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ORIGINAL RESEARCH

Polymorphisms in pre-miRNA genes and cooking oil fume exposure as well as their interaction on the risk of lung cancer in a Chinese nonsmoking female population

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Background: MicroRNAs (miRNAs) are suggested to be very important in the development of lung cancer. This study assesses the association between polymorphisms in miRNA-related (miR)-26a-1, miR-605, and miR-16-1 genes and risk of lung cancer, as well as the effect of gene–environment interaction between miRNA polymorphisms and cooking fume exposure on lung cancer.

Methods: A case–control study including 268 diagnosed nonsmoking female lung cancer patients and 266 nonsmoking female controls was carried out. Three miRNA polymorphisms (miR-26a-1 rs7372209, miR-605 rs2043556, and miR-16-1 rs1022960) were analyzed. Both additive and multiplicative interactions were assessed.

Results: MiR-16-1 rs1022960 may be associated with the risk of lung cancer. Carriers with TT genotype of miR-16-1 rs1022960 were observed to have a decreased risk of lung cancer compared with CC and CT genotype carriers (odds ratio =0.550, 95% confidence interval =0.308–0.983, P=0.044). MiR-26a-1 rs7372209 and miR-605 rs2043556 showed no statistically significant associations with lung cancer risk. There were no significant associations between the three single nucleotide polymorphisms and lung adenocarcinoma. People with exposure to both risk genotypes of miR-26a-1 rs7372209 and cooking oil fumes were more likely to develop lung cancer than those with only genetic risk factor or cooking oil fumes (odds ratios were 2.136, 1.255, and 1.730, respectively). The measures of biological interaction and logistic models indicate that gene–environment interactions were not statistically significant on additive scale or multiplicative scale.

Conclusion: MiR-16-1 rs1022960 may be associated with the risk of lung cancer in a Chinese nonsmoking female population. The interactions between miRNA polymorphisms (miR-26a-1 rs7372209, miR-605 rs2043556, and miR-16-1 rs1022960) and cooking oil fumes were not statistically significant.

Keywords: lung cancer, microRNA, single nucleotide polymorphism, cooking oil fume, interaction

Background

Among all kinds of malignancies, lung cancer has the highest morbidity and is the first leading cause of cancer-related death, which is a severe problem threatening people's health all around the world. Although accumulating epidemiological studies have shown that exposure to environmental factors such as tobacco smoking, air pollution, and toxic chemical compounds may significantly increase one's risk of developing lung cancer, there still exists a considerable proportion of lung cancer patients who had not been exposed to such factors. In addition, it was observed that only a small fraction

of smokers eventually develop lung cancer and ~53% of females with lung cancer are nonsmokers globally,[1] which suggest that not only environmental exposure factors play an important role in the development of lung cancer but genetic factors also contribute most to the susceptibility to lung malignancy.

MicroRNA (miRNA), a class of small, endogenous noncoding RNA, which is 18–25 nucleotides in length, can affect gene expression by binding to the 3′-untranslated region of the target messenger RNA (mRNA), leading to translation repression or cleavage of the target mRNA in the posttranscription stage.[2] Using bioinformatics tools, it was speculated that miRNAs can regulate almost >60% of human protein-coding genes among which some are cancer-related genes, and it was further demonstrated that miRNA is involved in central cellular processes, including cell proliferation, differentiation, and apoptosis. In addition, dysregulation of these biological processes is considered to be associated with the induction and progression of cancer pathogenesis, and several miRNAs were observed to act as tumor suppressors or oncogenes, depending on the target gene.[3–5] More established findings elucidated that one miRNA could regulate hundreds of target genes and one gene could be regulated by various miRNAs, functional mutations in human genome such as single nucleotide polymorphisms (SNPs) located in the miRNA-related region (miR-SNP). miR-SNP can exert its effect on mature miRNA processing or the binding activity of miRNA to target mRNA, so that it may play an extensively regulatory role in the expression of target gene,[6] thus affecting many molecular pathways that may be associated with tumorigenesis. Accumulating evidence shows that miR-SNPs are associated with cancer susceptibility. It was reported that the A allele of miR-605 rs2043556 may decrease the risk of breast cancer in Asian population.[7] Yang et al observed that TT genotype of miR-26a-1 rs7372209 decreased the susceptibility to bladder cancer compared with the CC/CT genotype.[8] However, the associations between the three SNPs (miR-26a-1 rs7372209, miR-605 rs2043556, and miR-16-1 rs1022960) and lung cancer risk are seldom studied. We conduct this molecular epidemiological study to validate the potential association between miR-SNPs and lung cancer risk in nonsmoking females.

Methods

Study subjects

This case–control study was carried out in Shenyang City, which is located in the northeast of the People's Republic of China. A total of 268 nonsmoking female patients diagnosed with lung cancer, who were recruited from the First Affiliated Hospital of China Medical University, the Liaoning Cancer Hospital and Institute, and others, were included in the case group. Patients with a previous history of metastasized cancer and those who had undergone radiotherapy or chemotherapy were excluded. The control group consisted of 266 cancer-free patients who were recruited from the medical examination centers during the same period. All controls were unrelated ethnic Han Chinese nonsmoking women. A written informed consent was obtained from each participant. This study was approved by the Institutional Review Board of China Medical University.

Every participant was interviewed to obtain demographic data and cooking oil fume exposure when they were admitted in the hospital, and 10 mL of venous blood was collected from each participant. Nonsmokers were defined as people who smoked not >100 cigarettes in their lifetime. The study subjects were asked about the frequency of cooking and types of oils to define cooking oil fume exposure. Participants were asked, "How often did the air in your kitchen become filled with oily 'smoke' during cooking?" There were four possible responses ranging from "never", "seldom", and "sometimes", to "frequently". Exposure to cooking oil fume was defined as an indicator variable equal to 0 if participants reported seldom or never and equal to 1 if participants reported frequently or sometimes.

SNP detecting

Genomic DNA sample of each subject was obtained from venous blood samples using phenol–chloroform method. The SNP detecting method was described in our previous study.[9]

Statistical analysis

Student's *t*-test and χ^2-test were used to evaluate the distribution of demographic variables and SNP genotypes among cases and controls. The relationship between SNPs and cooking oil fumes in patients with lung cancer was assessed by odds ratios (ORs) and their 95% confidence intervals (CIs), which were calculated by unconditional logistic regression analysis. Additive interactions were explored according to Tomas Andersson's report.[10] Relative excess risk due to interaction, attributable proportion due to interaction, and synergy index (S), including their 95% CIs, were computed to measure biological interaction. Logistic regression models were carried out to evaluate the multiplicative gene–environment interaction. All statistical analyses were carried out by IBM SPSS Statistics 20.0 (IBM SPSS, Inc. Chicago, IL, USA). All the tests were two sided, and the statistical significance was defined as $P<0.05$.

Results

Subject characteristics

A total of 268 cases and 266 controls, who were nonsmoking females, were included in this study. The mean ages for cases and controls were 55.30±11.85 and 56.71±11.69 years, respectively (mean ± standard deviation), with no statistically significant difference (t=1.382, P=0.167). Among the cases, 197 subjects had adenocarcinoma, 44 subjects had squamous cell lung cancer, and 27 subjects had other types. A total of 100 and 66 individuals had exposure to cooking oil fumes among the cases and controls, respectively, with a statistically significant difference (χ^2=9.739, P=0.002). Individuals with exposure to cooking oil fumes were at an increased 1.804-fold risk of lung cancer (Table 1).

SNP frequencies and association with lung cancer and lung adenocarcinoma

The distributions of the three miR-SNPs (miR-26a-1 rs7372209, miR-605 rs2043556, and miR-16-1 rs1022960) in cases and controls as well as their associations with lung cancer and lung adenocarcinoma risk are shown in Tables 2 and 3. Carriers with TT genotype of miR-16-1 rs1022960 were observed to have a decreased risk of lung cancer compared with CC and CT genotype carriers (OR =0.550, 95% CI =0.308–0.983, P=0.044), and the remaining SNPs showed no statistically significant associations with lung cancer risk. As shown in Table 3, no significant associations between the three SNPs and lung adenocarcinoma were observed.

Interaction between oil fume exposure and SNPs

We also conducted a crossover analysis to investigate the interaction of the three SNPs with exposure to oil fumes. The results are shown in Tables 4 and 5, which indicate that exposure to oil fumes can increase the risk of lung cancer in CT and TT genotype carriers of miR-26a-1 rs7372209 compared with the nonexposure CT and TT genotype carriers (OR =1.743, 95% CI =1.038–2.926, P=0.036). CC genotype carriers exposed to cooking oil fumes also had an increased risk of lung cancer (OR =2.177, 95% CI =1.274–3.719, P=0.004). AG and GG genotype carriers of miR-605 rs2043556 with exposure to cooking oil fumes had an elevated risk of lung cancer compared with AA genotype carriers who had no exposure to cooking oil fumes (OR =2.194, 95% CI =1.277–3.767, P=0.004). CT and TT genotype carriers of miR-16-1 rs1022960 with exposure to cooking oil fumes had higher risk of lung cancer compared with CT and TT genotype carriers who had no exposure to cooking oil fumes (OR =2.326, 95% CI =1.409–3.843, P=0.001), and CC genotype carriers who were exposed to cooking oil fumes also showed an elevated risk of lung cancer (OR =1.718, 95% CI =1.005–2.936, P=0.048).

In the lung adenocarcinoma subgroup shown in Table 5, we found that CC genotype carriers of miR-26a-1 rs7372209 with exposure to cooking oil fumes were more likely to develop lung adenocarcinoma than those with CT and TT genotype carriers (OR =2.136, 95% CI =1.196–3.814, P=0.010). Among the CT and TT genotype carriers of miR-16-1 rs1022960, we observed that exposure to cooking oil fumes increased the risk of lung adenocarcinoma in nonsmoking females (OR =2.340, 95% CI =1.371–3.993, P=0.002). No further statistically significant associations were found for the remaining miRNA SNPs.

The abovementioned crossover results suggested that there may be an interaction between miRNA SNPs and exposure to cooking oil fumes, and hence, the statistically significant tests were explored to assess the interaction on both additive scale and multiplicative scale. Table 6 shows the interaction results of an additive scale, including three measures of interaction, and their 95% CIs to suggest the biological interaction. The results indicate that interactions between miRNA SNPs and exposure to cooking oil fumes were not significant on an additive scale. The interactions on the multiplicative scale calculated by logistic models were not statistically significant. In the logistic analyses of lung cancer, ORs (95% CIs) and P-values of interaction terms were 1.077 (0.511–2.273) and 0.845 for oil*rs7372209, 2.020 (0.953–4.283) and 0.067 for oil*rs2043556, and 0.558 (0.263–1.183) and 0.128 for oil*rs1022960, respectively. In adenocarcinoma, ORs (95% CIs) and P-values of interaction terms were 0.983 (0.439–2.203) and 0.968 for oil*rs7372209, 1.815 (0.805–4.090) and 0.151 for oil*rs2043556, and 0.475 (0.210–1.077) and 0.075 for oil*rs1022960, respectively.

Discussion

Tumorigenesis is a complicated multistep process in which many factors such as environmental factors and genetic mutations play indispensable roles. Many established findings

Table 1 The association between cooking oil exposure and lung cancer in a Chinese nonsmoking female population

Oil	No of controls (%)	No of cases (%)	OR (95% CI)	*P*-value
Nonexposure	200 (75.2)	168 (62.7)	1.00 (Ref)	–
Exposure	66 (24.8)	100 (37.3)	1.804 (1.243–2.618)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference.

Table 2 Allele and genotype frequencies of miRNA polymorphisms among cases and controls as well as their effects on lung cancer risk in nonsmoking females

SNP	Controls (%)	Lung cancer cases (%)	OR (95% CI)	*P*-value
MiR-26a-1 rs7372209				
CC	125 (47.0)	137 (51.1)	1.00 (Ref)	
CT	129 (48.5)	111 (41.4)	0.785 (0.553–1.115)	0.177
TT	12 (4.5)	20 (7.5)	1.521 (0.714–3.237)	0.277
CT + TT vs CC			0.848 (0.604–1.191)	0.340
TT vs CC + CT			1.707 (0.817–3.566)	0.155
C allele	379 (71.2)	385 (71.8)	1.00 (Ref)	
T allele	153 (28.8)	151 (28.2)	0.972 (0.745–1.267)	0.831
MiR-605 rs2043556				
AA	141 (53.0)	139 (51.9)	1.00 (Ref)	
AG	105 (39.5)	104 (38.8)	1.005 (0.702–1.438)	0.979
GG	20 (7.5)	25 (9.3)	1.268 (0.673–2.388)	0.462
AG + GG vs AA			1.047 (0.745–1.470)	0.792
GG vs AA + AG			1.265 (0.685–2.339)	0.452
A allele	387 (72.7)	382 (71.3)	1.00 (Ref)	
G allele	145 (27.3)	154 (28.7)	1.076 (0.824–1.406)	0.591
MiR-16-1 rs1022960				
CC	110 (41.4)	118 (44.0)	1.00 (Ref)	
CT	122 (45.9)	130 (48.5)	0.993 (0.694–1.422)	0.971
TT	34 (12.8)	20 (7.5)	0.548 (0.298–1.010)	0.054
CT + TT vs CC			0.896 (0.636–1.263)	0.532
TT vs CC + CT			0.550 (0.308–0.983)*	0.044
C allele	342 (64.3)	366 (68.3)	1.00 (Ref)	
T allele	190 (35.7)	170 (31.7)	0.836 (0.648–1.078)	0.167

Note: *Significant result.
Abbreviations: CI, confidence interval; miRNA, microRNA; OR, odds ratio; SNP, single nucleotide polymorphism; Ref, reference.

Table 3 miRNA polymorphisms and lung adenocarcinoma risk in nonsmoking females

SNP	Controls (%)	Adenocarcinoma cases (%)	OR (95% CI)	*P*-value
MiR-26a-1 rs7372209				
CC	125 (47.0)	103 (52.3)	1.00 (Ref)	
CT	129 (48.5)	78 (39.6)	0.734 (0.500–1.077)	0.114
TT	12 (4.5)	16 (8.1)	1.618 (0.732–3.575)	0.234
CT + TT vs CC			0.809 (0.559–1.170)	0.260
TT vs CC + CT			1.871 (0.864–4.051)	0.112
C allele	379 (71.2)	284 (72.1)	1.00 (Ref)	
T allele	153 (28.8)	110 (27.9)	0.959 (0.718–1.281)	0.779
MiR-605 rs2043556				
AA	141 (53.0)	111 (56.3)	1.00 (Ref)	
AG	105 (39.5)	71 (36.0)	0.859 (0.581–1.269)	0.445
GG	20 (7.5)	15 (7.6)	0.953 (0.466–1.946)	0.894
AG + GG vs AA			0.874 (0.603–1.266)	0.476
GG vs AA + AG			1.014 (0.505–2.034)	0.969
A allele	387 (72.7)	293 (74.4)	1.00 (Ref)	
G allele	145 (27.3)	101 (25.6)	0.920 (0.684–1.237)	0.581
MiR-16-1 rs1022960				
CC	110 (41.4)	83 (42.1)	1.00 (Ref)	
CT	122 (45.9)	98 (49.7)	1.065 (0.721–1.572)	0.753
TT	34 (12.8)	16 (8.1)	0.624 (0.323–1.205)	0.160
CT + TT vs CC			0.968 (0.667–1.407)	0.867
TT vs CC + CT			0.603 (0.323–1.127)	0.113
C allele	342 (64.3)	264 (67.0)	1.00 (Ref)	
T allele	190 (35.7)	130 (33.0)	0.886 (0.673–1.167)	0.390

Abbreviations: CI, confidence interval; miRNA, microRNA; OR, odds ratio; SNP, single nucleotide polymorphism; Ref, reference.

Table 4 Effect of interaction between SNPs in miRNAs and cooking oil fume exposure on lung cancer susceptibility in a Chinese nonsmoking female population

SNP	Oil	No of controls (%)	No of cases (%)	OR (95% CI)	*P*-value
MiR-26a-1 rs7372209					
CT + TT	Nonexposure	105 (39.5)	82 (30.6)	1.00 (Ref)	–
CC	Nonexposure	95 (35.7)	86 (32.1)	1.159 (0.769–1.748)	0.481
CT + TT	Exposure	36 (13.5)	49 (18.3)	1.743 (1.038–2.926)*	0.036
CC	Exposure	30 (11.3)	51 (19.0)	2.177 (1.274–3.719)*	0.004
MiR-605 rs2043556					
AA	Nonexposure	102 (38.3)	93 (34.7)	1.00 (Ref)	–
AG + GG	Nonexposure	98 (36.8)	75 (28.0)	0.839 (0.556–1.267)	0.404
AA	Exposure	39 (14.7)	46 (17.2)	1.294 (0.776–2.156)	0.323
AG + GG	Exposure	27 (10.2)	54 (20.1)	2.194 (1.277–3.767)*	0.004
MiR-16-1 rs1022960					
CT + TT	Nonexposure	122 (45.9)	91 (34.0)	1.00 (Ref)	–
CC	Nonexposure	78 (29.3)	77 (28.7)	1.323 (0.873–2.006)	0.186
CT + TT	Exposure	34 (12.8)	59 (22.0)	2.326 (1.409–3.843)*	0.001
CC	Exposure	32 (12.0)	41 (15.3)	1.718 (1.005–2.936)*	0.048

Note: *Significant result.
Abbreviations: CI, confidence interval; miRNA, microRNA; OR, odds ratio; SNP, single nucleotide polymorphism; Ref, reference.

of genetic mutations in carcinogenesis are helpful biomarkers for evaluating cancer susceptibility and predicting prognosis as well as the development of targeting therapy. Ectopic expression levels of miRNAs in cancer cells compared with adjacent normal tissues were reported in many previous studies. Since miRNAs were observed to act as oncogenes or tumor suppressors in various malignancies, genomic mutations in the miRNA coding region such as SNPs may inactivate tumor suppressors or activate oncogenes in different contexts. Traditional Chinese-style cooking often involves heating oil to high temperature with stir frying and deep frying and therefore generates large amount of cooking oil fumes that contain a variety of toxic agents, which are classified as accepted or probable human carcinogens. Exposure to cooking oil fumes is common among Chinese females, and several studies have demonstrated that cooking oil fume is an important environmental risk factor.[11,12] Therefore, in the present study, we also evaluated the risk of exposure to cooking oil fumes conferred to the development of lung cancer.

Previous studies have demonstrated that the roles of miR-26a in the tumorigenesis of different tumors and tissue types are not consistent. MiR-26a was reported to suppress cell proliferation in breast cancer, nasopharyngeal carcinoma, and liver cancer,[13–15] whereas some studies observed that miR-26a may facilitate the proliferation of cancer cells in glioma.[16,17] A study conducted by Liu et al[18] aiming to

Table 5 Effect of interaction between SNPs in miRNAs and cooking oil fume exposure on lung adenocarcinoma susceptibility in a Chinese nonsmoking female population

SNP	Oil	No of controls (%)	No of cases (%)	OR (95% CI)	*P*-value
MiR-26a-1 rs7372209					
CT + TT	Nonexposure	105 (39.5)	59 (29.9)	1.00 (Ref)	–
CC	Nonexposure	95 (35.7)	67 (34.0)	1.255 (0.803–1.962)	0.319
CT + TT	Exposure	36 (13.5)	35 (17.8)	1.730 (0.984–3.041)	0.057
CC	Exposure	30 (11.3)	36 (18.3)	2.136 (1.196–3.814)*	0.010
MiR-605 rs2043556					
AA	Nonexposure	102 (38.3)	74 (37.6)	1.00 (Ref)	–
AG + GG	Nonexposure	98 (36.8)	52 (26.4)	0.731 (0.466–1.147)	0.173
AA	Exposure	39 (14.7)	37 (18.8)	1.308 (0.762–2.245)	0.330
AG + GG	Exposure	27 (10.2)	34 (17.3)	1.736 (0.965–3.123)	0.066
MiR-16-1 rs1022960					
CT + TT	Nonexposure	122 (45.9)	69 (35.0)	1.00 (Ref)	–
CC	Nonexposure	78 (29.3)	57 (28.9)	1.292 (0.823–2.029)	0.266
CT + TT	Exposure	34 (12.8)	45 (22.8)	2.340 (1.371–3.993)*	0.002
CC	Exposure	32 (12.0)	26 (13.2)	1.437 (0.792–2.607)	0.233

Note: *Significant result.
Abbreviations: CI, confidence interval; miRNA, microRNA; OR, odds ratio; SNP, single nucleotide polymorphism; Ref, reference.

Table 6 Effect of interaction between SNPs in miRNAs and cooking oil fume exposure on susceptibility to lung cancer and adenocarcinoma in a Chinese nonsmoking female population

SNP	Lung cancer			Lung adenocarcinoma		
	Measure	Estimate	95% CI	Measure	Estimate	95% CI
MiR-26a-1 rs7372209						
	RERI	0.275	−1.023 to 1.573	RERI	0.150	−1.245 to 1.545
	AP	0.126	−0.436 to 0.688	AP	0.070	−0.563 to 0.704
	S	1.305	0.356 to 4.775	S	1.152	0.302 to 4.393
MiR-605 rs2043556						
	RERI	1.061	−0.121 to 2.242	RERI	0.697	−0.391 to 1.785
	AP	0.483	0.096 to 0.871*	AP	0.401	−0.105 to 0.907
	S	8.974	0.020 to 4,085.717	S	18.828	0.000 to >100
MiR-16-1 rs1022960						
	RERI	−0.932	−2.362 to 0.497	RERI	−1.196	−2.697 to 0.306
	AP	−0.543	−1.501 to 0.416	AP	−0.832	−2.082 to 0.418
	S	0.435	0.121 to 1.568	S	0.267	0.041 to 1.727

Note: *Significant result.
Abbreviations: AP, attributable proportion due to interaction; CI, confidence interval; miRNA, microRNA; RERI, relative excess risk due to interaction; S, synergy index; SNP, single nucleotide polymorphism.

validate the function of miR-26a in lung cancer found that miR-26a enhances the metastatic potential of lung cancer cells by directly targeting phosphatase and tensin homolog (PTEN). For miR-26a-1 rs7372209, a study conducted by Boni et al[19] observed that C allele was a favorable factor to predict a relatively better prognosis in the treatment of colon cancer. In the present study, subjects with both cooking oil fume exposure and risk genotype showed a higher risk to develop lung cancer than the reference group. However, it was just a statistical association, and the underlying molecular mechanism needs to be validated.

Association of miR-605 rs2043556 polymorphism with cancer risk has been reported in other cancers. For example, Zhang et al reported an increased risk of gastric cancer in miR-605 AG/GG genotype carriers who engaged in smoke inhalation.[20] However, there is a lack of studies focusing on the association between miR-605 rs2043556 polymorphisms and lung cancer risk. Zhang et al reported a marginal significance in elevated susceptibility of miR-605 AG/GG genotype carriers to develop lung cancer than AA carriers;[21] however, we did not achieve a statistically significant result, which is consistent with the conclusion of Zhang et al in the overall association analysis of SNPs and risk of lung cancer. Subsequent analysis of gene–environment interactions in the present study showed that carriers with AG/GG genotype who were exposed to cooking oil fumes had a 2.19-fold increased risk than AA carriers without cooking oil fume exposure (OR =2.194, 95% CI =1.277–3.767).

For miR-16-1 rs1022960, CT or TT genotype carriers with exposure to cooking oil fumes showed a significantly elevated risk of lung cancer compared with those with no exposure to cooking oil fumes, consistent with the hypothesis that cooking oil fume is a risk factor of lung cancer. Ectopic expression of miR-16 was commonly observed, and it often exerts its effect of tumor suppression on various kinds of malignancies. In breast cancer model, Mobarra et al showed that upregulation of miR-16 can reduce mRNA of cyclin D1 and B-cell lymphoma-2 (BCL2) and protein levels in Michigan Cancer Foundation-7 (MCF-7) cell line thus decrease cell growth and proliferation and induce apoptosis in MCF-7 cells.[22] Jiang et al reported that miR-16 inhibits the proliferation of bladder cancer cells by negatively regulating the expression of cyclin D1.[23] The tumor suppressor role of miR-16 was also reported in colorectal cancer, glioma, and nasopharyngeal carcinoma.[24–27] However, the expression of miR-16 has never been reported in lung cancer; we presume that miR-16-1 rs1022960 polymorphism may affect the expression level of miR-16 and thus may affect the susceptibility to lung cancer, which needs to be validated in future studies.

The cause of cancer is accepted to be a complex gene–environment interaction. Previous studies seldom investigated the associations between the gene and environment. To the best of our knowledge, this is the first study to comprehensively explore the additive interaction and multiplicative interaction between SNPs in miR-26a-1, miR-605, and miR-16-1 with cooking oil fumes and lung cancer. Results indicated that there were no statistically significant associations between combinations of the three miR-SNPs with cooking oil fumes and lung cancer risk, which we attribute to the limitation of the relatively small sample size. The validation of gene–environment interaction needs to be set in future studies with larger sample sizes.

Some limitations in our study should be taken into account. First, the present study is a hospital-based case–control study,

and we enrolled the controls from the medical examination centers of the hospitals. These cancer-free controls may not be appropriate representatives for the overall population, which may result in selection bias in the study. Therefore, we should be cautious when we reach a conclusion. Second, the sample size may be a major obstacle for us to evaluate the gene–environment interaction; therefore, the sample size should be enlarged in a further study.

Conclusion

The present case–control study demonstrated the relationships between the SNPs in three miRNAs and the susceptibility to lung cancer; however, the gene–environment interaction between miRNA SNPs and cooking oil fume exposure was not statistically significant.

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Disclosure

The authors report no conflicts of interest in this work.

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