Int J Clin Exp Pathol 2016;9(2):2192-2199
www.ijcep.com /ISSN:1936-2625/IJCEP0018456

Original Article

Association between miR-146a, miR-149, miR-196a2 and miR-499 gene polymorphisms and the susceptibility to gastric cancer in a Chinese population

Rila Su[1,2], Wenxin Li[2,3], Rongcheng Luo[1]

[1]Cancer Center, Traditional Chinese Medicine-Integrated Hospital, Southern Medical University, Guangzhou 510315, China; [2]Department of Oncology, Inner Mongolia People's Hospital, Hohhot 010010, China; [3]Wuhan University, Wuhan 430072, China

Received October 25, 2015; Accepted December 23 2015; Epub February 1, 2016; Published February 15, 2016

Abstract: We performed a case-control study to investigate the role of miR-146a, miR-149, miR-196a2 and miR-499 gene polymorphisms in the development of gastric cancer. A total of 245 hospitalized gastric cancer patients and 315 control subjects were collected between January 2012 and October 2014. The genotyping of miR-146a, miR-149, miR-196a2 and miR-499 were performed using polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism (RFLP). We observed significant differences in the genotype frequencies of miR-146a between patients with gastric cancer and controls using the χ^2 test (χ^2=12.04, *P*=0.002). Multivariate logistic regression analyses revealed that individuals with the CC genotype and GC+CC genotype of miR-146a were associated with an increased risk of gastric cancer compared to the GG genotype, and the adjusted ORs (95% CI) were 2.50 (1.42-4.41) and 1.62 (1.12-2.33). However, no significant associations were found between the miR-149, miR-196a2 and miR-499 polymorphisms and the development of gastric cancer. In conclusion, our study found that miR-146a polymorphism was associated with gastric cancer development, but no significant association was found between miR-149, miR-196a2 and miR-499 polymorphisms and gastric cancer risk. Further studies are greatly needed to confirm the results of our findings.

Keywords: miR-146a, miR-149, miR-196a2, miR-499, polymorphism, gastric cancer

Introduction

Gastric cancer (GC) is one of the most common cancers in mortality and morbidity worldwide [1, 2]. The International Agency for Research on Cancer estimated that there were 952,000 new gastric cancer cases in 2012, making it the firth most common malignancy in the world, after cancers of the lung, breast, colorectal and prostate cancers [2]. 70% of new gastric cancer cases occur in the less developed regions, and half of the world total occurs in China [2]. Infection with Helicobacter pylori infections is a proved risk factor for gastric cancer [3, 4], and some environmental factors have been indicated to have a critical role in the development of gastric cancer, such as consumption of preserved food containing carcinogenic nitrates, lifestyle, tobacco and alcohol as well as obesity [5-7]. However, patients who are exposure to similar risk factors of gastric cancer always show high individualized susceptibility to gastric cancer, which suggest that genetic factors may be involved in the development of gastric cancer, such as XPD, LMP2, LMP7, insulin like growth facror-1, complement receptor 1, GSTM1, IL-17 and XRCC3 [8-14].

MiRNAs are well known classes of small noncoding RNAs, and they are responsible for promoting messenger RNA (mRNA) degradation, inhibiting mRNA translation, and affecting transcription through binding to the 3'-untranslated regions (3'-UTR) of their target mRNA [15, 16]. Experimental studies indicated that miRNAs are involved in a variety of biological processes, such as cell proliferation, differentiation and apoptosis through regulating approximately

Table 1. Primers, length of digested fragments and restriction enzymes of miR-146a, miR-149, miR-196a2 and miR-499 genes

Genotype	SNP	Primers (5'-3')	Restriction enzymes	Length of digested fragments
miR-146a	rs2910164	CATGGGTTGTGTCAGTGTCAGAGCT (Forward) TGCCTTCTGTCTCCAGTCTTCCAA (Reverse)	*Sac*I	C allele: 122 bp and 25 bp; G allele: 147 bp.
miR-149	rs2292832	TGTCTTCACTCCCGTGCTTGTCC (Forward) TGAGGCCCGAAACACCCGTA (Reverse)	*Pvu*II	C allele: 254 bp; T allele: 194 bp and 60 bp.
miR-196a2	rs11614913	CCCCTTCCCTTCTCCTCCAGATA (Forward) CGAAAACCGACTGATGTAACTCCG (Reverse)	*Msp*	T allele: 149 bp; C allele: 125 bp and 24 bp.
miR-499	rs3746444	CAAAGTCTTCACTTCCCTGCCA (Forward) GATGTTTAACTCCTCTCCACGTGATC (Reverse)	*Bc*lI	T allele: 26 bp and 120 bp. C allele: 146 bp.

60% of the human protein coding genes [17, 18].

Single-nucleotide polymorphisms (SNPs) are the most common sequence variation in human genome. SNPs in miRNA genes may influence the expression of the respective miRNAs. Four common variants rs2910164, rs2292832, rs11614913 and rs3746444 in miR-146a, miR-149, miR-196a2 and miR-499 are identified and implicated in the development of multiple-type cancers, such as colorectal cancer, lung cancer, breast cancer and renal cell cancer as well as head and neck [19-24]. Previous studies assessed the association between miR-146a, miR-149, miR-196a2 and miR-499 polymorphisms and development of gastric cancer, but the results are inconclusive [25-27]. In our study, we conducted a case-control study to investigate the role of miR-146a, miR-149, miR-196a2 and miR-499 gene polymorphisms in the development of gastric cancer.

Materials and methods

Subjects

A hospital-based case-control design was performed in this study. Initially, a total of 264 hospitalized gastric cancer patients were collected from our hospital between April 2012 and December 2014. All the gastric cancer patients were newly diagnosed and confirmed by two pathologists. Patients who had received chemotherapy or radiotherapy before participating in this study, or patients who had suffered from other malignant cancer and recurrent cancer as well as serious kidney or liver diseases were excluded. Finally, 245 patients with gastric cancer were included into our study, and the participation rate was 92.80%.

A total of 349 individuals were randomly selected from subjects who received regular health examination in our hospital between April 2012 and December 2014. Control subjects who had a history of cancer and any digestive diseases were excluded from this study. Ultimately, 315 subjects met the inclusion criteria and were included for analysis (participation rate was 90.26%).

H.pylori infection status was determined through a rapid urea breath test. The demographic and lifestyle characteristics were collected from a structured questionnaire, such as sex, age, tobacco smoking, alcohol drinking, family history of cancer, body mass index, *H.pylori* infection, TNM stage and Lauren classification. All the individuals were voluntarily participated into our study and signed an informed consent before enrolling into this study. The protocol of our study was according to the Ethical committee of our hospital, and our study was according to the standards of the Declaration of Helsinki.

DNA extraction and genotyping

A five ml peripheral blood was obtained from each gastric cancer patient and control subject, and stored in EDTA tubes. The DNA was extraction from the peripheral blood using the TIANamp Blood DNA Kit according to the manufacturer's instructions (Tiangen, Beijing, China). The genotyping of miR-146a, miR-149, miR-196a2 and miR-499 were performed using polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism (RFLP). The primers, restriction enzymes and length of digested fragments of miR-146a, miR-149, miR-196a2 and miR-499 were shown in **Table 1**. Cycling condition for PCR was started

Table 2. Demographic and lifestyle characteristics of gastric cancer patients and control subjects

Variables	Patients N=245	%	Controls N=315	%	χ^2 test or t test	OR (95% CI)	*P* value
Age, years	61.36±11.52		57.16±12.65		4.04	1.34 (1.07-1.62)	0.005
Gender							
Females	70	28.57	133	42.22		1.0 (Ref.)	-
Males	175	71.43	182	57.78	11.11	1.83 (1.26-2.65)	0.001
Smoking status							
No	138	56.33	201	63.81		1.0 (Ref.)	-
Yes	107	43.67	114	36.19	3.23	1.37 (0.96-1.95)	0.77
Drinking status							
No	156	63.67	215	68.25		1.0 (Ref.)	-
Yes	89	36.33	100	31.75	1.29	1.23 (0.85-1.77)	0.26
BMI							
<25	192	78.37	263	83.49		1.0 (Ref.)	-
≥25	53	21.63	52	16.51	2.38	1.40 (0.89-2.18)	0.12
Family history of cancer							
No	223	91.02	298	94.60		1.0 (Ref.)	-
Yes	22	8.98	17	5.40	2.73	1.73 (0.85-3.55)	0.10
H.pylori infection							
No	101	41.22	181	57.46		1.0 (Ref.)	-
Yes	144	58.78	134	42.54	14.53	1.93 (1.35-2.74)	<0.001
TNM stage							
I-II	107	43.67					
III-IV	138	56.33					
Lauren classification							
Intestinal	108	44.08					
Diffuse	137	55.92					

with a denaturation at 95°C for 5 min, 30 cycles of denaturation at 91°C for 1 min, annealing at 62°C for 1 min, extension 72°C for 1 min, and a final extension at 72°C for 5 min. The PCR products were confirmed with electrophoresis on ethidium bromide stained agarose gel, and visualized under ultraviolet fluorescence.

Statistical analysis

SPSS 16.0 version (SPSS Inc. Chicago, IL, USA) was taken to perform all statistical analysis. The demographic and lifestyle characteristics and genotype distributions between gastric cancer patients and control subjects were compared using chi-square (χ^2) test or student T test. A univariate logistic regression analysis was taken to analyze the association between demographic and lifestyle characteristics and gastric cancer risk. A χ^2 test with one degree of freedom was conducted to analyze whether the genotype distributions of miR-146a, miR-149, miR-196a2 and miR-499 confirmed with the Hardy-Weinberg equilibrium (HWE). Conditional multiple logistic regression analysis was taken to analyze the association between miR-146a, miR-149, miR-196a2 and miR-499 gene polymorphisms and susceptibility to gastric cancer, and the results were expressed by odds ratio (OR) and 95% confidence intervals (CIs). A two-tailed *P* value <0.05 was considered as statistically significant.

Results

The distributions of demographic and clinical characteristics of patients with gastric cancer and controls are summarized in **Table 2**. The mean ages of patients with gastric cancer and control subjects were 61.36±11.52 and 57.16±12.65 years, respectively. There were 70 females and 175 males in gastric cancer patients, and 133 females and 182 males in controls. We observed no significant differenc-

Table 3. Genotype distributions of miR-146a, miR-149, miR-196a2 and miR-499 polymorphism between patients with gastric cancer and control subjects

SNP	Patients N=245	%	Controls N=315	%	Chi-square test	*P* value	*P* value for HWE	
							In patients	In controls
miR-146a								
GG	77	31.43	134	42.54				
GC	122	49.80	149	47.30				
CC	46	18.78	32	10.16	12.04	0.002	0.85	0.31
miR-149								
CC	108	44.08	149	47.30				
TC	112	45.71	140	44.44				
TT	25	10.20	26	8.25	0.94	0.63	0.61	0.39
miR-196a2								
CC	83	33.88	119	37.78				
TC	128	52.24	158	50.16				
TT	34	13.88	38	12.06	1.05	0.59	0.17	0.19
MiR-499								
TT	99	40.41	143	45.40				
TC	119	48.57	149	47.30				
CC	26	10.61	23	7.30	2.57	0.28	0.27	0.06

Table 4. Association between miR-146a, miR-149, miR-196a2 and miR-499 polymorphisms and risk of gastric cancer

SNP	Patients N=245	%	Controls N=315	%	OR (95% CI)[1]	*P* value
miR-146a						
GG	77	31.43	134	42.54	1.0 (Reference)	-
GC	122	49.8	149	47.3	1.42 (0.97-2.10)	0.06
CC	46	18.78	32	10.16	2.50 (1.42-4.41)	0.001
GC+CC	168	68.58	181	57.46	1.62 (1.12-2.33)	0.007
miR-149						
CC	108	44.08	149	47.3	1.0 (Reference)	-
TC	112	45.71	140	44.44	1.10 (0.77-1.59)	0.58
TT	25	10.2	26	8.25	1.33 (0.69-2.53)	0.36
TC+TT	137	55.91	166	52.69	1.14 (0.80-1.62)	0.45
miR-196a2						
CC	83	33.88	119	37.78	1.0 (Reference)	-
TC	128	52.24	158	50.16	1.16 (0.79-1.70)	0.42
TT	34	13.88	38	12.06	1.28 (0.72-2.28)	0.37
TC+TT	162	66.12	196	62.22	1.19 (0.82-1.71)	0.34
MiR-499						
TT	99	40.41	143	45.4	1.0 (Reference)	-
TC	119	48.57	149	47.3	1.15 (0.80-1.67)	0.43
CC	26	10.61	23	7.3	1.63 (0.84-3.18)	0.12
TC+CC	145	59.18	172	54.6	1.22 (0.86-1.73)	0.25

[1]Adjsuted for sex, age and *H.pylori* infection.

es between patients with gastric cancer and control subjects in terms of smoking, drinking, BMI and family history of cancer. However, patients with gastric cancer were more likely to have older age (OR=1.34, 95% CI=1.07-1.62, *P*=0.005), be males (OR=1.83, 95% CI=1.26-2.65, *P*=0.001) and suffer from *H.pylori* infection (OR=1.93, 95% CI=1.35-2.74, *P*<0.001). Among the 245 patients with gastric cancer, 107 (43.67%) were at I-II TNM stage, 138 (56.33%) were at III-IV stage, 108 (44.08%) and 137 (55.92%) showed intestinal and diffuse type.

We observed significant differences in the genotype frequencies of miR-146a between patients with gastric cancer and controls using the χ^2 test (χ^2=12.04, *P*=0.002); however, there were no significant differences in the genetic distributions of miR-149 (χ^2=0.94, *P*=0.63), miR-196a2 (χ^2=1.05, *P*=0.59) and miR-499 (χ^2=2.57, *P*=0.28) (**Table 3**). The genotypic distributions of miR-146a, miR-149, miR-196a2 and miR-499 in the

Table 5. Interaction between miR-146a polymorphism and demographic characteristics in the risk of gastric cancer

Variables	Patients		Controls		OR (95% CI)[1]	*P* value
	GG	GC+CC	GG	GC+CC		
Tobacco smoking						
No	45	93	86	115	1.55 (0.96-2.50)	0.06
Yes	32	75	48	66	1.70 (0.94-3.09)	0.06
Alcohol drinking						
No	50	106	90	125	1.53 (0.97-2.41)	0.06
Yes	27	62	44	56	1.80 (0.95-3.44)	0.05
BMI						
<25	63	129	111	152	1.45 (0.95-2.01)	0.06
≥25	14	39	23	29	2.21 (0.87-5.37)	0.07
Family history of cancer						
No	72	151	120	178	1.41 (0.97-2.07)	0.06
Yes	5	17	14	3	15.87 (2.65-111.95)	0.0002
H.pylori infection						
No	32	69	76	105	1.56 (0.91-2.70)	0.09
Yes	45	99	58	76	1.62 (0.96-2.75)	0.07

[1]Adjusted for sex and age.

gastric cancer patients and controls conformed to the HWE.

Multivariate logistic regression analyses revealed that individuals with the CC genotype of miR-146a were associated with an increased risk of gastric cancer compared to the GG genotype, and the adjusted OR (95% CI) was 2.50 (1.42-4.41) (**Table 4**). Moreover, individuals carrying both the GC+CC genotype of miR-146a were correlated with an elevated risk of gastric cancer compared to the GG genotype (OR=1.62, 95% CI=1.12-2.33; *P*=0.007). However, no significant associations were found between the miR-149, miR-196a2 and miR-499 polymorphisms and the development of gastric cancer.

We further analyzed the association between the miR-146a polymorphism and the risk of gastric cancer based on the tobacco smoking, alcohol drinking, BMI, family history of cancer and *H.pylori* infection (**Table 5**). Logistic regression analyses revealed that the miR-146a polymorphism was correlated with the family history of cancer in increasing the risk of gastric cancer (OR=15.87, 95% CI=2.65-111.95, *P*=0.0002). However, no correlation was found between miR-146a polymorphism and tobacco smoking, alcohol drinking, BMI and *H.pylori* infection in the risk of gastric cancer.

Discussion

MicroRNAs (miRs) are noncoding RNAs that are transcribed from endogenous DNA molecules. Most miRs span about 22 nucleotides and functions negative regulation on its target mRNAs in the post-transcriptional processes [28]. Cellular processes that in volve miRs include development, differentiation, proliferation, apoptosis, and stress response [29]. MiRs break the structure of target mRNAs or inhibit translation to down-regulate the expression of target mRNAs, and act as tumor suppressor genes or oncogenes in tumorigenesis [18, 30]. In this hospital based case-control study, we assessed the role of miR-146a, miR-149, miR-196a2 and miR-499 polymorphisms in the development of gastric cancer. We found that the CC genotype and GC+CC genotype of miR-146a were associated with an increased risk of gastric cancer compared to the GG genotype.

It is well known that polymorphism in miRNAs region plays a critical role in the expression and transcriptional regulation of miRNAs. The rs2910164 is located in the precursor of miR-146a, and the variation could affect the miRNA through affecting processing of the pre-miR-146a to the mature form [31]. Therefore, the genetic variations of pre-miR-146a could influence the expression of mature miR-146a and binding activity of target mRNA, and thus alter the gene function.

Many previous studies have investigated the role of miR-146a polymorphism in the development of several kinds of human cancers, such as lung cancer, squamous cell cancer, breast cancer, hepatocellular cancer and colorectal cancer [32-37]. Sodhi et al. conducted a case-control study with 250 patients with lung cancer and 255 controls, and they reported that miR-146a polymorphism showed a positive

association with the risk of lung cancer [32]. Zhang et al. conducted a meta-analysis with 12 studies, and they reported that miR-146a polymorphism was associated with increased risk of cervical and skin squamous cell carcinoma, and was related to decreased risk for nasopharyngeal and oral squamous cell carcinoma [33]. Qi et al. conducted a case-control study in a Chinese population, and they suggested that miR-146a polymorphism may be a biomarker for predicting breast cancer risk [34]. Peng et al. pooled 12 studies in a meta-analysis and suggested that the miR-146a polymorphism contributes to increased hepatocellular cancer, especially in Asian populations [35]. Dikaiakos et al. suggest that the miR-146a polymorphism may be associated with the risk of colorectal cancer [36].

Currently, several studies have reported the association between miR-146a polymorphism and development of gastric cancer, but the results are inconclusive [26, 38-42]. Two studies reported a positive association between the CC and GC genotypes of miR-146a and susceptibility to gastric cancer [38, 41]. Two studies conducted in Chinese populations found a negative significant association between the CC and GC genotypes of miR-146a and development of gastric cancer [40, 42]. Another two studies did not find significant association between miR-146a polymorphism and risk of gastric cancer [26, 39]. In our study, we find that the CC genotype and GC+CC genotype of miR-146a could influence the development of gastric cancer. The discrepancies of these studies may be caused by differences in population, selection of patients and controls and sample size.

Our study has several limitations. First, the patient and control subjects were selected from only one hospital, which could cause a selection bias. However, the genotype frequencies confirmed with the HWE in patients and controls, which suggest that the study population could represent the general population. Second, the role of polymorphisms other than those in the miR-146a, miR-149, miR-196a2 and miR-499 genes in the development of gastric cancer was not studied. Finally, the limited sample size may lead to a lack of power. Further studies are greatly needed to confirm the results of our findings.

In conclusion, our study found that miR-146a polymorphism was associated with gastric cancer development, but no significant association was found between miR-149, miR-196a2 and miR-499 polymorphisms and gastric cancer risk. Future studies using larger sample sizes and employing similar or different analytical strategies may help elucidate the impact of these polymorphisms on the development of gastric cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Rongcheng Luo, Cancer Center, Traditional Chinese Medicine-Integrated Hospital Southern Medical University, Guangzhou, Guangdong 510315, China. Tel: +86-20-61650051; Fax: +86-21-61650009; E-mail: luorco0101@sina.com; luorc0101@163.com

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] International Agency for Research on Cancer. Stomach Cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. 2012. Accessed in 2015-10-10.

[3] Alberts SR, Cervantes A, van de Velde CJ. Gastric cancer: epidemiology, pathology and treatment. Ann Oncol 2003; 14 Suppl 2: ii31-6.

[4] Konturek PC, Konturek SJ, Brzozowski T. Helicobacter pylori infection in gastric cancerogenesis. J Physiol Pharmacol 2009; 60: 3-21.

[5] McNamara D, El-Omar E. Helicobacter pylori infection and the pathogenesis of gastric cancer: a paradigm for host-bacterial interactions. Dig Liver Dis 2008; 40: 504-9.

[6] Wu MS, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 1878-82.

[7] Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. JAMA 2008; 299: 2423-36.

[8] Ji HX, Chang WS, Tsai CW, Wang JY, Huang NK, Lee AS, Shen MY, Chen WY, Chiang YC, Shih TC, Hsu CM, Bau DT. Contribution of DNA Repair Xeroderma Pigmentosum Group D Genotype to Gastric Cancer Risk in Taiwan. Anticancer Res 2015; 35: 4975-81.

[9] Ma X, Yang C, Tang R, Xu Z, Zhang Z, Wang Y, Zhang J, Yang LI. Association between LMP2 and LMP7 gene polymorphisms and the risk of gastric cancer: A case-control study. Oncol Lett 2015; 10: 509-517.
[10] Farahani RK, Azimzadeh P, Rostami E, Malekpour H, Aghdae HA, Pourhoseingholi MA, Nazemalhosseini Mojarad E, Zali MR. Evaluation of insulin like growth facror-1 genetic polymorphism with gastric cancer susceptibility and clinicopathological features. Asian Pac J Cancer Prev 2015; 16: 4215-8.
[11] Zhao L, Zhang Z, Lin J, Cao L, He B, Han S, Zhang X. Complement receptor 1 genetic variants contribute to the susceptibility to gastric cancer in chinese population. J Cancer 2015; 6: 525-30.
[12] Zhang XL, Cui YH. GSTM1 null genotype and gastric cancer risk in the Chinese population: an updated meta-analysis and review. Onco Targets Ther 2015; 8: 969-75.
[13] Long ZW, Yu HM, Wang YN, Liu D, Chen YZ, Zhao YX, Bai L. Association of IL-17 polymorphisms with gastric cancer risk in Asian populations. World J Gastroenterol 2015; 21: 5707-18.
[14] Cheng S, Wang L, Wang L, Wang Z. Association of XRCC3 gene rs861539 polymorphism with gastric cancer risk: evidence from a case-control study and a meta-analysis. Int J Clin Exp Pathol 2015; 8: 1911-9.
[15] Nana-Sinkam SP, Croce CM. Clinical applications for microRNAs in cancer. Clin Pharmacol Ther 2013; 93: 98-104.
[16] Gromak N. Intronic microRNAs: a crossroad in gene regulation. Biochem Soc Trans 2012; 40: 759-761.
[17] Ambros V. MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. Cell 2003; 113: 673-676.
[18] Esquela-Kerscher A, Slack FJ. Oncomirs-microRNAs with a role in cancer. Nat Rev Cancer 2006; 6: 259-69.
[19] Hu Z, Liang J, Wang Z, Tian T, Zhou X, Chen J, Miao R, Wang Y, Wang X, Shen H. Common genetic variants in pre-microRNAs were associated with increased risk of breast cancer in Chinese women. Hum Mutat 2009; 30: 79-84.
[20] Liu XX, Wang M, Xu D, Yang JH, Kang HF, Wang XJ, Lin S, Yang PT, Liu XH, Dai ZJ. Quantitative Assessment of the Association between Genetic Variants in MicroRNAs and Colorectal Cancer Risk. Biomed Res Int 2015; 2015: 276410.
[21] Du M, Lu D, Wang Q, Chu H, Tong N, Pan X, Qin C, Yin C, Wang M, Zhang Z. Genetic variations in microRNAs and the risk and survival of renal cell cancer. Carcinogenesis 2014; 35: 1629-35.
[22] Fan X, Wu Z. Effects of four single nucleotide polymorphisms in microRNA-coding genes on lung cancer risk. Tumour Biol 2014; 35: 10815-24.
[23] Liu Z, Li G, Wei S, Niu J, El-Naggar AK, Sturgis EM, Wei Q. Genetic variants in selected pre-microRNA genes and the risk of squamous cell carcinoma of the head and neck. Cancer 2010; 116: 4753-60.
[24] Dai ZJ, Shao YP, Wang XJ, Xu D, Kang HF, Ren HT, Min WL, Lin S, Wang M, Song ZJ. Five common functional polymorphisms in microRNAs (rs2910164, rs2292832, rs11614913, rs3746444, rs895819) and the susceptibility to breast cancer: evidence from 8361 cancer cases and 8504 controls. Curr Pharm Des 2015; 21: 1455-63.
[25] Ma XP, Zhang T, Peng B, Yu L, Jiang de K. Association between microRNA polymorphisms and cancer risk based on the findings of 66 case-control studies. PLoS One 2013; 8: e79584.
[26] Dikeakos P, Theodoropoulos G, Rizos S, Tzanakis N, Zografos G, Gazouli M. Association of the miR-146aC>G, miR-149T>C, and miR-196a2T>C polymorphisms with gastric cancer risk and survival in the Greek population. Mol Biol Rep 2014; 41: 1075-80.
[27] Xu Q, Liu JW, Yuan Y. Comprehensive assessment of the association between miRNA polymorphisms and gastric cancer risk. Mutat Res Rev Mutat Res 2015; 763: 148-160.
[28] de la Chapelle A, Jazdzewski K. MicroRNAs in thyroid cancer. J Clin Endocrinol Metab 2011; 96: 3326-36.
[29] Croce CM, Calin GA. miRNAs, cancer, and stem cell division. Cell 2005; 122: 6-7.
[30] Zhang BH, Pan XP, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol 2007; 302: 1-12.
[31] Nikolić ZZ, Savić Pavićević DLj, Vukotić VD, Tomović SM, Cerović SJ, Filipović N, Romac SP, Brajušković GN. Association between genetic variant in hsa-miR-146a gene and prostate cancer progression: evidence from Serbian population. Cancer Causes Control 2014; 25: 1571-5.
[32] Sodhi KK, Bahl C, Singh N, Behera D, Sharma S. Functional genetic variants in pre-miR-146a and 196a2 genes are associated with risk of lung cancer in North Indians. Future Oncol 2015; 11: 2159-73.
[33] Zhang X, He R, Ren F, Tang R, Chen G. Association of miR-146a rs2910164 polymorphism with squamous cell carcinoma risk: a meta-analysis. J BUON 2015; 20: 829-41.
[34] Qi P, Wang L, Zhou B, Yao WJ, Xu S, Zhou Y, Xie ZB. Associations of miRNA polymorphisms and expression levels with breast cancer risk in the

Chinese population. Genet Mol Res 2015; 14: 6289-96.
[35] Peng Q, Li S, Lao X, Chen Z, Li R, Deng Y, Qin X. The association of common functional polymorphisms in mir-146a and mir-196a2 and hepatocellular carcinoma risk: evidence from a meta-analysis. Medicine (Baltimore) 2014; 93: e252.
[36] Dikaiakos P, Gazouli M, Rizos S, Zografos G, Theodoropoulos GE. Evaluation of genetic variants in miRNAs in patients with colorectal cancer. Cancer Biomark 2015; 15: 157-62.
[37] Xie WQ, Tan SY, Wang XF. Effect of a common genetic variant microRNA-146a rs2910164 on colorectal cancer: a meta-analysis. J Dig Dis 2014; 15: 647-53.
[38] Song MY, Su HJ, Zhang L, Ma JL, Li JY, Pan KF, You WC. Genetic polymorphisms of miR-146a and miR-27a, H. pylori infection, and risk of gastric lesions in a Chinese population. PLoS One 2013; 8: e61250.
[39] Wu D, Wang F, Dai WQ, He L, Lu J, Xu L, Guo CY. The miR-146a rs2910164 G > C polymorphism and susceptibility to digestive cancer in Chinese. Asian Pac J Cancer Prev 2013; 14: 399-403.
[40] Zhou F, Zhu H, Luo D, Wang M, Dong X, Hong Y, Lu B, Zhou Y, Zhou J, Zhang Z, Gong W. A functional polymorphism in Pre-miR-146a is associated with susceptibility to gastric cancer in a Chinese population. DNA Cell Biol 2012; 31: 1290-5.
[41] Okubo M, Tahara T, Shibata T, Yamashita H, Nakamura M, Yoshioka D, Yonemura J, Ishizuka T, Arisawa T, Hirata I. Association between common genetic variants in pre-microRNAs and gastric cancer risk in Japanese population. Helicobacter 2010; 15: 524-31.
[42] Zeng Y, Sun QM, Liu NN, Dong GH, Chen J, Yang L, Wang B. Correlation between pre-miR-146a C/G polymorphism and gastric cancer risk in Chinese population. World J Gastroenterol 2010; 16: 3578-83.