

RESEARCH ARTICLE

Association between the DICER rs1057035 Polymorphism and Cancer Risk: Evidence from a Meta-analysis of 1,2675 Individuals

Yan-Yan Yu¹, Dan Kuang¹, Xiao-Xv Yin^{2*}

Abstract

Background: DICER, one of the microRNA (miRNA) biogenesis proteins, is involved in the maturation of miRNAs and is implicated in cancer development and progression. The results from previous epidemiological studies on associations between DICER rs1057035 polymorphism and cancer risk were inconsistent. Therefore we performed this meta-analysis to summarize possible associations. **Materials and Methods:** We searched all relevant articles on associations between DICER rs1057035 polymorphism and cancer risk from PubMed, EMBASE, Chinese Biomedical Literature and Chinese National Knowledge Infrastructure until August 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess any associations. Heterogeneity tests, sensitivity analyses and publication bias assessments were also performed in this meta-analysis. All analyses were conducted using STATA software. **Results:** Seven case-control studies, including 4,875 cancer cases and 7,800 controls were included in the meta-analysis. Overall, the results indicated that the C allele of DICER rs1057035 polymorphism was significantly associated with decreased cancer risk in allelic comparison, heterozygote and dominant genetic models (C vs T: OR=0.88, 95% CI 0.81-0.95, $p=0.002$; TC vs TT: OR=0.85, 95% CI 0.77-0.93, $p=0.001$; CC/TC vs TT: OR=0.86, 95% CI 0.78-0.94, $p=0.001$). In the subgroup analysis by ethnicity, a significantly decreased cancer risk was found in Asian but not Caucasian populations. **Conclusions:** The present meta-analysis suggests that the C allele of the DICER rs1057035 polymorphism probably decreases cancer risk. However, this association may be Asian-specific and the results should be treated with caution. Further well-designed studies based on larger sample sizes and group of populations are needed to validate these findings.

Keywords: DICER - cancer - polymorphism - meta-analysis

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Introduction

MicroRNAs (miRNAs) are a class of small, single-stranded, non-protein-coding RNA gene products of about 21- to 24-nucleotide-long that can regulate gene expression by base pairing with target mRNAs, leading to mRNA degradation or translational repression (Ambros, 2004; Bartel, 2004). It has been suggested that miRNAs are predicted to regulate 30% of human genes (Carthew, 2006). Many studies have identified that miRNAs are potent drivers of various biological processes, including cell proliferation, cell differentiation, apoptosis and tumorigenesis (Zamore and Haley, 2005; Li et al., 2014; Tufekci et al., 2014). Recent emerging evidences have suggested that differential expression of miRNAs was related to various human cancers development and progression by regulating the expression of tumor suppressor genes or proto-oncogenes (Cui et al., 2014; Donadelli et al., 2014; Gu et al., 2014).

RNase enzymes play a role in the miRNAs processing. In the nucleus, primary miRNAs (pri-miRNAs) are processed by the microprocessor machinery and then precursor miRNAs (pre-miRNAs) were released with a stem-loop structure by the RNase enzymes (Błaszczuk et al., 2001; Lee et al., 2004). The pre-miRNAs are exported to the cytoplasm via Ran-GTPase and Exportin-5. In the cytoplasm, pre-miRNAs are processed to produce the mature miRNAs by RNase enzyme DICER (Bartel, 2004; Liu et al., 2008). Accumulated evidences have shown that imbalance DICER expression levels are associated with cancer risk and progression by affecting cell proliferation and cell apoptosis (Bian et al., 2014; Gao et al., 2014). Rs1057035 C>T polymorphism is located in 3'-untranslated region of DICER gene and it has reported that this variant might regulate the expression of DICER by interfering the binding of has-miR-574-3p, the candidate tumor promoter miRNA, to the 3' UTR of the DICER (Liu et al., 2013). Therefore, DICER rs1057035

¹Chengdu Municipal Center for Disease Control and Prevention, Chengdu, ²School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China *For correspondence: yuyanyan19850626@126.com

variant may result in predisposition to and prognosis of cancers.

There are several epidemiological case-control studies have examined the association between DICER rs1057035 polymorphism and cancer risk (Ma et al., 2012; Chen et al., 2013; Jiang et al., 2013; Liu et al., 2013; Slaby et al., 2013; Yuan et al., 2013). Though, the findings were inconclusive or even contradictory which may be attributed to ethnicity of the population, different cancer types or small size from individual studies. Therefore, we performed a meta-analysis to systematically clarify the association between the DICER rs1057035 polymorphism and cancer risk.

Materials and Methods

Literature search

We searched electronic research literature from PubMed, Excerpta Medica Database (EMBASE), Chinese Biomedical Literature (CBM) and Chinese National Knowledge Infrastructure (CNKI) web databases with the combination of following terms “DICER or microRNA biogenesis” and “gene polymorphism or allele or variation” and “cancer or carcinoma or neoplasm or tumor” updated until August 26, 2014. The search was focused on studies that had examined the association between DICER rs1057035 polymorphism and cancer risk. In order to retrieve the most eligible literatures, we manually screened all associated publications and their reference lists. We included published paper on relevant studies carried out in human subjects with no restriction on publication language.

Inclusion and exclusion criteria

Eligible studies for further meta-analysis had to meet all of the following criteria: a) must investigated the association between DICER gene polymorphism and cancer risk, b) used a case-control study design, c) have available detail genotype frequencies in case and control groups. The major exclusion criteria were: a) overlapping data, b) abstract, review, comment and editorial, c) case-only studies, d) family or sibling pairs based studies, e) genotype frequencies or numbers of the subjects were unavailable, even contacting the corresponding author of the relevant articles. If there was more than one study published using the same patients population, only the complete design and larger sample size study would be selected in the meta-analysis.

Data extraction

Two reviewers (Yu and Kuang) independently extracted the following information from the eligible studies: The data of the eligible studies, including first author’s surname, year of publication, country of origin, ethnicity, source of control, cancer type, genotyping method, sample size of genotyped cases and controls, genotype frequencies in case and control groups. If studies involving more than one type of cancer, data were extracted separately as independent study. Any disagreements on the data from the collected studies were fully debated with investigators to reach the final consensus.

Statistical analysis

The genotype frequencies of DICER rs1057035 polymorphism for Hardy-Weinberg equilibrium (HWE) in control groups were measured via Chi-square test and a *P*-value<0.05 was considered as significant disequilibrium (Schaid and Jacobsen, 1999). In order to assess the strength of the association between DICER rs1057035 polymorphism and cancer risk, pooled ORs and their 95%CI in each comparison were performed for allelic comparison (C vs T), homozygote model (CC vs TT), heterozygote model (TC vs TT), dominant model (CC/TC vs TT) and recessive model (CC vs TC/TT), respectively. The Z test was conducted to determine the significance of the pooled ORs. The chi-square based Cochran’s Q test were carried out to assess the heterogeneity assumption between studies across the eligible comparison. Heterogeneity was considered to be significant at *P*-value<0.10 (Higgins et al., 2002; Zintzaras and Ioannidis, 2005). The fixed-effects model (Mantel-Haenszel method) was applied to calculate the pooled ORs when the *P* value was >0.10; otherwise, the random-effects model (DerSimonian-

Table 1. Characteristics of the Eligible Studies in the Meta-Analysis

First Authors	Year	Country	Ethnicity	Source of controls	Cancer type	No. of case/control	Genotyping method	Case			Control			HWE P-value
								TT	TC	CC	TT	TC	CC	
Lin Yuan	2013	China	Asian	PB	Bladder cancer	685/730	TaqMan	548	120	17	577	145	8	0.741
Jiaping Chen	2013	China	Asian	PB	Cervical cancer	1475/1528	TaqMan	1163	293	19	1198	307	23	0.513
Yue Jiang	2013	China	Asian	PB	Breast cancer	878/900	TaqMan	696	145	7	711	161	9	0.973
Hongxia Ma	2012	China	Asian	PB	Oral cancer	290/891	TaqMan	240	48	2	678	204	9	0.138
Hongxia Ma	2012	China	Asian	PB	Head and Neck cancer	104/891	TaqMan	77	27	0	678	204	9	0.138
Ondrej Slaby	2013	Czech	Caucasian	PB	Colorectal cancer	198/209	TaqMan	96	82	20	86	91	32	0.333
Li Liu	2013	China	Asian	PB	Hepatocellular carcinoma	1275/2670	TaqMan	1063	196	16	2107	538	25	0.145

PB: population-based; TaqMan: TaqMan allelic discrimination Assay; HWE: Hardy-Weinberg equilibrium

Laird method) was used (DerSimonian and Laird, 1986). Also, and I^2 was employed to qualify variation in OR attributable to heterogeneity. In order to evaluate the influence of each study on the overall estimate, we carried out sensitivity analysis by sequentially removing individual study. Finally, Egger's linear regression test was conducted to measure the funnel plot asymmetry, and P -value < 0.05 was considered to be statistically significant publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). All P values were two sided, and all statistical analyses were conducted by using STATA statistical software (version 11.0; Stata Corp, College Station, Texas USA).

Results

Characteristics of eligible studies

295 relevant publications were identified after initial screening based on our search strategy. The flow chart in Figure 1 illustrated the study selection procedures for DICER rs1057035 polymorphism and cancer risk. After

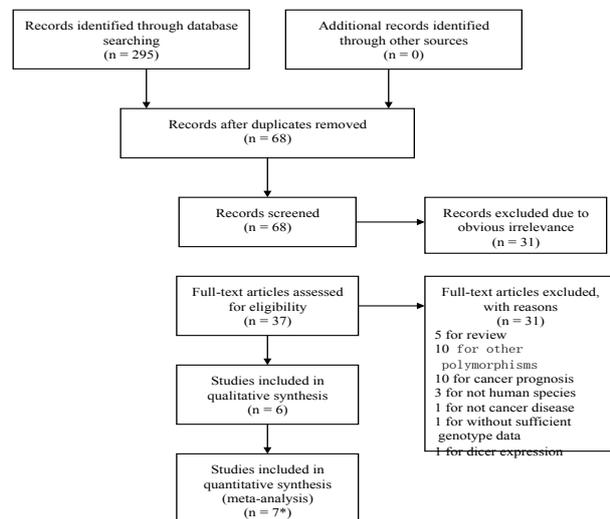


Figure 1. Flow Diagram of the Study Selection Process.

*one publication included two types of cancers, we extracted data separately for each cancer, thus 7 studies were included

careful search and selection, 6 eligible articles were met the selection criteria. Besides, 1 article (Ma et al.) provided 2 kinds of cancers (oral cancer and other head and neck cancer), thus, each type of cancer was considered as a separated case-control study. So, there were a total of 7 case-control studies with 4, 875 cases and 7, 800 controls included in our meta-analysis. The main characteristics of each study were summarized in Table 1. Among the 7 applicable studies, 6 studies were carried out in Chinese populations and 1 in Czech population. In view of control source, all of them were population-based. According to the cancer types, the 7 studies focus on bladder cancer, cervical cancer, breast cancer, oral cancer, head and neck cancer, colorectal cancer, hepatocellular carcinoma, respectively. The genotyping method in all studies was TaqMan allelic discrimination Assay. Distributions of genotypes in the controls and cases also have been given in Table 1. As shown in Table 1, the genotype distributions in the controls were all in agreement with HWE.

Association of rs1057035 and overall cancer susceptibility

Overall, when all include studies were pooled into the meta-analysis, we found that the DICER rs1057035 polymorphism was significantly associated with decreased cancer risk in allelic comparison, heterozygote and dominant genetic models (C vs T: OR=0.88, 95%CI 0.81-0.95, $p=0.002$; TC vs TT: OR=0.85, 95%CI 0.77-0.93, $p=0.001$; CC/TC vs TT: OR=0.86, 95%CI 0.78-0.94, $p=0.001$). In the subgroup analysis stratified by ethnicity, a significantly decreased cancer risk was found in Asian population (C vs T: OR=0.89, 95%CI 0.82-0.97, $p=0.008$; TC vs TT: OR=0.85, 95%CI 0.77-0.94, $p=0.001$; CC/TC vs TT: OR=0.86, 95%CI 0.79-0.95, $p=0.002$), but not in Caucasian population (Table 2, Figure 2, 3 and 4).

Heterogeneity analysis

In order to assess the heterogeneity among the included studies, Q -test and I^2 were carried out. No significant heterogeneity was observed in all the genetic models for overall and subgroup analysis ($P_Q > 0.05$ for all). Thus, fixed effects model was applied to synthesize the data for this meta-analysis (Table 2).

Table 2. Meta-analysis of DICER rs1057035 Polymorphism and Cancer Risk

Comparisons	Population	N	Test of association				Heterogeneity analysis		
			OR (95%CI)	Z	P-value	Model	Q-value	P	I^2 (%)
C vs T	Overall	7	0.88 (0.81-0.95)	3.07	0.002	F	8.53	0.202	29.6
	Asian	6	0.89 (0.82-0.97)	2.64	0.008	F	7.38	0.194	32.3
	Caucasian	1	0.76 (0.57-1.01)	1.89	0.059	F	-	-	-
CC vs TT	Overall	7	0.94 (0.69-1.27)	0.43	0.67	F	8.19	0.224	26.8
	Asian	6	1.10 (0.78-1.55)	0.53	0.598	F	4.84	0.436	0
	Caucasian	1	0.56 (0.30-1.05)	1.8	0.071	F	-	-	-
TC vs TT	Overall	7	0.85 (0.77-0.93)	3.41	0.001	F	9.89	0.13	39.3
	Asian	6	0.85 (0.77-0.94)	3.26	0.001	F	9.82	0.081	49.1
	Caucasian	1	0.81 (0.53-1.23)	1.01	0.314	F	-	-	-
CC/TC vs TT	Overall	7	0.86 (0.78-0.94)	3.31	0.001	F	9.19	0.163	34.7
	Asian	6	0.86 (0.79-0.95)	3.05	0.002	F	8.63	0.125	42.1
	Caucasian	1	0.74 (0.50-1.10)	1.49	0.137	F	-	-	-
CC vs TC/TT	Overall	7	0.97 (0.72-1.30)	0.21	0.835	F	7.94	0.242	24.4
	Asian	6	1.13 (0.80-1.59)	0.69	0.49	F	5.06	0.408	1.3
	Caucasian	1	0.62 (0.34-1.13)	1.56	0.118	F	-	-	-

F: fixed-effect model

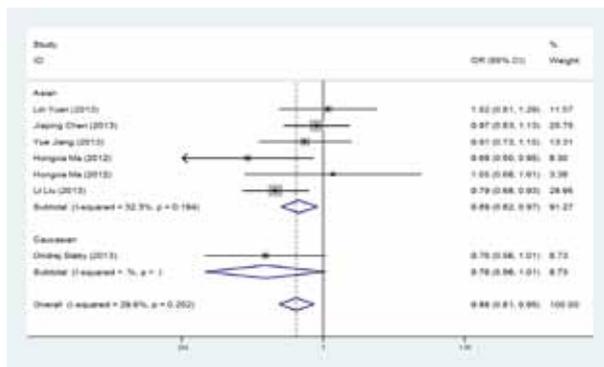


Figure 2. Forest Plot for the Association between the DICER rs1057035 Polymorphism and Cancer Risk (allelic comparison, C vs T)

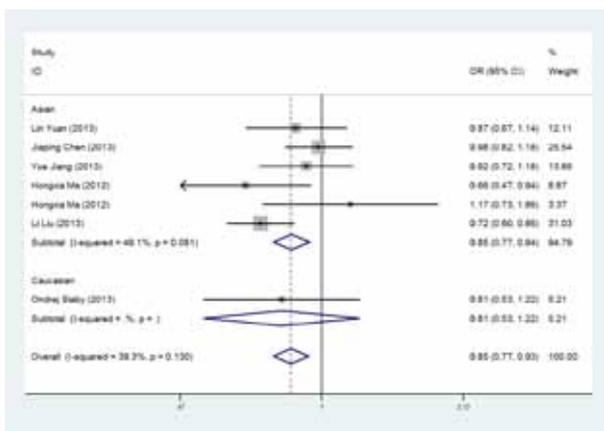


Figure 3. Forest Plot for the Association between the DICER rs1057035 Polymorphism and Cancer Risk (Heterozygote Genetic Model, TC vs TT)

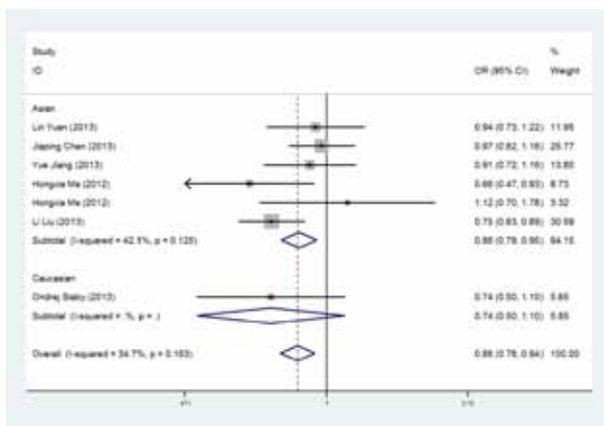


Figure 4. Forest Plot for the Association between the DICER rs1057035 Polymorphism and Cancer Risk Dominant Genetic Model, CC/TC vs TT)

Sensitivity analysis

In order to evaluate the robustness of the results of the meta-analysis, we performed the sensitivity analysis by sequentially omitting each individual study for all genetic models to determine whether the individual data affected the results or not. After removal of one independent study by Liu et al., the pooled ORs have been dramatically changed, equal to 0.91 (95%CI: 0.83-1.01) in allelic comparison model, 0.91 (95%CI: 0.81-1.01) in heterozygote genetic model and 0.90 (95%CI:

Table 3. Egger’s Linear Regression Test to Measure the Funnel Plot Asymmetric

Comparisons	Egger’s regression analysis		
	Intercept	95% CI	P-value
C vs T	-0.2	-8.21	0.847
CC vs TT	-0.21	-6.55	0.841
TC vs TT	0.18	-8.31	0.867
CC/TC vs TT	-0.06	-8.04	0.957
CC vs TC/TT	-0.16	-6.37	0.876

0.81-1.01) in dominant genetic model (Data not shown). The sensitivity analysis suggested that the results of the meta-analysis were not reliable enough and should be treated with caution.

Publication bias

Funnel plot and Egger’s linear regression test were performed to assess the potential publication bias among the included articles. The shape of the funnel plots were seemed symmetrical in all genetic models of this study (not shown). And the results of Egger’s linear regression test also showed no publication bias (Table 3).

Discussion

The present meta-analysis included seven case-control studies, including 4, 875 cancer cases and 7, 800 controls to explore the association between the DICER rs1057035 polymorphism and cancer risk. The result demonstrated that DICER rs1057035 C allele conferred a decreased cancer risk in allelic comparison, heterozygote and dominant genetic models. In the subgroup analysis by ethnicity, a significantly decreased cancer risk was observed in Asian populations but not in Caucasian populations. To the best of our knowledge, this is the first meta-analysis study examining the precision effect of DICER rs1057035 variation on overall cancer risk. miRNAs can regulate cell proliferation, cell differentiation, apoptosis by interfering (mainly inhibiting) gene expression at the posttranscriptional level and thus indicate an important role in cancer development and progression (Li et al., 2013; Hu et al., 2014; Kavitha et al., 2014; Orang and Barzegari, 2014). Many studies have investigated that miRNAs were deregulated in various types of human cancer (Guo et al., 2013; Xiu et al., 2014). DICER is a member of RNase enzymes and an important nuclease responsible for the cleavage of miRNA precursors (Liu et al., 2008). DICER possesses a complex role in cancer through its ability to regulate the maturation of miRNA (Lyle et al., 2014). Growing research suggests that dysregulated expression of DICER might play a vital role in cancer risk and prognosis (Caffrey et al., 2013; Avery-Kiejda et al., 2014; He et al., 2014). Given the critical function of DICER in miRNA processing and the involvement of miRNAs in cancer development and progression, it is rational to speculate that host genomic polymorphism of DICER may influence the cancer risk. Rs1057035 C>T polymorphism is located in 3’-untranslated region of DICER gene. In recent years, several investigators have studied the rs1057035 C>T

polymorphism and its role in the etiology of several types of cancer. However, the outcomes were inconclusive or even contradictory. In order to derive a more precise estimation of this association, we performed the current meta-analysis to systematically clarify the association between the rs1057035 C>T polymorphism and cancer risk. In overall meta-analysis, the C allele of DICER rs1057035 polymorphism was significantly associated with decreased cancer risk in allelic comparison, heterozygote and dominant genetic models. The C allele of rs1057035 polymorphism may elevate binding of has-miR-574-3p, which has been identified as a candidate tumor promoter miRNA, leading to decrease the expression of the DICER gene and thus contributes to decrease the risk of cancers (Liu et al., 2013).

We performed the subgroup analysis by ethnicity, significantly decreased cancer risks with rs1057035 C allele were found in Asian populations under allelic comparison, heterozygote and dominant genetic models. However, DICER rs1057035 polymorphism is not associated with cancer risk in Caucasian populations. One potential explanation is that only one study was Caucasian population and all other included studies were Asian populations, individual study with a small sample size has not sufficient statistical power to investigate this association. The other reason may be that different ethnicities have varied genetic backgrounds, various dietary habits and expose to different environmental factors, and thus may lead to different degrees of cancer susceptibility.

Finally, we should not ignore the results of sensitivity analysis by sequentially omitting each individual study for all genetic models to determine. The sensitivity analysis indicated that the pooled ORs had been dramatically changed after removal of one independent study by Liu et al., and thus suggested that the results of the meta-analysis were not reliable enough and should be treated with caution. This can potentially be explained by the following reasons. First, the sample size of independent study by Liu et al. (1,275 cancer cases and 2,670 controls) were larger than any other included studies, we could not obtain sufficient statistical power to detect this association when excluding this study. Second, each of the included studies has different cancer type, and the rs1057035 polymorphism may have different roles in different cancers.

Despite the significant findings from our current meta-analysis, some limitations should also be acknowledged. First, only one included study was Caucasian population and the other studies were Asian population. Thus, it is of importance to clarify the association including more studies and samples from other ethnicities for more accurate conclusions. Second, there are other important genetic polymorphisms involved in miRNAs biogenesis that may affect the cancer risk such as DROSHA, RAN, HIWI gene polymorphisms. However, we did not investigate the potential interactions of the DICER rs1057035 with them as the shortage of original data. Third, this meta-analysis was based on unadjusted estimates as not all included studies stated adjusted ORs, and a more precise estimation taking account of

other confounders such as age, sex, body mass index, smoking and drinking status, diet habit, family history and environmental exposures.

In conclusion, our meta-analysis supports that the C allele of DICER rs1057035 polymorphism probably decreases cancer risk. However, this association may be Asian-specific and the results should be treated with caution. Further well-designed studies with larger sample sizes are warranted to validate these findings and better clarify these associations.

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