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RESEARCH

Associations of Polymorphisms in mir-196a2, mir-146a and mir-149 with Colorectal Cancer Risk: A Meta-Analysis

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Abstract MicroRNAs (miRNAs) are non-coding RNAs which act as tumor suppressors or oncogenes. And single nucleotide polymorphism (SNP) in miRNA regions is one type of genetic variations in human genome. Various studies have investigated the associations of miRNAs SNP and kinds of cancers. In this article, we searched eligible studies to explore the relationships between mir-196a2 /mir-146a /mir-149 polymorphisms and colorectal cancer (CRC). A literature search of PubMed, Web of Science and ScienceDirect was conducted to identify all relevant studies. Three genetic models with pooled ratio and 95 % confidence interval were used to evaluate the associations. We found that mir-196a2 polymorphism was significantly associated with CRC in Asian group (additive model: OR=1.197, 95 %CI 1.084~1.32, $P<0.001$; dominant model: OR=1.247, 95 %CI 1.065~1.46, $P=0.006$; recessive model: OR=1.298, 95 %CI 1.101~1.531, $P=0.002$). And no associations were observed between SNPs of mir-146a, mir-149 and CRC in three genetic models. We also found CRC risk was not associated with mir-146a and mir-149 polymorphisms in population subgroup analysis. The current meta-analysis suggests that mir-196a2 polymorphism is associated with CRC, especially in Asian group. While, no associations have been found between mir-146a /mir-149 polymorphisms and CRC.

Keywords mir-196a2 · mir-146a · mir-149 · CRC · SNP

Abbreviation

CRC	colorectal cancer
miRNA	microRNA
SNP	single nucleotide polymorphism
OR	odds ratio
CI	confidence interval
HWE	Hardy-Weinberg equilibrium

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Introduction

MircroRNAs (miRNAs) are endogenous, non-coding RNAs of 18–25 nucleotides that regulate target genes expression [1,2]. There may be more than 1,000 miRNA genes in human genome, and one miRNA could combine hundreds of mRNA targets [3–6]. Many researches imply that more than half of miRNA genes are sited in cancer associated regions, which implies that miRNAs are important factors in oncogenesis. Sequence variants in miRNA genes are associated with deregulation, and miRNAs transcription or mature miRNAs formation may be affected by mutation or single nucleotide polymorphism (SNPs) [7,8]. Sometimes SNPs reduce or silence miRNA expression [8].

Colorectal cancer (CRC), as one kind of prevalent malignancies [9], its susceptibility and mortality increased rapidly in the past years [10], and it is one of the top three common malignancies in western countries [11]. Although early diagnosis methods are improved and various therapy methods arise, the mortality rate remains high [12]. So it is of great significance to develop early and safe diagnostic biomarkers for patients with CRC.

Recently, various miRNA SNPs were estimated with kinds of cancers. Among them, the polymorphisms of mir-196a2, mir-146a, mir-149 were explored deeply. It was demonstrated that mir-196a2 polymorphism was associated with lung cancer [13,14], breast cancer [15,16], and hepatocellular carcinoma [17]. Also, the associations between polymorphisms of mir-146a or mir-149 and multiple cancers were illustrated by

previous studies. The aim of this article was to further declare the relationship between genetic variants in miRNAs of mir-196a2, mir-146a, mir-149 and CRC susceptibility.

Materials and Methods

Identification of Eligible Studies

By using the database of PubMed, Web of Science, ScienceDirect, literatures containing "mir-196a2", "mir-146a", "mir-149", "colorectal cancer/CRC", "polymorphism", "miRNA" were searched, and no language restrictions were done in searching process. We adjusted the searching terms to retrieve the most eligible studies. And reference lists were used to identify other eligible publications.

Inclusion and Exclusion Criteria

Studies were adopted in this meta-analysis if they met all of the criteria: (1) case–control studies; (2) evaluation of SNP in mir-196a2, mir-146a, mir-149 and CRC; (3) available genotype frequency to estimate an odds ratio with 95 % confidence interval. The exclusion criteria were: (1) not a case–control study; (2) studies were not about CRC and these three mirRNAs polymorphisms; (3) data were not useful or sufficient.

Data Extraction

Information like: author, population, year of publication, case number, control number, P values for Hardy-Weinberg equilibrium (HWE) were extracted from all the eligible articles according to the inclusion and exclusion criteria. P values for HWE in control groups were also done among all control samples.

Statistical Analysis

The departure of frequencies of SNP in mir-196a2, mir-146a, mir-149 from HWE in control group was evaluated by X^2 test, P value<0.05 was considered statistically significant.

Crude ORs and corresponding 95 %CIs were used to evaluate the strength of association between three miRNAs polymorphism and CRC susceptibility. The meta-analysis examined the association by three genetic models respectively: additive model, dominant model and recessive model. Subgroup analysis was also done by population. Chi-square based Q-test was explored to evaluate the heterogeneity, and P value<0.05 was considered significant, a random- effect model was used. Otherwise, a fixed-effect model was chosen. Publication bias was accessed with Begg's test and Egger's linear regression test [18], and p value<0.05 indicated representative of statistically significant publication bias. Statistical analysis was implemented with Stata software.

Results

Characteristics of the Studies

The characteristics of included literatures were presented in Table 1, a total of eleven studies involving 6,022 cases and 7,290 controls were selected from 139 studies [12,19–27], and the records which were not about case–control studies or not about these three miRNAs SNP and CRC were removed (Fig. 1). Six studies were used to analyze the association of mir-196a2 polymorphism with CRC, seven studies were about mir-146a SNP and three were about mir-149 SNP. Genotype distributions of control groups in eleven studies were all in accordance with HWE.

Meta-Analysis Results

All studies were pooled into this meta-analysis, and results of the three miRNAs SNPs and CRC were shown in Table 2.

In this analysis of six studies, mir-196a2 polymorphism was significantly associated with CRC in Asian group (Fig. 2 additive model: OR=1.197, 95 %CI 1.084~1.32, P<0.001; dominant model: OR=1.247, 95 %CI 1.065~1.46, P=0.006; recessive model: OR=1.298, 95 %CI 1.101~1.531, P=0.002). While, no correlation was observed in Caucasian group (p>0.05).

There was no significant association between mir-146a polymorphism and CRC susceptibility in three genetic models (p>0.05, Fig. 3). However, because the data in Chae's study had publication bias in the Begg's test, we deleted the data to analyze again. And a significant risk association was observed in Asian group between mir-146a polymorphism and CRC in additive model (G vs C) (p<0.01).

When three studies concerning mir-149 SNP were performed in this analysis, no significant CRC risk was found in all genetic models (p>0.05, Fig. 4). And we also could not find any associations in the subgroup analysis of population.

Publication Bias

Begg's funnel plot and Egger's regression test were explored to evaluate the publication bias of 11 studies. They did not show evidence of publication bias based

Table 1 Characteristics of studies included in this meta-analysis

Author	Population	Year	Cancer type	Case	Control	P^*
mir-196a2 (rs11614913):						
Vinci S	Caucasian	2013	CRC	160	178	0.788
Hezova R	Caucasian	2012	CRC	197	212	0.633
Chen H	Asian	2012	CRC	126	407	0.849
Min KT	Asian	2012	CRC	446	502	0.79
zhu LJ	Asian	2012	CRC	573	588	0.291
Zhan JF	Asian	2011	CRC	252	543	0.087
mir-146a(rs2910164):						
Ma	Asian	2013	CRC	1147	1203	0.075
Lv	Asian	2013	CRC	331	513	0.08
Chen**	Asian	2013	CRC	547	561	0.768
Chae YS	Asian	2013	CRC	399	568	0.98
Vinci S	Caucasian	2013	CRC	160	178	0.59
Hezova R	Caucasian	2012	CRC	197	212	0.415
Min KT	Asian	2012	CRC	446	502	0.443
mir-149(rs2292832):						
Vinci S	Caucasian	2013	CRC	160	178	0.912
Min KT	Asian	2012	CRC	446	502	0.948
Zhang MW	Asian	2012	CRC	435	443	0.584

*P value for Hardy-Weinberg equilibrium in control group. **not published

on Begg's and Egger's tests except for mir-146a polymorphism in recessive model.

Discussion

CRC is one of the most common cancers worldwide, it occurs through a multiple carcinogenic processes [28]. MiRNAs are important factors in human cancers. Previous evidences suggested that miRNAs could act as tumor suppressors and oncogenes. And a mutation or SNP in miRNA gene could influence the miRNA precursors progressing or miRNA interactions [7]. Many SNPs located in miRNA genes have been identified; however, the mechanisms of miRNAs inducing cancers were still complex and unclear. In the present study, we selected three miRNAs of mir-196a2, mir-146a, mir-149 which were commonly explored in previous researches, to evaluate the associations between the functional polymorphisms in sequences of these three miRNAs and CRC susceptibility respectively.

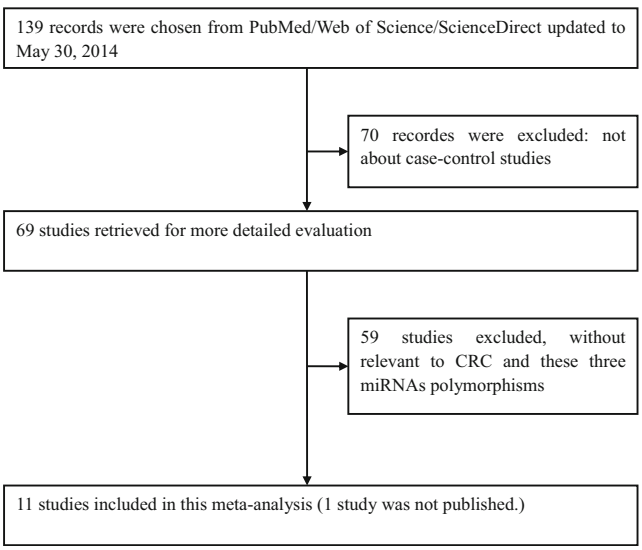

Fig. 1 Flow diagram of selection of studies with criteria for inclusion and exclusion

Studies indicated that mir-196a2 targeted several genes to influence cancer pathogenesis. It was shown that the loss of mir-196a2 in melanoma cells caused a decreased expression of several genes which may take part in melanoma progression to elevate HOX-C8 levels. The expression of HOX transcription factors which normally were not expressed in differentiated melanocytes may influence tumorigenic pathways to drive mir-196a2 negative melanoma cells to an aggressive phenotype [29]. In addition, the inhibition of HOXA5 expression significantly resulted in cell proliferation, migration and invasion, indicating that decreased HOXA5 level may be a mechanism by which mir-196a2 exerted its oncogenic functions [30]. Recently, mir-196a2 polymorphism also has been reported to be associated with various cancers. Yuan et al. did the meta-analysis and demonstrated that mir-196a2 polymorphism

Table 2 Meta-analysis results for the three polymorphisms and CRC risk

Genetic model	No. of studies	Population	Pooled OR [95 % CI] p	Heterogeneity *p*-value	Begg's test *p*-value	Egger's test *p*-value
mir-196a2(rs11614913):						
Additive(C vs. T)	6	Asian	1.197[1.084~1.320]0	0.281	0.497	0.321
		Caucasian	0.887[0.715~1.099]0.272	0.462	0.317	———
		overall	1.136[1.039~1.242]0.005	0.061	0.335	0.191
Dominant(C-carriers vs. TT)	6	Asian	1.247[1.065~1.460]0.006	0.198	0.497	0.583
		Caucasian	0.778[0.476~1.273]0.318	0.903	0.317	———
		overall	1.193[1.027~1.386]0.021	0.165	0.748	0.516
Recessive(CC vs. T-carriers)	6	Asian	1.298[1.101~1.531]0.002	0.377	0.497	0.323
		Caucasian	0.876[0.655~1.171]0.371	0.246	0.317	———
		overall	1.179[1.021~1.360]0.025	0.082	0.335	0.193
mir-146a(rs2910164):						
Additive(G vs. C)	7	Asian	1.027[0.861~1.225]0.765	0	1	0.542
		Caucasian	0.906[0.717~1.146]0.412	0.703	0.317	———
		overall	1.002[0.865~1.161]0.980	0.001	0.812	0.493
Dominant(G-carriers vs.CC)	7	Asian	1.148[0.817~1.614]0.425	0	0.327	0.357
		Caucasian	0.671[0.378~1.194]0.175	0.959	0.317	———
		overall	1.052[0.775~1.429]0.744	0	0.234	0.278
Recessive(GG vs. C-carriers)	7	Asian	0.922[0.705~1.205]0.551	0.004	0.624	0.057
		Caucasian	0.954[0.714~1.275]0.749	0.753	0.317	———
		overall	0.935[0.765~1.143]0.512	0.014	0.812	0.003
mir-149(rs2292832):						
Additive(T vs. C)	3	Asian	1.009[0.878~1.159]0.899	0.432	0.317	———
		Caucasian	1.091[0.788~1.510]0.599	———	———	———
		overall	1.021[0.899~1.160]0.746	0.669	0.602	0.704
Dominant(T-carriers vs. CC)	3	Asian	1.003[0.745~1.350]0.983	0.65	0.317	———
		Caucasian	0.958[0.625~1.469]0.846	———	———	———
		overall	0.988[0.774~1.261]0.925	0.889	0.602	0.765
Recessive(TT vs. C-carriers)	3	Asian	1.015[0.844~1.220]0.876	0.187	0.317	———
		Caucasian	1.590[0.816~3.098]0.173	———	———	———
		overall	1.048[0.878~1.251]0.605	0.186	0.602	0.544

was associated with the increased risk of lung cancer [31]. Chen et al. reported that mir-196a2 T allele might be protective factor for breast cancer [19]. Besides, the analysis has been done between mir-196a2 polymorphism and the susceptibility of congenital heart disease [32], non-small cell lung cancer [33], esophageal cancer [34], gastric cancer [35], or hepatocellular carcinoma [36] through changing mature mir-196a2 expression and target mRNA binding activity. There were associations between some of them, and others were not. Based on previous studies, we predict that mir-196a2 polymorphism will be likely to be associated with progression of CRC. This present study has done the meta-analysis between them, and the result showed that mir-196a2 C genotype was significantly associated with CRC, similarly to the most of previous studies, especially in Asian group.

Mir-146a polymorphism is located in the stem region, and its G/C polymorphism leads to a change in the stem structure of mir-146a precursor [37]. Researchers suggested that mir-146a was part of a negative feedback loop through targeting IRAK1 and TRAF6, and acted as an inhibitor of the activated NF-kappa B pathway, indicating that mir-146a could be involved in regulation of various independent physiological processes [38]. Other studies also evaluated that mir-146a C allele displayed a higher stability and binding affinity for 3′-untranslated regions of BRCA1 than G allele, which led to higher efficiency in targeting BRCA1 mRNA for degradation. And it may explain the C variant ability to promote early cancer onset [39]. Various studies were performed to explore the association between mir-146a SNP and kinds of cancers, and the results were not consistent. In Wang's research, they analyzed the studies relevant to breast cancer and failed to find

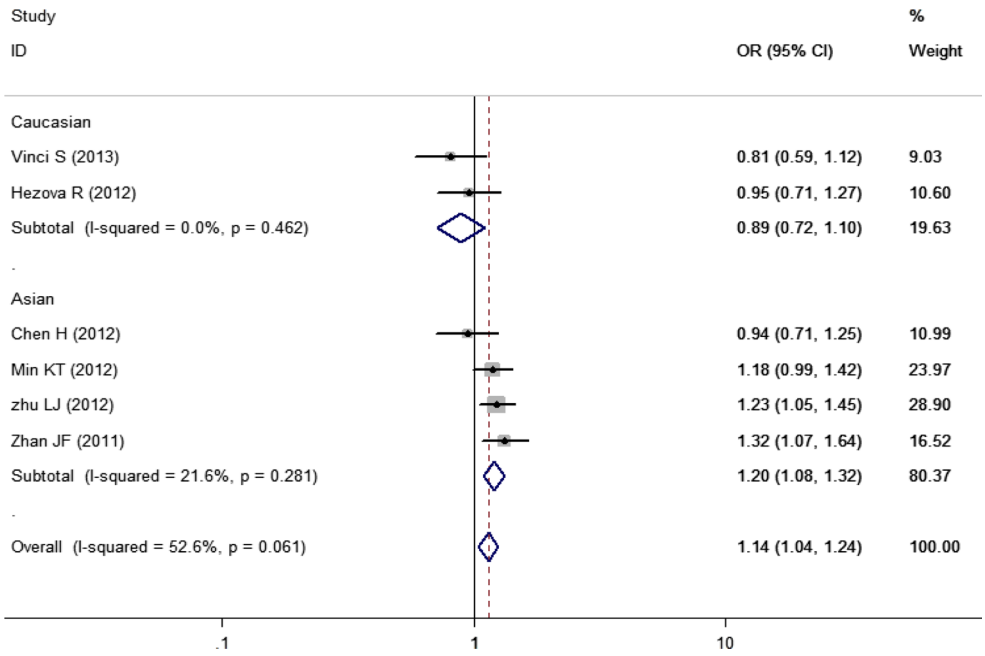

Fig. 2 Forest plot of ORs of CRC and mir-196a2 polymorphism under a fixed-effect model (additive: C vs T). The squares and horizontal lines correspond to the study-specific OR and 95 %CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95 %CI

an association between mir-146a polymorphism and breast cancer susceptibility [40]. Meanwhile, Xu summarized eligible studies of lung cancer and also could not discover any association between SNP in mir-146a and lung cancer risk. However, Zhou confirmed that mir-146a G>C variants were associated with an increased risk of hepatocelluar carcinoma in his study [41]. In this article, we selected seven studies to evaluate the relationship between mir-146a polymorphism and CRC, thus no association was observed. While, when we removed Chae's study which had publication bias in Begg's test, an increased risk of CRC in Asian group was associated with mir-146a SNP in additive model (G vs C) ($p<0.01$), indicating that G allele may lead to an increasing CRC risk in Asian.

Polymorphism in mir-149 involving a T/C nucleotide substitution, influenced cancer risk by altering the expression of mature mir-149 or its binding activity to target mRNA. Previous studies found significantly lower expression of mir-

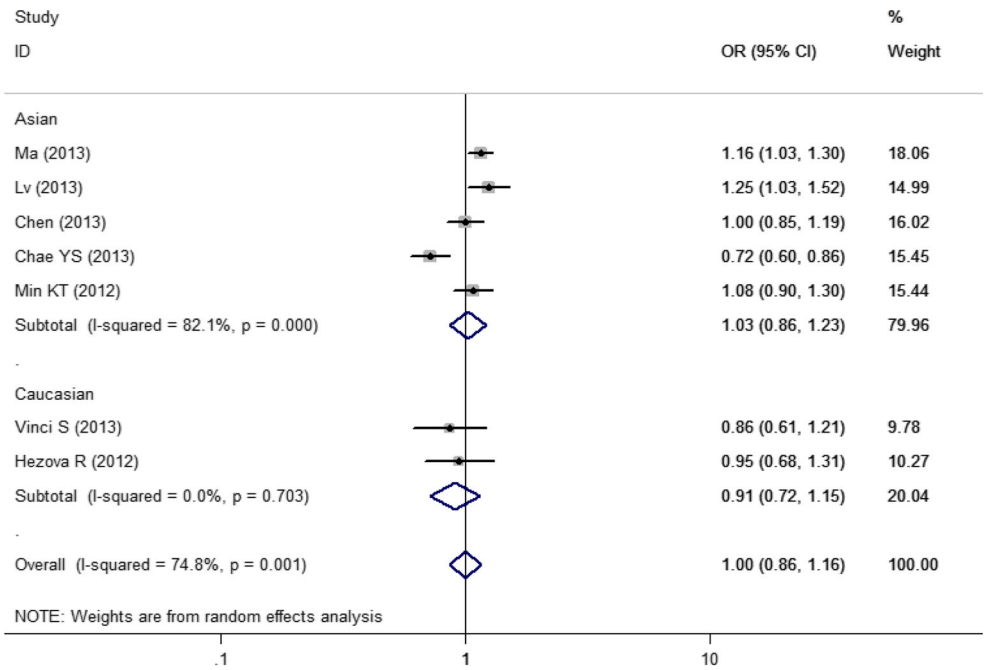

Fig. 3 Forest plot of ORs of CRC and mir-146a polymorphism under a random-effect model (additive: G vs C). The squares and horizontal lines correspond to the study-specific OR and 95 %CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95 %CI

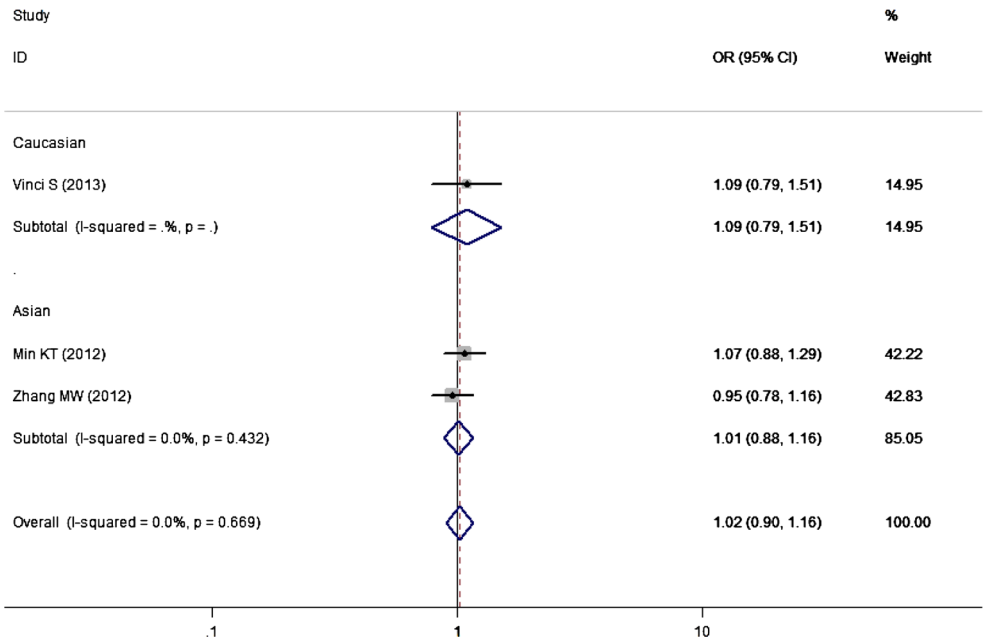

Fig. 4 Forest plot of ORs of CRC and mir-149 polymorphism under a fixed-effect model (additive: T vs C). The squares and horizontal lines correspond to the study-specific OR and 95 %CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95 % CI

149 in tumors of high-risk group than tumors of low-risk groups, which indicated that mir-149 induced apoptosis. Akt1 and E2F1, as the direct targets of mir-149, were also involved in apoptosis. And mir-149 was a pro-apoptotic miRNA by repressing the expression of Akt1 and E2F1 [42]. In addition, on average mir-149 was down-regulated in carcinoma tissue with an inverse correlation to SRPX2 expression, and the association was highly significant in the CRC patients. It was possible that SRPX2 in CRC had functions in tumor processes, such activity of SRPX2 was consistent with carcinoma transition. Study further suggested that mir-149 contributed to the regulation of the SRPX2 transcript level and SRPX2/APOLD1 expression was frequently up-regulated in CRC [43]. Multiple case–control studies have been investigated the association of SNP in mir-149 with various cancers. Zhang thought mir-149 polymorphism may not contribute to lung/breast/colorectal cancers susceptibility [44]. And the rs2292832 polymorphism also showed no association in both overall pooled analysis and subgroup of cancer types in other researcher's study [45]. Our study chose 3 eligible literatures and no significantly risks were found in three models in the subgroup analysis by population ($p>0.05$).

In conclusion, our data demonstrate that mir-196a2 polymorphism is associated with CRC. In Asian group, the association is extremely significant, and people with C allele are more susceptible to CRC than the ones with T allele. The SNP in mir-196a2 may play an important role in carcinogenesis. However, no association has been observed in polymorphisms of mir-146a, mir-149 and CRC. And we need more published data to conform these associations in the future.

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References

1. Ambros V (2004) The functions of animal microRNAs. Nature 431: 350–355
2. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116:281–297
3. Bartels CL, Tsongalis GJ (2009) MicroRNAs: novel biomarkers for human cancer. Clin Chem 55:623–631
4. Rosenfeld N, Aharonov R, Meiri E et al (2008) MicroRNAs accurately identify cancer tissue origin. Nat Biotechnol 26:462–469
5. Bentwich I (2005) Prediction and validation of microRNAs and their targets. FEBS Lett 579:5904–5910
6. Brennecke J, Stark A, Russell RB et al (2005) Principles of microRNA-target recognition. PLoS Biol 3:e85
7. Yang W, Chendrimada TP, Wang Q et al (2006) Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. Nat Struct Mol Biol 13:13–21
8. Wu M, Jolicoeur N, Li Z et al (2008) Genetic variations of microRNAs in human cancer and their effects on the expression of miRNAs. Carcinogenesis 29:1710–1716
9. Jemal A, Siegel R, Ward E et al (2009) Cancer statistics, 2009. CA Cancer J Clin 59:225–249
10. Yang L, Parkin DM, Li L et al (2003) Time trends in cancer mortality in China: 1987–1999. Int J Cancer 106:771–783
11. Center MM, Jemal A, Ward E (2009) International trends in colorectal cancer incidence rates. Cancer Epidemiol Biomarkers Prev 18: 1688–1694
12. Zhan JF, Chen LH, Chen ZX et al (2011) A functional variant in microRNA-196a2 is associated with susceptibility of colorectal cancer in a Chinese population. Arch Med Res 42:144–148

13. Tian T, Shu Y, Chen J et al (2009) A functional genetic variant in microRNA-196a2 is associated with increased susceptibility of lung cancer in Chinese. Cancer Epidemiol Biomarkers Prev 18:1183–1187
14. Kim MJ, Yoo SS, Choi YY et al (2010) A functional polymorphism in the pre-microRNA-196a2 and the risk of lung cancer in a Korean population. Lung Cancer 69:127–129
15. Hu Z, Liang J, Wang Z et al (2009) Common genetic variants in pre-microRNAs were associated with increased risk of breast cancer in Chinese women. Hum Mutat 30:79–84
16. Hoffman AE, Zheng T, Yi C et al (2009) microRNA miR-196a-2 and breast cancer: a genetic and epigenetic association study and functional analysis. Cancer Res 69:5970–5977
17. Qi P, Dou TH, Geng L et al (2010) Association of a variant in MIR 196A2 with susceptibility to hepatocellular carcinoma in male Chinese patients with chronic hepatitis B virus infection. Hum Immunol 71:621–626
18. Egger M, Davey SG, Schneider M et al (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
19. Chen H, Sun LY, Chen LL et al (2012) A variant in microRNA-196a2 is not associated with susceptibility to and progression of colorectal cancer in Chinese. Intern Med J 42:e115–e119
20. Min KT, Kim JW, Jeon YJ et al (2012) Association of the miR-146aC>G, 149C>T, 196a2C>T, and 499A>G polymorphisms with colorectal cancer in the Korean population. Mol Carcinog 51(Suppl 1):E65–E73
21. Zhu L, Chu H, Gu D et al (2012) A functional polymorphism in miRNA-196a2 is associated with colorectal cancer risk in a Chinese population. DNA Cell Biol 31:350–354
22. Hezova R, Kovarikova A, Bienertova-Vasku J et al (2012) Evaluation of SNPs in miR-196-a2, miR-27a and miR-146a as risk factors of colorectal cancer. World J Gastroenterol 18:2827–2831
23. Vinci S, Gelmini S, Mancini I et al (2013) Genetic and epigenetic factors in regulation of microRNA in colorectal cancers. Methods 59:138–146
24. Zhang MW, Jin MJ, Yu YX et al (2012) Associations of lifestyle-related factors, hsa-miR-149 and hsa-miR-605 gene polymorphisms with gastrointestinal cancer risk. Mol Carcinog 51(Suppl 1):E21–E31
25. Lv M, Dong W, Li L et al (2013) Association between genetic variants in pre-miRNA and colorectal cancer risk in a Chinese population. J Cancer Res Clin Oncol 139:1405–1410
26. Chae YS, Kim JG, Lee SJ et al (2013) A miR-146a polymorphism (rs2910164) predicts risk of and survival from colorectal cancer. Anticancer Res 33:3233–3239
27. Ma L, Zhu L, Gu D et al (2013) A genetic variant in miR-146a modifies colorectal cancer susceptibility in a Chinese population. Arch Toxicol 87:825–833
28. Vogelstein B, Kinzler KW (2004) Cancer genes and the pathways they control. Nat Med 10:789–799
29. Mueller DW, Bosserhoff AK (2011) MicroRNA miR-196a controls melanoma-associated genes by regulating HOX-C8 expression. Int J Cancer 129:1064–1074
30. Liu XH, Lu KH, Wang KM et al (2012) MicroRNA-196a promotes non-small cell lung cancer cell proliferation and invasion through targeting HOXA5. BMC Cancer 12:348
31. Yuan Z, Zeng X, Yang D et al (2013) Effects of common polymorphism rs11614913 in Hsa-miR-196a2 on lung cancer risk. PLoS One 8:e61047
32. Xu J, Hu Z, Xu Z et al (2009) Functional variant in microRNA-196a2 contributes to the susceptibility of congenital heart disease in a Chinese population. Hum Mutat 30:1231–1236
33. Hu Z, Chen J, Tian T et al (2008) Genetic variants of miRNA sequences and non-small cell lung cancer survival. J Clin Invest 118:2600–2608
34. Wei J, Zheng L, Liu S et al (2013) MiR-196a2 rs11614913 T>C polymorphism and risk of esophageal cancer in a Chinese population. Hum Immunol 74:1199–1205
35. Wang S, Tao G, Wu D et al (2013) A functional polymorphism in MIR196A2 is associated with risk and prognosis of gastric cancer. Mol Carcinog 52(Suppl 1):E87–E95
36. Zhang H, Su YL, Yu H et al (2012) Meta-analysis of the association between Mir-196a-2 polymorphism and cancer susceptibility. Cancer Biol Med 9:63–72
37. Li YJ, Zhang ZY, Mao YY et al (2014) A genetic variant in MiR-146a modifies digestive system cancer risk: a meta-analysis. Asian Pac J Cancer Prev 15:145–150
38. Taganov KD, Boldin MP, Chang KJ et al (2006) NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A 103:12481–12486
39. Pastrello C, Polesel J, Della PL et al (2010) Association between hsa-mir-146a genotype and tumor age-of-onset in BRCA1/BRCA2-negative familial breast and ovarian cancer patients. Carcinogenesis 31:2124–2126
40. Wang PY, Gao ZH, Jiang ZH et al (2013) The associations of single nucleotide polymorphisms in miR-146a, miR-196a and miR-499 with breast cancer susceptibility. PLoS One 8:e70656
41. Zhou B, Dong LP, Jing XY et al (2014) Association between miR-146aG>C and miR-196a2C>T polymorphisms and the risk of hepatocellular carcinoma in a Chinese population. Biol, Tumour
42. Lin RJ, Lin YC, Yu AL (2010) miR-149* induces apoptosis by inhibiting Akt1 and E2F1 in human cancer cells. Mol Carcinog 49:719–727
43. Oster B, Linnet L, Christensen LL et al (2013) Non-CpG island promoter hypomethylation and miR-149 regulate the expression of SRPX2 in colorectal cancer. Int J Cancer 132:2303–2315
44. Zhang J, Liu YF, Gan Y (2012) Lack of association between miR-149 C>T polymorphism and cancer susceptibility: a meta-analysis based on 4,677 cases and 4,830 controls. Mol Biol Rep 39:8749–8753
45. Zhang YG, Shi JX, Song CH et al (2013) Association of mir-499 and mir-149 polymorphisms with cancer risk in the Chinese population: evidence from published studies. Asian Pac J Cancer Prev 14:2337–2342