RESEARCH ARTICLE

Association Between the hsa-mir-27a Variant and Breast Cancer Risk: a Meta-analysis

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Abstract

Introduction: Although a number of studies were published in the past several years on associations between hsa-mir-27a and cancer risk, the findings remain conflicting rather than conclusive. To derive a more precise effect on the association between SNP hsa-mir-27a rs895819 and breast cancer risk, we conducted a meta-analysis for the first time. Materials and Methods: Through retrieval from PubMed for the period up to August 2012, a total of four studies were identified with 3,287 cases and 4,298 controls for SNP hsa-mir-27a rs895819.We calculated summary odds ratio (ORs) and corresponding 95% confidence intervals (CIs) using a fixed effects model (when the heterogeneity was absent, P>0.10). Otherwise, the random-effects model was used. Results: We found that hsa-mir-27a rs895819 polymorphism also did not reveal any relationship with breast cancer susceptibility (AG versus AA: OR = 0.98; 95%CI, 0.73-1.32; GG versus AA: OR = 0.86; 95% CI, 0.72-1.03; AG/GG versus AA: OR = 0.92; 95% CI, 0.74-1.14), while significantly decreased risk was found among Europeans in AG versus AA and AG/GG versus AA models tested (AG versus AA: OR = 0.83; 95%CI, 0.72-0.97; GG versus AA: OR = 0.86; 95% CI, 0.71-1.05; AG/GG versus AA: OR = 0.84; 95% CI, 0.75-0.94). Conclusion: These findings suggest that hsa-mir-27a rs895819 polymorphism may play an important role in breast cancer development.

Keywords: Breast cancer - meta-analysis - gene polymorphism- ethnic groups

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Introduction

MicroRNAs (miRNAs) are about 20-nucleotide-long small noncoding RNAs, which control gene activity and affect the expression of proteins by base pairing with target mRNAs at the 3'-untranslated regions (3'UTR), leading to mRNA cleavage or translational repression (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee et al., 2001). Although the underlying biological functions are not completely clear, it has been shown to play important roles in a variety of cellular processes including apoptosis, differentiation and cell proliferation (Brennecke et al., 2003; Chan et al., 2004) Recent studies have identified that aberrant miRNAs expression correlated with various human cancers such as colon tumors, breast cancer, lung cancer, pancreatic cancer and gastric cancer (Volinia et al., 2006).

Breast cancer is the leading cause of cancer-related death in women and next to lung cancer, and is the second most common cancer in the world (Parkin et al., 2005). Up to 10% of women, who are diagnosed with breast cancer, report a family history (Hopper, 2001; Narod, 2002). According to the polygenic model of inherited breast cancer, unfavorable combinations of polymorphic genetic variants in low-penetrance susceptibility genes contribute to the excess familial breast cancer risk. Most of these susceptibility genes have not been discovered yet (Pharoah et al., 2002). In our pervious study (Hu et al., 2010), we found that MTRR A66G polymorphism is not associated with breast cancer risk, especially in Caucasians and Asians. We also found that GPX1 Pro198Leu polymorphism is not associated with breast cancer risk in Caucasians, and an elevated risk in Africans needs large-scale investigations to confirm.

A lot of single nucleotide polymorphisms (SNPs), such as rs2910164, rs11614913, rs3746444, and rs6505162 located within miR-146a, miR-196a2, miR-499, and miR-423, respectively, were repored to be associated with breast cancer risk (Le et al., 2010; Ryan et al., 2010). Although the single nucleotide polymorphisms (SNPs) in miRNAs target sites have been studied (Landi et al., 2008; Kapeller et al., 2008; Tchatchou et al., 2009), the effects of SNPs in miRNAs remain largely unknown.

MiR-27a is a key regulator on cell growth, colony formation and migration in pancreatic cancer (Ma et al., 2010). Highly expressed miR-27a and suppressed ZBTB10 expression was involved in enhanced estrogen receptor alpha expression in MCF-7 cell (Guttilla et al.,

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Table 1. Main Characteristics of Studies Included in This Meta-analysis

References	Year	Origin	Tumor type	Sample size	Genotype (case/control)			Genotyping methods	HWE
				(cases/control)	AA	AG	GG		
Sun et al.	2010	Chinese	Gastric cancer	304/304	115/145	135/119	54/40	PCR-RFLP	Yes
Yang et al.	2010	German	Breast cancer	1189/1416	576/605	486/660	127/151	TaqMan SNP assay	Yes
Zhang et al.	2011	Chinese	Breast cancer	245/243	60/75	144/109	41/59	PCR-RFLP	No
Catucci et al.	2012	Italian	Breast cancer	1025/1593	547/803	388/633	90/157	TaqMan SNP assay	No

HWE, Hardy–Weinberg equilibrium

2009; Li et al., 2010) In MDA-MB-231 breast cancer cells, miR-27a was found to be responsible for regulating specificity protein transcription factors and the G2-M checkpoint (Mertens-Talcott et al., 2007).

As breast cancer is one of the most common cancers in women, with a relatively high mortality rate, in recent years, several studies to address the association between hsa-mir-27a rs895819 variant and breast cancer risk were conducted, with contradictory results. Yang R's study (Yang et al., 2010) reported that G-variant of rs895819 might impair the maturation of the oncogenic miR-27a and thus, is associated with familial breast cancer risk, while in Catucci I's study (Zhang et al., 2012), no association was found.

Because the relatively small sample size in a single study might have low power to detect the effect of these polymorphisms on breast cancer risk, for better understanding of the association between hsa-mir-27a rs895819 variant and breast cancer risk, we conducted a meta-analysis to derive a more precise estimation of the association.

Materials and Methods

Identification and eligibility of relevant studies

We have attempted to include all the case control studies published to date on cancers with genotyping data for Hsa-miR-27a (rs895819). In order to obtain all possible articles we need, we searched the electronic literature PubMed for relevant reports (last search update Aug 2012) using the search terms "miRNA or microRNA and cancer and polymorphism".

The inclusion criteria were: (1) evaluation of the has-miR-27a rs895819 polymorphism and cancer risk; (2) study designed as case-control; and (3) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs).

Data Extraction

Two investigators (Wang B and Ma N) independently extracted data and reached consensus on all of the items. Data collected from these articles included the first author's name, year of publication, country of origin, ethnicity, type of cancer, number of cases and controls, genotype frequencies for cases and controls, characteristics of cancer cases and controls, and racial descent.

Statistical analysis

The strength of association between the has-miR-27a rs895819 polymorphisms and breast cancer risk was assessed by crude ORs with their 95% CIs. The

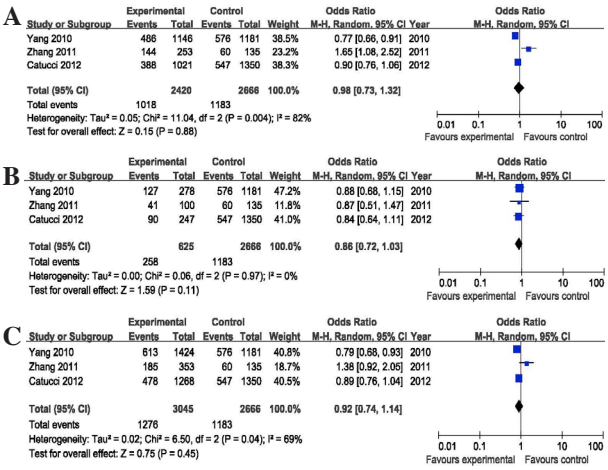

Figure 1. Overall Meta-analysis of Rs895819 in Breast Cancer. a: AG versus AA; b: GG versus AA; c: AG/GG versus AA

statistical heterogeneity among studies was checked by the chi-square-based Q-test (Higgins et al., 2002).When the heterogeneity was absent (P>0.10), the fixed-effects model was used to estimate the summarized OR (Mantel et al., 1959); otherwise, the random-effects model was used (DerSimonian et al., 1986). Subgroup analyses were processed, according to tumor type [categorized as breast cancer and other cancers (only breast cancer has more than two published studies)] and ethnicity (categorized as Asian and European descents). Publication bias of literatures was assessed using Begg's funnel plot, and it was considered representative of statistically significant publication bias with P<0.05 (Egger et al., 1997). All statistical analyses were carried out with STATA software, version 10.0.

Results

Characteristics of studies

In total, four studies fulfilled the inclusion criteria (Yang et al., 2010; Sun et al., 2010; Zhang et al., 2012; Catucci et al 2012) with 2763 cases and 3556 controls for hsa-mir-27a rs895819 polymorphism. The studies identified and their main characteristics are summarized in Table 1. Among these publications, there were two studies of European descent (Yang et al., 2010; Zhang et al., 2012), two study of Asian descent (Sun et al., 2010; Catucci et al., 2012). All of the cases were histologically confirmed as breast cancer or Gastric cancer. Controls were mainly healthy populations, and matched with age, sex, menopause status, or cancer-free.

Main results

The main results of this meta-analysis are shown in Table 2. When all the eligible studies were pooled into the

Table 2. Associations of rs895819 and Cancer Risk

	No. of Comparisons		AG vs AA	P	GG vs AA	P	AG/GG vs AA	P
Total	F	4	0.95(0.90-1.01)	0.0005	0.94(0.80-1.11)	0.08	0.92(0.83-1.01)	0.001
	R	4	1.07(0.80-1.44)	0.0004	0.98(0.75-1.29)	0.08	1.05(0.8-1.37)	0.001
Ethnicity								
Asian	F	2	1.23(1.07-1.42)	0.66	1.25(0.88-1.78)	0.06	1.45(1.13-1.86)	0.75
	R	2	1.52(1.16-1.98)	0.61	1.23(0.63-2.37)	0.06	1.45(1.13-1.86)	0.75
European	F	2	0.90(0.84-0.96)	0.27	0.86(0.71-1.05)	0.8	0.84(0.75-0.94)	0.32
(Breast cancer)	R	2	0.83(0.72-0.97)	0.2	0.86(0.71-1.05)	0.8	0.84(0.75-0.94)	0.32
Tumor type								
Breast	F	3	0.93(0.87-0.99)	0.005	0.86(0.72-1.03)	0.97	0.87(0.78-0.97)	0.04
	R	3	0.98(0.73-1.32)	0.004	0.86(0.72-1.03)	0.97	0.92(0.74-1.14)	0.04

F, Fixed-effects model; R, Random-effects model; P, values for heterogeneity

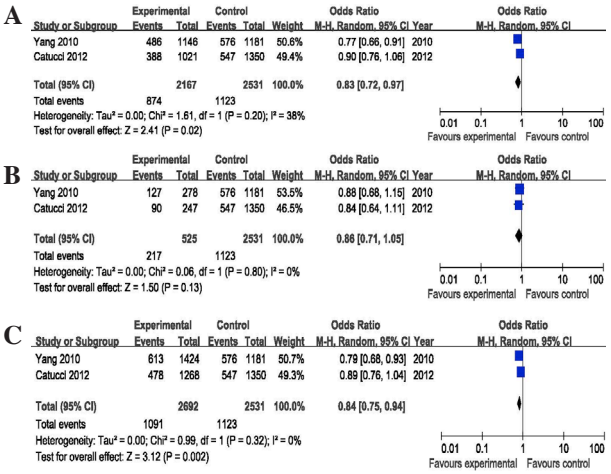

Figure 2. Subgroup Analysis (Europeans) of rs895819 in Breast Cancer. a: AG versus AA; b: GG versus AA; c: AG/GG versus AA

meta-analysis, Hsa-mir-27a rs895819 polymorphism did not reveal any relationship with cancer susceptibility.

In the subgroup analyses, Hsa-mir-27a rs895819 polymorphism also did not reveal any relationship with breast cancer susceptibility (AG versus AA: OR = 0.98; 95%CI, 0.73-1.32; GG versus AA: OR = 0.86; 95% CI, 0.72-1.03; AG/GG versus AA: OR = 0.92; 95% CI, 0.74-1.14) (Table 2, Figure 1), while significantly decreased risk was found among Europeans in AG versus AA and AG/GG versus AA models tested (AG versus AA: OR = 0.83; 95%CI, 0.72-0.97; GG versus AA: OR = 0.86; 95% CI, 0.71-1.05; AG/GG versus AA: OR = 0.84; 95% CI, 0.75-0.94) (Table 2, Figure 2).

Publication bias

We used Egger's test to access the publication bias of literatures. The result of Egger's test did not show any statistically significant evidence for publication bias for the SNPs rs895819 (P>0.05).

Discussion

Highly expressed miR-27a and suppressed ZBTB10 expression was involved in enhanced estrogen receptor alpha expression in MDA-MB-231 and MCF-7 cell, probably in turn, results in over expression of Sp proteins and Sp-dependent genes that are important for cell survival and angiogenesis (Guttilla et al., 2009; Li et al., 2009). In MDA-MB-231 breast cancer cells, miR-27a was also observed suppresses the cdc2/cyclin B inhibitor yt-1 in MDA-MB-231 cells and thereby facilitates breast cancer cell proliferation by repressing a gene that blocks cancer cell division by arresting cells at G2-M (Li et al., 2009). Hsa-mir-27a is reportedly down regulated in breast, colon, lung, pancreas, prostate and gastric cancer (Volinia et al., 2006; Porkka et al., 2007) and upregulated in head and neck cancer cell lines (Tran et al., 2007). However, the association between hsa-mir-27a rs895819 polymorphisms and breast cancer risk was not very clear now.

In this meta-analysis, the association between Hsa-mir-27a rs895819 and breast cancer risk was explored. We found that Europeans carrying AG genotype of Hsa-mir-27a rs895819 polymorphism was associated with a decreased breast cancer risk compared with AA genotype, indicating that Hsa-mir-27a rs895819 polymorphism may play an important role in breast cancer development.

However, we failed to find any association between rs895819 polymorphism and breast cancer risk in Europeans and Asian altogether.

We also failed to find any association between rs895819 polymorphism and all the cancers we analyzed in our meta-analysis.

What's more, we found that Asian carrying AG genotype of Hsa-mir-27a rs895819 polymorphism was associated with an increased cancer risk (breast cancer and gastric cancer) compared with AA genotype. In fact, the number of Asian in our meta-analysis is so small that this conclusion may not very accurate.

Some limitations of this meta-analysis should be discussed. First, the number of studies included in the meta-analysis was not very large to perform subgroup analysis. Second, lack of available information prevented a more precise evaluation with adjusted ORs by age, menopausal status and express of ER/PR or Her2, etc. Third, there was no study of other population except Europeans and Asian.

In conclusion, this meta-analysis provided evidence that Hsa-mir-27a rs895819 polymorphism in Europeans carrying AG genotype was associated with a decreased breast cancer risk compared with AA genotype. Well-designed studies with larger sample size are of great value to confirm these findings.

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