Genetic variants in *RAN, DICER* and *HIWI* of microRNA biogenesis genes and risk of cervical carcinoma in a Chinese population

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Objective: Recent evidence indicates that dysregulation of microRNA (miRNA) biogenesis is implicated in cancer development and progression. Based on the important role of miRNA biogenesis genes in carcinogenesis, we hypothesized that genetic variations of the miRNA biogenesis genes may modulate susceptibility to cervical cancer.

Methods: We identified three single nucleotide polymorphisms (SNPs) located in the 3'-untranslated regions (3'-UTR) of of miRNA biogenesis key genes (rs1057035 in *DICER*, rs3803012 in *RAN* and rs10773771 in *HIWI*) and genotyped these SNPs in a case-control study of 1,486 cervical cancer cases and 1,549 cancer-free controls in Chinese women.

Results: Logistic regression analyses showed that no significant associations were observed between the three SNPs and cervical cancer risk [rs3803012 in *RAN* AG/GG *vs*. AA adjusted OR =1.104, 95% confidence interval (CI): 0.859-1.419; rs1057035 in *DICER* CT/CC *vs*. TT adjusted OR =0.962, 95% CI: 0.805-1.149; rs10773771 in *HIWI* CT/CC *vs*. TT adjusted OR =0.963, 95% CI: 0.826-1.122].

Conclusions: The findings did not suggest that genetic variants in the 3'-UTR of *RAN, DICER* and *HIWI* of miRNA biogenesis genes were associated with the risk of cervical cancer in this Chinese population.

Keywords: miRNA biogenesis gene; genetic variant; cervical cancer

Introduction

Cervical cancer is one of the most common malignancies among women worldwide, with an estimated 530,000 new cases and 275,000 deaths in 2008 (1), and 83% of the cases had occurred in developing countries (2). As a developing country, cervical cancer incidence and mortality rates have been substantial declines in the past 30 years, but 135,000 new cases are still diagnosed in China every year (3). Epidemiologic and laboratory-based studies indicated that the prevalence of genital human papillomavirus (HPV) infection in developing countries is very high in young females, but most of the infected can regress without intervention in two years, only a little high-risk HPV persistent infection might ultimately lead to cervical cancer (4). Given the mounting evidence that HPV infection is necessary but not sufficient cause for cervical cancer development, epidemiologic studies have suggested that host genetic variations may play an important contribution to cervical cancer susceptibility (5,6).

Recently discovered microRNAs (miRNAs) are a class of small noncoding RNAs, which are about 22 nucleotides in length, and modulate gene expression by targeting mRNA for deregulation or translational repression (7,8). These

molecules control the expression of the majority of protein-encoding genes in humans. Therefore, miRNA appears to play critical roles either in physiological and pathological mechanisms, including cancer (9,10). A global deregulation of mature miRNA expression has been shown in several human cancers including cervical cancer, and specific miRNAs could be used to define molecular subtypes of different cancers (11). Along with these studies, it has been suggested that impaired miRNA processing could promote cellular transformation and tumorigenesis (12).

miRNA genes are initially transcribed by RNA polymerase II to form large primary miRNAs (pri-miRNAs). After transcription, pri-miRNAs are processed in the nucleus by the microprocessor machinery containing the RNase III Drosha and RNA binding protein DGCR8.This processing releases 60-70 nucleotide precursor miRNAs (pre-miRNAs), which are exported to the cytoplasm via Ran-GTPase and Exportin-5 (XPO5). Then pre-miRNAs are processed to produce the mature miRNAs through a protein complex that includes DICER, TRBP, AGO1, AGO2, HIWI, GEMIN3, GEMIN4, *etc* (7). In addition to deregulation of miRNAs, the aberrations of miRNA processing genes have been associated with several types of cancer. For example, altered expression of *DICER* modified the development of lung cancer, breast cancer, colorectal cancer and prostate cancers (13-16). Li *et al*. found that *HIWI* was universally upregulated in many types of cancer including cervical cancer and played an important role in oncogenesis (17). Given the critical function of miRNA biogenesis and the involvement of cancer development and progression, it is not surprising that genetic variations in miRNA biogenesis pathway could affect risk of cancers.

Single nucleotide polymorphisms (SNPs) are the most common human genetic variants and may contribute to an individual's susceptibility to cancer. At present, multiple studies have revealed that the presence of SNPs in miRNA biogenesis pathway genes as well as miRNA genes and their target binding sites could affect the risk of cancer development, treatment response, and patient survival (18). Genetic variants in miRNA biogenesis pathway genes have been reported to be associated with the risk of several cancers such as bladder cancer, renal cell carcinoma, lung cancer, esophageal cancer, and breast cancer (19-23). However, few studies had shown the association between the polymorphisms in the miRNA biogenesis pathway genes and the risk of cervical cancer. Therefore, we hypothesized that SNPs in the miRNA processing genes may influence their expression or activity, thereby modulating

susceptibility to cervical cancer. To test this hypothesis, we conducted a case-control study to evaluate the associations between SNPs in the miRNA processing genes (rs1057035 in *DICER1*, rs10773771 in *HIWI* and rs3803012 in *RAN*) and cervical cancer risk.

Materials and methods

Study population

The case-control study was approved by the Institutional Review Board of Nanjing Medical University. A total of 1,486 cervical cancer cases and 1,549 cancer-free controls were included in this study. All subjects were genetically unrelated Han Chinese women, and informed consents of approximately 95% of them were obtained. In brief, cervical cancer cases were recruited from the First Affiliated Hospital of Nanjing Medical University and the Tumor Hospital of Nantong City, Jiangsu, China, from March 2006 to January 2010. All cervical cancer cases in the study were newly diagnosed and histologically confirmed without restrictions of age or histological type in the two hospitals. Cancer-free women controls were randomly selected from a cohort of more than 30,000 participants in a community-based screening program for non-infectious diseases conducted in Jiangsu Province during the same time period as the cases were recruited. These control subjects had no self-reported cancer history and were frequency matched to the cases on age (±5 years) and residential areas (urban and rural). Each individual was interviewed by trained interviewers so as to collect information on demographic data, menstrual and reproduction history, and environment exposure history. After an informed consent, 5 mL of venous blood sample was collected from each subject for later genotyping assays.

SNP selection and genotyping

Based on the databases of the International HapMap Project (http://www.hapmap.org), dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and bioinformatics prediction (http://snpinfo.niehs. nih.gov/snpfunc.htm), we searched the potentially functional polymorphisms (MAF >0.05) in *RAN*, *DICER* and *HIWI* genes for Asians. As a result, we selected three common SNPs located at 3'-untranslated regions (UTR): rs3803012 (A > G) in *RAN*, rs1057035 (C > T) in *DICER* and rs10773771 (C > T) in *HIWI*.

Genomic DNA was extracted from leukocytes of venous blood by proteinase K digestion and was followed by phenol-chloroform extraction and ethanol

Table 1 Demographic and selected variables in cervical cancer cases and controls

Variables	Cases [n (%)]	Controls [n (%)]	P
Age (year, $\bar{x}\pm s$)	53.78±12.67	53.19±11.88	0.188
Age at menarche (year, $\bar{x}\pm s$)	15.55±1.97	16.07±1.92	<0.0001
Menopausal status			
Premenopausal	618 (41.59)	606 (39.12)	<0.015
Postmenopausal	862 (58.01)	943 (60.88)	
Unknown	6 (0.40)	0 (0)	
Parity			
0-1	638 (42.93)	762 (49.19)	<0.001
≥2	848 (57.07)	787 (50.81)	
Histological types			
Squamous cell carcinoma	1,363 (91.72)		
Adenocarcinoma	97 (6.53)		
Adenosquamous carcinoma	26 (1.75)		
Stage			
CIN 3	10 (0.67)		
I	352 (23.69)		
II	776 (52.22)		
III	224 (15.07)		
IV	43 (2.89)		
Unclassified	81 (5.45)		

precipitation. The genotyping of the SNPs was performed by using TaqMan allelic discrimination Assay (primer: sense, 5'-TTTG GAACGCAGTTGATTCCT-3', antisense, 5'-GTAAC AAACAAGATTTCACCAC TGAATAT-3', probe: allele A, FAM-AGTTTCATATA TAAGACTGC, allele G, HEX-AGTTTCATATGTA AGACTG for rs3803012; primer: sense, 5'-TCTGCAGTTGCTTTTTCAAGACA-3', antisense, 5'-GAGACCG AATGTAATATGGAAAACCT-3', probe: allele C, FAM-TACACACGCGCTCAG, allele T, HEX-TACACACGTGCTCAGG for rs1057035; primer: sense, 5'-GTATCTTATCCA CATTTCTTC-3', antisense, 5'-TTCTAGCATTGCTATTCAC-3', probe: allele C, FAM-ACGTATAA AATAAGGAAGC, allele T, HEX-TACAT ATAAAATAAGGAAGC for rs10773771) on ABI PRISM 7900 HT platform (Applied Biosystems, Inc.). All the genotyping assays were performed without knowing the subjects' case or control status, and approximately equal numbers of case and control samples were assayed in each 384-well plate with two blank controls. We also randomly selected 96 samples to genotype in duplicate for all the SNPs, and the results were 100% concordant.

Statistical analysis

We used χ^2 test and student *t*-test to analyze the differences in demographic characteristics, selected variables and frequencies of the genotypes between the cases and controls. The associations between genotypes and cervical cancer risk were estimated by calculating the odds ratios (ORs) and their 95% confidence intervals (95% CIs) from logistic regression analyses. The adjustment factors for the associations included age, age at menarche, menopausal status and parity. Genotype distributions in the control subjects were checked for Hardy-Weinberg equilibrium by using goodness-of-fit χ^2 test. All of the statistical analyses were performed with Statistical Analysis System software (9.1.3; SAS institute, Cary, NC, USA).

Results

Characteristics of study population

Basic characteristics of the study objects are presented in *Table 1*. The age was comparable between cases and controls (P>0.05) after frequency-matching. Compared

Table 2 General characteristics of genetic variants in miRNA processing genes

SNP	Chr	Position	Location	Major/minor allele	Call rate	HWE	MAF (HCB)	MAF (case/control)
rs3803012	12q24.3	22,052,134	3'-UTR of *RAN*	A > G	98.8	0.990	5.8	5.13/4.41
rs10773771	12q24.3	80,515,417	3'-UTR of *DICER*	T > C	98.7	0.245	41.9	40.81/42.13
rs1057035	14q32	5,926,740	3'-UTR of *HIWI*	T > C	98.9	0.513	10.5	11.22/11.55

HWE, Hardy-Weiberger equilibrium; MAF, minor allele frequency.

Table 3 Distribution of rs1057035, rs10773771 and rs3803012 and their associations with risk of cervical cancer

Genotype	Cases [n (%)]	Controls [n (%)]	OR (95% CI)*	P*
rs1057035				
TT	1,163 (78.85)	1,198 (78.40)	1	
CT	293 (19.86)	307 (20.09)	0.972 (0.810-1.166)	0.759
CC	19 (1.29)	23 (1.51)	0.941 (0.505-1.755)	0.849
CT/ CC	312 (21.15)	330 (21.60)	0.962 (0.805-1.149)	0.67
rs10773771				
TT	517 (35.19)	522 (34.21)	1	
CT	705 (47.99)	722 (47.31)	1.007 (0.857-1.183)	0.935
CC	247 (16.81)	282 (18.48)	0.891 (0.721-1.102)	0.288
CT/ CC	952 (64.81)	1,004 (65.79)	0.963 (0.826-1.122)	0.628
rs3803012				
AA	1,325 (90.07)	1,397 (91.37)	1	
AG	141 (9.59)	129 (8.44)	1.091 (0.846-1.407)	0.501
GG	5 (0.34)	3 (0.20)	1.877 (0.435-8.104)	0.399
AG/GG	146 (9.93)	132 (8.63)	1.104 (0.859-1.419)	0.441

*, adjusted by age, age at menarche, menopausal status and parity.

with the control subjects, the cervical cancer cases had an earlier menarche (P<0.05), and showed a lower proportion of menopause and higher parity (P<0.05). Out of the 1,486 cervical cancer cases, 1,363 (91.7%) were squamous cell carcinoma, 97 (6.5%) were adenocarcinoma, 26 (1.8%) were adenosquamous carcinoma. Only 10 (0.7%) patients had cervical intraepithelial neoplasia (CIN) grade 3, 352 (23.7%) were stage I carcinoma, 776 (52.2%) stage II, 224 (15.1%) stage III, 43 (2.9%) stage IV, and 81 (5.5%) unclassified.

Genotype distributions of rs3803012, rs1057035 and rs10773771 and cervical cancer risk

The general characteristics and genotype distributions of *RAN* rs3803012, *DICER* rs1057035 and *HIWI* rs10773771 are shown in *Table 2* and *Table 3*. The genotyping calling rates were 98.8% for rs3803012, 98.9% for rs1057035 and 98.7% for rs10773771, respectively, and the observed

genotype frequencies for these three polymorphisms in the controls were all in Hardy-Weinberg equilibrium (P=0.990, 0.513 and 0.245 for rs3803012, rs1057035 and rs10773771 respectively). However, in the multivariate logistic regression models, none of the three SNPs was significantly associated with the risk of cervical cancer. *RAN* rs3803012 AG/GG *vs.* AA adjusted OR =1.104, 95% CI: 0.859-1.419; *DICER* rs1057035 CT/CC *vs.* TT adjusted OR =0.962, 95% CI: 0.805-1.149; *HIWI* rs10773771 CT/CC *vs.* TT adjusted OR =0.963, 95% CI: 0.826-1.122 (*Table 3*).

Stratified analyses

Additionally, we further performed stratification analyses based on age, age at menarche, parity and menopausal status, histological types and tumor stage. As shown in *Table 4*, the association with rs3803012 was more evident in patients with stage III carcinoma (adjusted OR =0.613; 95% CI: 0.420-

Table 4 Stratified analyses on associations between rs1057035, rs10773771 and rs3803012 and risk of cervical cancer

	rs1057035 (case/control)				rs10773771 (case/control)				rs3803012 (case/control)			
	TT	CT/TT	OR*	P#	TT	CT/TT	OR*	P#	AA	AG/GG	OR*	P#
Age (year)												
<53	592/626	154/157	1.055 (0.816-1.363)	0.403	278/279	462/504	0.945 (0.763-1.171)	0.947	668/722	75/63	1.254 (0.875-1.799)	0.411
≥53	571/572	158/173	0.905 (0.704-1.164)		239/243	490/500	0.955 (0.764-1.194)		657/675	71/69	1.014 (0.710-1.448)	
Age at menarche (year)												
<16	672/465	166/125	0.886 (0.681-1.153)	0.336	284/201	548/389	0.996 (0.795-1.247)	0.586	747/537	86/55	1.161 (0.777-1.737)	0.870
≥16	491/733	146/205	1.056 (0.829-1.346)		233/321	404/615	0.914 (0.740-1.130)		578/860	60/77	1.112 (0.802-1.542)	
Menopausal status												
Premenopausal	482/478	133/115	1.191 (0.891-1.592)	0.094	229/208	380/386	0.916 (0.718-1.169)	0.670	551/544	61/52	1.097 (0.766-1.572)	0.852
Postmenopausal	677/720	177/215	0.868 (0.690-1.092)		285/314	569/618	0.981 (0.803-1.199)		768/853	85/80	1.151 (0.806-1.642)	
Parity												
0-1	512/599	122/152	0.980 (0.747-1.282)	0.996	232/246	398/504	0.838 (0.668-1.052)	0.129	573/692	59/60	1.200 (0.818-1.542)	0.639
≥2	651/599	190/178	0.981 (0.773-1.246)		285/276	554/500	1.065 (0.863-1.315)		752/705	87/72	1.074 (0.766-1.505)	
Histological types												
Squamous cell carcinoma	1,068	291	1.016 (0.846-1.219)	0.585	477	877	1.048 (0.896-1.227)	0.880	1,215	140	0.851 (0.659-1.099)	0.224
Adenocarcinoma	72	18	1.084 (0.635-1.853)		31	58	1.065 (0.677-1.676)		86	4	2.141 (0.769-5.962)	
Adenosquamous carcinoma	22	3	1.934 (0.570-6.563)		8	17	0.841 (0.358-1.976)		23	2	1.078 (0.248-4.684)	
Stage												
CIN 3	8	2	0.921 (0.554-1.532)	0.985	4	6	1.018 (0.648-1.600)	0.999	8	2	0.615 (0.330-1.147)	0.163
I	284	67	1.049 (0.798-1.379)		122	228	0.983 (0.779-1.240)		310	35	0.795 (0.552-1.146)	
II	600	168	0.996 (0.809-1.227)		271	493	1.028 (0.788-1.340)		709	61	1.078 (0.793-1.467)	
III	176	46	1.017 (0.749-1.380)		77	144	1.018 (0.648-1.600)		190	32	0.613 (0.420-0.895)	
IV	33	10	0.921 (0.594-1.428)		16	27	1.049 (0.710-1.548)		38	5	0.678 (0.386-1.191)	

*, adjusted by age, age at menarche, menopausal status and parity; #, P for heterogeneity.

0.895). No significant heterogeneity was observed between the stratified subgroups (P>0.100 for heterogeneity tests).

Discussion

This study evaluated the relationship of common genetic variants at miRNA biogenesis pathway and the risk of cervical cancer in a Chinese population and found that none of these SNPs was significantly associated with Chinese cervical cancer risk.

DICER plays an important role in the cleavage of pre-miRNAs into their mature form and has previously been implicated in the oncogenic process of several cancers (13-16). To investigate the impact of functional SNPs of *DICER* gene on tumor development, molecular epidemiological studies were conducted for several cancer types or related diseases, including bladder cancer, lung cancer, renal cell carcinoma, breast cancer and oral premalignant lesions (19-24). However, the results remained inconsistent. Clague *et al.* reported that rs3742330 in the 3'-UTR of *DICER* was associated with an increased risk of premalignant oral lesions in Caucasians (OR =2.09, 95% CI: 1.03-4.24, P=0.04) (24). Nevertheless, other studies showed that this SNP in the 3'-UTR of *DICER* was not associated with risk of cancers such as bladder cancer, lung cancer, renal cell carcinoma and esophageal cancer (19-22). Later, Sung *et al.* conducted a population-based case control study of 559 breast cancer cases and 567 controls in Korean women and found that rs1057035 in the 3'-UTR of *DICER* was not associated with risk of breast cancer (OR =0.64, 95% CI: 0.23-1.77, P=0.39) (23). Similarly, our data also did not support an association of cervical cancer risk with the SNP rs1057035 in the 3'-UTR of *DICER* in Chinese women (OR =0.962, 95% CI: 0.805-1.149).

RAN is a key ingredient for the transportation of pre-miRNAs from nucleus to cytoplasm through the nuclear pore complex in a GTP-dependent manner (25). Overexpression of RAN GTPase has been observed in various other malignancies including stomach, colon, pancreas, lung and ovarian cancer (26-28). The association between *RAN* polymorphisms and risk of other kind of cancers has been evaluated in several recent studies, but the results were conflicted (19-23). Ye *et al.* reported that rs14035 in the 3'-UTR of *RAN* was associated with an increased esophageal cancer risk in Caucasian population (OR =1.99, 95% CI: 1.17-3.38, P=0.011), while other studies reported that this SNP in the 3'-UTR of *RAN* was not associated with risk of cancers such as bladder cancer, lung cancer and renal cell

carcinoma (20-22). In this study, we did not observe the significant association between the rs3803012 in the 3'-UTR of *RAN* and the risk of cervical cancer.

As a human member of *PIWI* family, *HIWI* is suggested to play an important role in stem cell self-renewal, division, RNA silencing and translational regulation (29), and its expression usually upregulated in many types of cancer (17,30,31). Numerous studies have suggested that the rs1106042 (Lys527Arg) in the cording region of *HIWI* gene was not associated with the risk of cancers such as esophageal cancer, bladder cancer, breast cancer, lung cancer and renal cell carcinoma (19-24). In our study, bioinformatics predict that the SNP rs10773771 (C > T) in the 3'-UTR of *HIWI* gene could influence the has-miR-1264 binding to *HIWI* transcript, nevertheless we did not found that this SNP contributed to the risk of cervical cancer.

In the current study, the potential functional SNPs at miRNA biogenesis pathway genes were not significantly associated with the risk of cervical cancer. Although it is difficult to explain the basis for the conflicting results from different studies, the differences of genetic backgrounds and environmental factors in the study populations might contribute to the discrepancy. Another possible explanation is that the discrepancy between the different studies may be that different cell types of cancer have specific etiologies and carcinogenesis pathways. There is increasing evidence that miRNA expression profiles are different according to human cancers (9,11). Therefore, genetic variations in miRNA biosynthesis pathway genes might play different roles in different cell types of cancer.

Several limitations in our study need to be addressed. Firstly, although this is a population based case-control study, the selection bias may not be avoidable and the subjects may not be representative of the general population. Secondly, the polymorphisms conducted in our study, based on their functional considerations, may not give a comprehensive view about genetic variability in miRNA biogenesis pathway genes.

In conclusion, our data did not support an association of cervical risk with genetic variations in the 3'-UTR of *RAN*, *DICER* and *HIWI* genes in a Chinese population. Further tagging and functional SNP-based studies in the whole miRNA biogenesis pathway genes are warranted to confirm and extend the results.

Acknowledgements

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