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Association between miR34b/c Polymorphism rs4938723 and Cancer Risk: A Meta-Analysis of 11 Studies including 6169 Cases and 6337 Controls

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BE Xinjing Wang*
CE Xiongxiong Lu*
CD Yuan Fang
F Hao Chen
A Xiaxing Deng
F Chenghong Peng
E Hongwei Li
A Baiyong Shen

Department of General Surgery, Ruijin Hospital, affiliated with Shanghai Jiaotong University School of Medicine, Shanghai Institute of Digestive Surgery, Shanghai, China

* Xinjing Wang and Xiongxiong Lu contributed equally to this work

Corresponding Authors: Baiyong Shen, e-mail: profshenby@gmail.com, Xiaxing Deng, e-mail: dxx888888@gmail.com
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Background: The functional polymorphism rs4938723 in the promoter region of pri-miR-34b/c is potentially associated with susceptibility to several cancers, including hepatocellular carcinoma, colorectal cancer, and breast cancer. Here we conducted a comprehensive meta-analysis to investigate the association between rs4938723 and cancer risk.

Material/Methods: Eligible studies extracted from the databases of PubMed, Web of Science, and Cochrane Library were evaluated. Statistical analysis was performed using Revman 5.2 and STATA 12.0 software.

Results: By characterizing the extracted data, a total of 11 studies reported in 10 publications including 6169 cases and 6337 controls were selected for further analysis. Our results revealed a significant association between the rs4938723 polymorphism and cancer risk in the codominant model (TC *vs.* TT: OR=1.10, 95% CI=1.02–1.19, P=0.009) but not in other genetic models. In the stratified analysis of different cancer types, a significant association was found in nasopharyngeal cancer, osteosarcoma, and renal cell cancer. Furthermore, stratified analysis of ethnicity indicated that a highly significant association was shown in the Asian population in a codominant model (TC *vs.* TT: OR=1.13, 95% CI=1.03–1.24, P=0.007) when compared with African-Americans and Caucasians.

Conclusions: Overall, the current study suggests that the miR-34b/c rs4938723 polymorphism may be associated with the risk of cancers, including nasopharyngeal cancer, osteosarcoma, and renal cell cancer, and to some extent this polymorphism is closely related to cancer susceptibility in Asians.

MeSH Keywords: Genes, Neoplasm • Meta-Analysis • MicroRNAs • Polymorphism, Genetic

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Background

Cancers are still the leading cause of death worldwide and cancer burden continues to increase, receiving great public attention [1–3]. Investigators showed that genetic factors have significantly important functions in the development and progression of cancer.

MicroRNAs (miRNAs) are small, noncoding, single-stranded RNA molecules that participate in the transcriptional regulation of eukaryotic genes and lead to mRNA degradation or the translational repression of targeted genes [4–6]. MiRNAs were thought to be associated with many biological processes with critical roles in carcinogenesis, including cell differentiation, proliferation, and apoptosis. Furthermore, the variation of miRNAs through physiological processes may cause the incidence and development of tumors [7,8]. Recently, a potentially functional polymorphism rs4938723 has been discovered in the promoter region of miR-34b/c. The T to C shift of the rs4938723 polymorphism is thought to influence the GATA-X binding sites. It can bind to the GATA-X when the location is C; otherwise, it cannot bind to the GATA-X. In the past several years, many reported studies have focused on the association between miR34b/c rs4938723 polymorphism and cancer susceptibility in several populations and diverse types of cancer [9–18]. However, the results were inconclusive and controversial, and to the best of our knowledge no one has performed a meta-analysis to investigate the association of this polymorphism with cancer risk. Therefore, we conducted a meta-analysis of all eligible studies to further study the roles of miR-34b/c rs4938723 polymorphism in carcinogenesis.

Material and Methods

Search for study

A systematic search was conducted by 2 investigators independently. Studies were mainly searched in PubMed, Web of Science, and Cochrane Library databases from their inception to June 2014 with the following terms: 'miR-34b/c', 'polymorphism', and 'cancer'. The search was limited to case-control studies in the English language. Reference lists from relevant articles were also examined to find additional publications. To avoid double-counting or other errors, 2 investigators compared their results discreetly and disagreements were resolved by consensus or by a third investigator.

Selection of study

All the included studies met the following criteria: 1) case-control study; 2) evaluation of the association between miR-34b/c rs4938723 polymorphism and cancer risks; 3) sufficient data for analysis, including genotype frequency in cases and controls; 4) genotype frequency in the control group was in Hardy-Weinberg equilibrium (HWE); and 5) the study was published in English. We excluded studies without eligible data for meta-analysis.

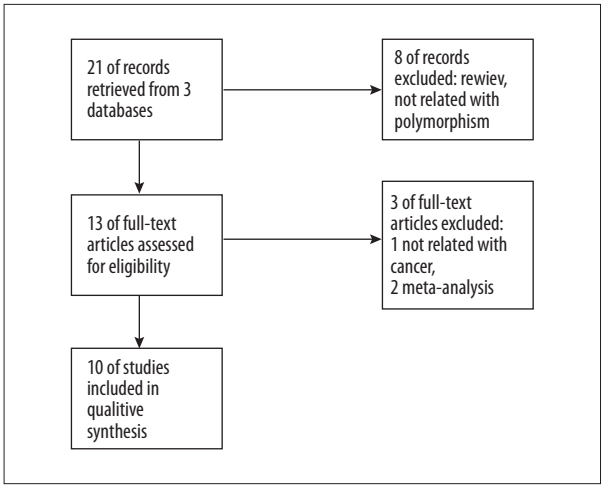

Figure 1. Study flow diagram.

Data extraction

Two investigators who were blinded to each other abstracted the data in a traditional format and reached consensus on all items. The collected data included first author, publication year, country, ethnicity, cancer type, and available genotypes.

Statistical analysis

Statistical analysis was performed using Revman 5.2 and STATA 12.0 software. χ^2 tests and I^2 statistic were used to measure the study heterogeneity between trials. Both fixed- and random-effects models were used where appropriate [19,20]. I^2 >50% was considered representative of significant statistical heterogeneity and the random-effects model was used; otherwise, the calculations were performed with the fixed-effects model. Odds ratio (OR) with 95% confidence interval (95% CI) was used to evaluate the association between polymorphism and cancer risk with the codominant model (TC *vs.* TT), codominant model (CC *vs.* TT), dominant model (TC+ CC *vs.* TT), recessive model (TC+TT *vs.* CC), and allele model (T *vs.* C). Subgroup analysis based on cancer type and ethnicity was also performed. Sensitivity analysis was used to identify sources of significant heterogeneity by removing individual studies and analyzing the effect on the overall results. Publication bias was further assessed by Begg's test [21]. P value less than 0.05 was considered statistically significant in all statistics.

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

Author	Year	Country	Ethnicity	Type of cancer	No. (cases/ controls)	Genotypes case (%)			Genotypes control (%)		
						TT	TC	CC	TT	TC	CC
Bensen et al.	2013	America	African American	Breast cancer	742/658	362 (48.8)	317 (42.7)	63 (8.5)	343 (52.1)	257 (39.1)	58 (8.8)
Bensen et al.	2013	America	Caucasian	Breast cancer	1203/1088	496 (41.2)	563 (46.8)	144 (12.0)	430 (39.5)	503 (46.2)	155 (14.2)
Gao et al.	2013	China	Asian	Colorectal cancer	347/488	175 (50.4)	144 (41.5)	28 (8.1)	216 (44.3)	210 (43.0)	62 (12.7)
Han et al.	2013	China	Asian	Hepatocellular carcinoma	1013/999	451 (44.5)	444 (43.8)	118 (11.6)	456 (45.6)	424 (42.4)	119 (11.9)
Li et al.	2013	China	Asian	Nasopharyngeal carcinoma	217/360	82 (37.8)	104 (47.9)	31 (14.3)	168 (46.7)	155 (43.1)	37 (10.3)
Oh et al.	2014	Korea	Asian	Colorectal cancer	545/428	272 (49.9)	233 (42.8)	40 (7.3)	216 (50.5)	171 (40.0)	41 (9.5)
Son et al.	2014	Korea	Asian	Hepatocellular carcinoma	157/201	69 (43.9)	75 (47.8)	13 (8.3)	110 (54.7)	74 (36.8)	17 (8.5)
Tian et al.	2014	China	Asian	Osteosarcoma	133/133	41 (30.8)	62 (46.6)	30 (22.6)	62 (46.6)	53 (39.8)	18 (13.5)
Xu et al.	2011	China	Asian	Hepatocellular carcinoma	502/549	204 (40.64)	236 (47.01)	62 (12.35)	266 (48.45)	229 (41.71)	54 (9.84)
Yin et al.	2013	China	Asian	Esophageal cancer	600/673	277 (46.2)	278 (46.3)	45 (7.5)	310 (46.1)	290 (43.1)	73 (10.8)
Zhang et al.	2014	China	Asian	Renal cell cancer	710/760	302 (42.5)	324 (45.6)	84 (11.8)	352 (46.3)	344 (45.3)	64 (8.4)

Results

Characteristics of the studies

A study flow diagram is shown in Figure 1. Twenty-one studies of miR-34b/c polymorphism and cancers were found in a primary literature search in the PubMed, Web of Science, and Cochrane Library databases. After reviewing each publication, 11 articles were found to be inappropriate for the current meta-analysis because some of them were review articles, irrelevant to the current study or they contained duplicate data. Ten publications, including 11 studies with 6169 cases and 6337 controls (Table 1), were identified as being appropriate for inclusion in the current meta-analysis [9–18]. Of the 11 selected studies, 9 were matched for age and sex but 2 studies of breast cancer were not matched for sex. Furthermore, 9 studies were done in Asians and the other 2 studies of breast cancer were in Caucasians and African-Americans. The genotype distribution of control populations was in Hardy-Weinberg equilibrium in all 11 studies.

Quantitative synthesis

We analyzed the association between miR-34b/c polymorphism and cancer risks within 5 genetic models, as mentioned in the Methods section. The main results of the meta-analysis are shown in Table 2. The data were extracted to estimate the association with the overall risk of all types of cancer. The pooled results revealed a significant association between rs4938723 genotype TC and increased cancer risk in the codominant model (TC *vs.* TT: OR=1.10, 95% CI=1.02–1.19, P=0.009). In contrast, no statistically significant association was found in the other 4 genetic models. We performed stratification analysis based on the cancer types and ethnicities. In the stratified analysis of cancer types, the significantly increased risk of nasopharyngeal cancer was found to be associated with the C allele carriers (TC + CC genotypes) in the dominant model (TC + CC *vs.* TT: OR=1.44, 95% CI=1.02–2.03, P=0.04) and allele comparison (C *vs.* T: OR=1.33, 95% CI=1.04–1.70, P=0.03). Except for the recessive model (CC *vs.* TC + TT), the other 4 compared models showed significant association with increased risk of osteosarcoma (TC *vs.* TT: OR=1.77, 95% CI=1.03–3.03, P=0.04; CC *vs.* TT: OR=2.52, 95% CI=1.25–5.10, P=0.01; TC+ CC *vs.* TT: OR=1.96, 95% CI=1.19–3.24, P=0.009; C *vs.* T: OR=1.68, 95% CI=1.19–2.39, P=0.004, respectively). We also found that the significantly increased risk of renal cell cancer was associated with C allele (C *vs.* T: OR=1.18, 95% CI=1.01–1.37, P=0.04) and homozygous genotype CC in the codominant (CC *vs.* TT: OR=1.53, 95% CI=1.07–2.19, P=0.02) and recessive (CC *vs.* TC+TT: OR=1.46, 95% CI=1.04–2.06, P=0.03)

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

Variables	No. of studies	Codominant model: TC *vs.* TT			Codominant model: CC *vs.* TT			Dominant model: TC + CC *vs.* TT			Recessive model: CC *vs.* TC+TT			Allele: C *vs.* T		
		OR (95%CI)	P value	I^2 (%)	OR (95%CI)	P value	I^2 (%)	OR (95%CI)	P value	I^2 (%)	OR (95%CI)	P value	I^2 (%)	OR (95%CI)	P value	I^2 (%)
All cancers	11	**1.10 (1.02, 1.19)**	**0.009**	**34**	1.06 (0.85, 1.33)	0.6	69	1.12 (1.00, 1.26)	0.06	59	0.99 (0.82, 1.20)	0.91	59	1.07 (0.97, 1.19)	0.18	70
Cancer type																
Digestive tract cancer	6	1.10 (0.99, 1.22)	0.07	42	0.90 (0.67, 1.20)	0.46	61	1.07 (0.91, 1.26)	0.39	60	0.87 (0.74, 1.03)	0.1	47	1.01 (0.88, 1.16)	0.88	67
Breast cancer	2	1.04 (0.91, 1.20)	0.55	40	0.87 (0.70, 1.08)	0.21	6	1.02 (0.84, 1.25)	0.84	55	0.86 (0.70, 1.05)	0.14	0	0.98 (0.84, 1.15)	0.83	58
Nasopharyngeal carcinoma	1	1.37 (0.96, 1.98)	0.09	/	1.72 (0.99, 2.96)	0.05	/	**1.44 (1.02, 2.03)**	**0.04**	/	1.45 (0.87, 2.42)	0.15	/	**1.33 (1.04, 1.70)**	**0.03**	/
Osteosarcoma	1	**1.77 (1.03, 3.03)**	**0.04**	/	**2.52 (1.25, 5.10)**	**0.01**	/	**1.96 (1.19, 3.24)**	**0.009**	/	1.86 (0.98, 3.54)	0.06	/	**1.68 (1.19, 2.39)**	**0.004**	/
Renal cell cancer	1	1.10 (0.88, 1.36)	0.4	/	**1.53 (1.07, 2.19)**	**0.02**	/	1.17 (0.95, 1.43)	0.15	/	**1.46 (1.04, 2.06)**	**0.03**	/	**1.18 (1.01, 1.37)**	**0.04**	/
Ethnicity																
Asian	9	**1.13 (1.03, 1.24)**	**0.007**	**37**	1.12 (0.84, 1.49)	0.44	72	1.16 (1.00, 1.33)	0.05	61	1.03 (0.81, 1.31)	0.83	64	1.10 (0.97, 1.25)	0.14	72
Caucasian	1	0.97 (0.81, 1.16)	0.74	/	0.81 (0.62, 1.05)	0.1	/	0.93 (0.79, 1.10)	0.41	/	0.82 (0.64, 1.04)	0.11	/	0.92 (0.81, 1.04)	0.16	/
African American	1	1.17 (0.94, 1.46)	0.17	/	1.03 (0.70, 1.51)	0.88	/	1.14 (0.93, 1.41)	0.21	/	0.96 (0.66, 1.39)	0.83	/	1.08 (0.91, 1.27)	0.38	/

models. Stratified analysis of ethnicity showed a statistically increased cancer risk in Asians with heterozygous genotype TC in the codominant model (TC *vs.* TT: OR=1.13, 95% CI=1.03–1.24, P=0.007) but not in African-Americans or Caucasians.

Sensitivity analysis

To assess the stability of the results, sensitivity analysis was performed by omitting 1 study at a time. The omission of any 1 study made no substantial change in the statistical results, which indicated that the results were statistically reliable.

Publication bias

Funnel plots and Begg's test were used to estimate the publication bias of the articles included in this study. There was no obvious evidence of asymmetry in the shape of funnel plots in the recessive model (CC *vs.* TC + TT) (Figure 2). In addition, the results of Begg's test showed no evidence of publication bias (Z=0.16, P=0.876).

Discussion

The reports from several laboratories demonstrated that miR-34 family members are the direct targets of TP53, and their upregulation induces cancer cell apoptosis and cell-cycle arrest [22–28]. miR-34 has been shown to be associated with carcinogenesis, prognosis, and survival of various cancers, including pancreatic cancer, gastric cancer, ovarian cancer, prostate cancer, and many other cancers [29–32]. Given that the polymorphism of rs4938723, which is capable of creating a

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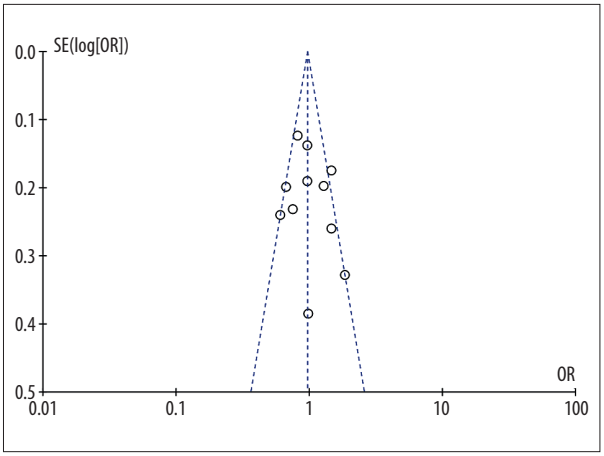

Figure 2. Funnel plots for assessing publication bias in the meta-analysis.

predicted GATA-binding site, was found in the promoter region of miR-34b/c, this polymorphism may affect miR-34b/c expression via genetic and epigenetic mechanisms. Thus, several studies investigated the association between the polymorphism of rs4938723 and cancer risk. Three studies have reported that rs4938723 is associated with an increased risk of hepatocellular carcinoma [11,14,16], while Liang et al. presented a meta-analysis and disapproved this conclusion [33]. Furthermore, Gao et al. [10] and Oh et al. [13] have demonstrated that rs4938723 is associated with a reduced risk of colorectal cancer. Therefore, the results of association between rs4938723 and cancer risk are still controversial.

According to the current meta-analysis of 11 case-control studies of 6169 cases and 6337 controls, rs4938723 was found to be associated with increased cancer risk in a codominant model when compared TC with TT in the overall analysis. We further performed stratification analysis based on cancer type and ethnicity. The stratified analysis of cancer type revealed that a significantly elevated risk was associated with C allele and C allele carriers in nasopharyngeal carcinoma. Moreover, rs4938723 polymorphism was associated with osteosarcoma in 4 compared models (TC *vs.* TT; CC *vs.* TT; TC+CC *vs.* TT; and C *vs.* T). For renal cell cancer, the association analyses of codominant model (CC *vs.* TT), recessive model (CC *vs.* TC+TT), and allelic comparison (C *vs.* T) consistently supported that this polymorphism was statistically related to increased risks. A significant association was not observed in the digestive cancers, including hepatocellular carcinoma, colorectal cancer, and esophageal cancer, within 3164 cases and 3338 controls, although the original studies of these cancers supported a genetic association between rs4938723 and susceptibility to the respective cancer. In addition, the stratified analysis of ethnicity indicated that a statistically significant association was detected in Asians in the codominant model that compared TC with TT. These findings suggest that the polymorphism of miR34b/c rs4938723 may play an important role in carcinogenesis and its development.

However, limitations in our analysis should also be considered. First, as far as we know, the 10 publications, including 11 case-control studies, were relatively limited, especially for nasopharyngeal cancer, osteosarcoma, and renal cell cancer, which were only involved in a single study. Second, the ORs we got were unadjusted, and many other clinical factors such as age and sex in each study might lead to bias. Third, we restricted our included studies to English language. Fourth, our meta-analysis was limited by the quality of the original studies. Fifth, since 9 publications were done in Asians with only 1 study from a Western country, it is necessary to include investigations from other countries.

Conclusions

This meta-analysis investigated the relationship between rs4938723 and cancer risk. Although there are several limitations, our work indicates that the miR-34b/c rs4938723 polymorphism may be associated with risk of cancers in Asians.

Conflict of interest

None.

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