the meta-analysis, C-A variation at pre-miR-423 rs6505162 polymorphism sit did not exert significant genetic effect on cancer risk. Subgroup analysis revealed that the variant AA and CA/AA genotypes were associated with a decreased risk of breast cancer compared with wild-type CC genotype. However, an increased risk of lung cancer was found in co-dominant genetic model (CC vs. AA) and the recessive genetic model (CC vs. CA+AA). MiR-423 is highly expressed in multiple cancer types, including breast cancer. Both the mature miR-423-3p and miR-423-5p have been reported to be

involved in tumorigenesis. For example, Lin reported that only miR-423-3p could promote cell growth and regulate G1/S transition by targeting p21Cip1/Waf1 in hepatocellular carcinoma [36]. In gastric cancer cells, miR-423-5p could regulate cell proliferation and invasion by targeting trefoil factor 1 [38]. Another example was that Zhao found miR-423 promoted cell proliferation in breast cancer cell lines through its miR-423-3p strand, but not miR-423-5p. Lower expression level of mature miR-423-3p has the relative lower proliferation ability of pre-miR-423-12C in the stable breast cancer cell population [37]. The different expression levels of mature miR-423-3p and miR-423-5p may result in the different effect of the pre-miR-423 polymorphism on the risk of breast cancer and lung cancer. In the stratification analysis of ethnicity, the variant AA and CA/AA genotypes were associated with a decreased risk of cancer in the Caucasian population, which is consistent with the subgroup analysis of breast cancer. This could be attributed to the fact that 2 eligible studies in the Caucasian population all focused on breast cancer. However, no significant association was found in Asians and other ethnicities in the meta-analysis.

In interpreting the current results, several limitations of this study should also be considered. Firstly, eligible studies are still so inadequate that they may have an influence on our results of subgroup analysis. Secondly, a certain degree of heterogeneity was obvious in some comparisons, which could interfere with our results. Thirdly, lack of original data of the reviewed studies, consisting of age, gender, family history and environment factors, limited our further meta-analysis. Last but not the least, only studies published in English were included in our meta-analysis, while studies published in other languages were not available, which may have biased our results. Therefore, more studies with available complete information are still required to achieve a more comprehensive and reliable result.

In summary, the results of our meta-analysis indicate a significant association between pre-miR-423 rs6505162 polymorphism and risk of breast cancer and lung cancer. To some extent, this polymorphism is closely related to cancer susceptibility in Caucasians. However, these results should be treated with some caution due to the limitations above. Additional studies from different ethnic groups and different types of cancers are necessary for further identification.

Disclosure of conflict of interest

None.

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References

[1] Ebert MS and Sharp PA. Roles for microRNAs in conferring robustness to biological processes. Cell 2012; 149: 515-524.
[2] Pritchard CC, Cheng HH and Tewari M. MicroRNA profiling: approaches and considerations. Nat Rev Genet 2012; 13: 358-369.
[3] Valencia-Sanchez MA, Liu J, Hannon GJ and Parker R. Control of translation and mRNA degradation by miRNAs and siRNAs. Genes Dev 2006; 20: 515-524.
[4] Ambros V. The functions of animal microRNAs. Nature 2004; 431: 350-355.
[5] Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136: 215-233.
[6] Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A and Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. Nucleic Acids Res 2006; 34: D140-144.
[7] He L and Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5: 522-531.
[8] Krol J, Loedige I and Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. Nat Rev Genet 2010; 11: 597-610.
[9] Johnnidis JB, Harris MH, Wheeler RT, Stehling-Sun S, Lam MH, Kirak O, Brummelkamp TR, Fleming MD and Camargo FD. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. Nature 2008; 451: 1125-1129.
[10] Mocellin S, Pasquali S and Pilati P. Oncomirs: from tumor biology to molecularly targeted anticancer strategies. Mini Rev Med Chem 2009; 9: 70-80.
[11] Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, Yuen ST, Chan TL, Kwong DL, Au GK, Liu CG, Calin GA, Croce CM and Harris CC. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. JAMA 2008; 299: 425-436.
[12] Landi D, Gemignani F, Naccarati A, Pardini B, Vodicka P, Vodickova L, Novotny J, Försti A, Hemminki K, Canzian F and Landi S. Polymor-

phisms within micro-RNA-binding sites and risk of sporadic colorectal cancer. Carcinogenesis 2008; 29: 579-584.
[13] Boni V, Zarate R, Villa JC, Bandres E, Gomez MA, Maiello E, Garcia-Foncillas J and Aranda E. Role of primary miRNA polymorphic variants in metastatic colon cancer patients treated with 5-fluorouracil and irinotecan. Pharmacogenomics J 2010; 11: 429-436.
[14] Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC and Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A 2006; 103: 2257-2261.
[15] Omrani M, Hashemi M, Eskandari-Nasab E, Hasani SS, Mashhadi MA, Arbabi F and Taheri M. hsa-mir-499 rs3746444 gene polymorphism is associated with susceptibility to breast cancer in an Iranian population. Biomark Med 2014; 8: 259-267.
[16] Lian H, Wang L and Zhang J. Increased risk of breast cancer associated with CC genotype of Has-miR-146a Rs2910164 polymorphism in Europeans. PLoS One 2012; 7: e31615.
[17] Wang L, Qian S, Zhi H, Zhang Y, Wang B and Lu Z. The association between hsa-miR-499 T.C polymorphism and cancer risk: a meta-analysis. Gene 2012; 508: 9-14.
[18] Guo J, Jin M, Zhang M and Chen K. A genetic variant in miR-196a2 increased digestive system cancer risks: a meta-analysis of 15 case-control studies. PLoS One 2012; 7: e30585.
[19] Kontorovich T, Levy A, Korostishevsky M, Nir U and Friedman E. Single nucleotide polymorphisms in miRNA binding sites and miRNA genes as breast/ovarian cancer risk modifiers in Jewish high-risk women. Int J Cancer 2010; 127: 589-597.
[20] Smith RA, Jedlinski DJ, Gabrovska PN, Weinstein SR, Haupt L and Griffiths LR. A genetic variant located in miR-423 is associated with reduced breast cancer risk. Cancer Genomics Proteomics 2012; 9: 115-118.
[21] Shen F, Chen J, Guo S, Zhou Y, Zheng Y, Yang Y, Zhang J, Wang X, Wang C, Zhao D, Wang M, Zhu M, Fan L, Xiang J, Xia Y, Wei Q, Jin L, Wang J and Wang M. Genetic variants in miR-196a2 and miR-499 are associated with susceptibility to esophageal squamous cell carcinoma in Chinese Han population. Tumour Biol 2016; 37: 4777-4784.
[22] Lau J, Ioannidis JP and Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.
[23] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[24] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[25] Wang Y, Vogelsang M, Schäfer G, Matejcic M and Parker MI. MicroRNA polymorphisms and environmental smoke exposure as risk factors for oesophageal squamous cell carcinoma. PLoS One 2013; 8: e78520.
[26] Yin J, Wang X, Zheng L, Shi Y, Wang L, Shao A, Tang W, Ding G, Liu C, Liu R, Chen S and Gu H. Hsa-miR-34b/c rs493723 T>C and hsa-miR-423 rs6505162 C>A polymorphisms are associated with the risk of esophageal cancer in a Chinese population. PLoS One 2013; 8: e80570.
[27] Jiang J, Jia ZF, Cao DH, Wu YH, Sun ZW and Cao XY. Association of the miR-146a rs2910164 polymorphism with gastric cancer susceptibility and prognosis. Future Oncol 2016; 12: 2215-2226.
[28] Zhu J, Yang L, You W, Cui X, Chen Y, Hu J, Liu W, Li S, Song X, Wei Y, Zhang W and Li F. Genetic variation in miR-100 rs1834306 is associated with decreased risk for esophageal squamous cell carcinoma in Kazakh patients in northwest China. Int J Clin Exp Pathol 2015; 8: 7332-7340.
[29] Ma Y, Wang R, Zhang J, Li W, Gao C, Liu J and Wang J. Identification of miR-423 and miR-499 polymorphisms on affecting the risk of hepatocellular carcinoma in a large-scale population. Genet Test Mol Biomarkers 2014; 18: 516-524.
[30] Yin Z, Cui Z, Ren Y, Xia L, Wang Q, Zhang Y, He Q and Zhou B. Association between polymorphisms in pre-miRNA genes and risk of lung cancer in a Chinese non-smoking female population. Lung Cancer 2016; 94: 15-21.
[31] Ryan BM, Robles AI and Harris CC. Genetic variation in microRNA networks: the implications for cancer research. Nat Rev Cancer 2010; 10: 389-402.
[32] Morales S, Gulppi F, Gonzalez-Hormazabal P, Fernandez-Ramires R, Bravo T, Reyes JM, Gomez F, Waugh E and Jara L. Association of single nucleotide polymorphisms in Pre-miR-27a, Pre-miR-196a2, Pre-miR-423, miR-608 and Pre-miR-618 with breast cancer susceptibility in a South American population. BMC Genet 2016; 17: 109.
[33] Kim YD, Lee JY, Oh KM, Araki M, Araki K, Yamamura K and Jun CD. NSrp70 is a novel nuclear speckle-related protein that modulates alternative pre-mRNA splicing in vivo. Nucleic Acids Res 2011; 39: 4300-4314.
[34] Hui AB, Lenarduzzi M, Krushel T, Waldron L, Pintilie M, Shi W, Perez-Ordonez B, Jurisica I, O'Sullivan B, Waldron J, Gullane P, Cummings

B and Liu FF. Comprehensive microRNA profiling for head and neck squamous cell carcinomas. Clin Cancer Res 2010; 16: 1129-1139.

[35] Farazi TA, Horlings HM, Ten Hoeve JJ, Mihailovic A, Halfwerk H, Morozov P, Brown M, Hafner M, Reyal F, van Kouwenhove M, Kreike B, Sie D, Hovestadt V, Wessels LF, van de Vijver MJ and Tuschl T. Micro-RNA sequence and expression analysis in breast tumors by deep sequencing. Cancer Res 2011; 71: 4443-4453.

[36] Lin J, Huang S, Wu S, Ding J, Zhao Y, Liang L, Tian Q, Zha R, Zhan R and He X. MicroRNA-423 promotes cell growth and regulates G (1)/S transition by targeting p21Cip1/Waf1 in hepatocellular carcinoma. Carcinogenesis 2011; 32: 1641-1647.

[37] Zhao H, Gao A, Zhang Z, Tian R, Luo A, Li M, Zhao D, Fu L, Fu L, Dong JT and Zhu Z. Genetic analysis and preliminary function study of miR-423 in breast cancer. Tumour Biol 2015; 36: 4763-4771.

[38] Guan G, Zhang D, Zheng Y, Wen L, Yu D, Lu Y and Zhao Y. MicroRNA-423-3p promotes tumor progression via modulation of AdipoR2 in laryngeal carcinoma. Int J Clin Exp Pathol 2014; 7: 5683-5691.