Evaluation of the pri-miR-34b/c rs4938723 polymorphism and its association with breast cancer risk

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Abstract. MicroRNAs (miRNAs or miRs) are a family of small non-coding RNAs that function as oncogenes or tumor suppressor genes. Recent evidence suggests that the pri-miR-34b/c rs4938723 variant is associated with the development of cancer. At present, there is an inconsistent association between the single-nucleotide polymorphism in pri-miR-34b/c and cancer in the limited studies. The present study is a case-control investigation, with 263 breast cancer (BC) patients and 221 control women, which examined the potential association of the pri-miR-34b/c rs4938723 polymorphisms with BC susceptibility. The polymorphisms were genotyped by the polymerase chain reaction restriction fragment length polymorphism method. No significant association between the pri-miR-34b/c rs4938723 variant and BC was identified [TC vs. TT: Odds ratio (OR), 0.87; 95% confidence interval (CI), 0.60-1.26; P=0.506; CC vs. TT: OR, 1.22; 95% CI, 0.61-2.47; P=0.600; TC+CC vs. TT: OR, 0.91; 95% CI, 0.64-1.31; P=0.648; CC vs. TT+TC: OR, 1.32; 95% CI, 0.67-2.59; P=0.498; C vs. T: OR, 0.99; 95% CI, 0.75-1.31; P=0.986]. However, a significant association was observed between the pri-miR-34b/c rs4938723 genotypes and clinicopathological characteristics, such a grade, progesterone receptor and human epidermal growth factor receptor 2 status were observed (P<0.05). These findings suggest that the pri-miR-34b/c rs4938723 variant may not be a risk factor for the development of BC.

Introduction

Breast cancer (BC), the most prevalent type of cancer in women, is a major public and global health problem and accounts for 14% of total annual cancer fatalities worldwide (1). Similarly, BC is the most common malignancy affecting Iranian women (2). Although the etiology of BC remains to be identified, genetic factors are shown to have important roles in the pathogenesis and progress of this malignancy (3-8).

MicroRNAs (miRNAs or miRs) are a class of single-stranded non-coding RNA typically 17-25 nucleotides in length that have key roles in the regulation of cellular processes by targeting mRNAs for cleavage or translational repression (9,10). They regulate the expression of genes at the post-transcriptional level by targeting the 3' untranslated regions of mRNAs. Cumulative evidence suggests that the dysregulation of miRNA expression is involved in the tumorigenesis by acting as tumor suppressors or oncogenes (11-15). Single-nucleotide polymorphisms (SNPs) or mutations in miRNA genes can affect the miRNA biosynthesis and expression of target genes, therefore resulting in diverse functional consequences and thereby possibly representing potentially important biomarkers for the prognosis of cancer (7,16-18).

The pri-miR-34b/c gene resides in a CpG island within the intron of the B-cell translocation gene 4. Therefore, it is expected that pri-miR-34b/c is co-transcribed by either the promoter of the protein-coding gene or by its own transcription initiation region, as is the case with the majority of miRNAs, whether they are intergenic or located within the introns of protein coding genes (9). A putatively functional rs4938723 C>T is located within the CpG island of the promoter of pri-miR-34b/c and is a 423-base pair (bp) upstream from the transcription start site (19). The variation of rs4938723 C to T may affect a predicted GATA-X transcription factor binding and subsequently affect the expression and carcinogenesis (19-21).

It is well known that the expression of miRNAs, particularly the miR-34 family members (such as miR-34a, miR-34b and miR-34c) can be regulated by p53. These three mature miRNAs are encoded by two different primary miRNAs. miR-34a is encoded by its own transcript, while miR-34b and miR-34c share a common primary transcript (pri-miR-34b/c) (9). The promoter region of miR-34b/c transcripts contains p53-binding sites (22).

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Numerous studies investigated the impact of miR-34b/c rs4938723 on the risk of various cancers, but the results are inconsistent (19,23-31). To the best of our knowledge, there is only one previous study regarding the impact of the miR-34b/c variant on BC risk (32). Therefore, the present case-control study aimed to evaluate the possible association between the pri-miR-34b/c rs4938723 polymorphism and susceptibility to BC in a sample of Iranian population.

Materials and methods

Patients. This case-control study consisted of 263 BC patients and 221 age-matched healthy women with no history of cancer of any type (as the control group) in Zahedan (southeast Iran). The enrolment procedure and study design were as described previously (7,33). Ethical approvals for recruitment were provided from the local Ethics Committee of Zahedan University of Medical Sciences, and informed consent was obtained from all patients and healthy individuals. Blood samples were collected in EDTA-containing tubes from the cases and controls, and genomic DNA was extracted using the salting out method, as described previously (34).

Genotyping. Genotyping of pri-miR-34b/c rs4938723 was analyzed by polymerase chain reaction (PCR) restriction fragment length polymorphism methods. Briefly, forward and reverse primers were 5'-CCTCTGGGAACCTTCTTT GACCTGT-3' and 5'-CCTGGGCCTTCTAGTCAAATA GTGA-3', respectively. A 0.20-ml reaction solution included 1 μl genomic DNA (~100 ng/ml), 1 μl forward and reverse primers and 10 μl 2X Prime Taq Premix (Genet Bio, Chungnam, Korea) and 7 μl double-distilled H_2O. The PCR conditions were justified as follows: 5 min preheating at 95˚C, 30 cycles of 95˚C for 30 sec, 57˚C for 30 sec and 72˚C for 30 sec, followed by a final extension step for 10 min at 72˚C. Following this, 10 μl of the PCR product was digested by the *Nmu*CI restriction enzyme (Fermentas, Thermo Fisher Scientific, Inc., Waltham, MA, USA). The C allele produced a 26- and 186-bp pattern, while the T allele was undigested and produced a 212-bp fragment (Fig. 1).

Statistical analysis. Statistical analysis was performed using statistical package SPSS 20 software (IBM, Corp., Armonk, NY, USA). The categorical and continuous data were analyzed using χ^2 and t-test, respectively. The association between genotypes and BC were assessed by computing the odds ratio (OR) and 95% confidence intervals (CIs) from logistic regression analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The study group consisted of 256 BC patients with an average age of 49.0±11.1 years and 221 healthy women with a mean age of 49.7±12.6 years. No significant difference was identified between the groups regarding age (P=0.549).

The genotype and allele frequencies of the pri-miR-34b/c rs4938723 T>C polymorphism in the BC patients and healthy women are shown in Table I. The results indicated that the rs4938723 polymorphism was not significantly associated with the BC risk in the codominant (TC vs. TT: OR, 0.87; 95% CI, 0.60-1.26; P=0.506; CC vs. TT: OR, 1.22; 95% CI, 0.61-2.47; P=0.600), dominant (TC+CC vs. TT: OR, 0.91; 95% CI, 0.64-1.31; P=0.648), recessive (CC vs. TT+TC: OR, 1.32; 95% CI, 0.67-2.59; P=0.498) and overdominant (TC vs. TT+CC: OR, 0.84; 95% CI, 0.59-1.21; P=0.361) inheritance models tested. Furthermore, the rs4938723 C allele was not a risk factor for BC (OR, 0.99; 95% CI, 0.75-1.31; P=0.986).

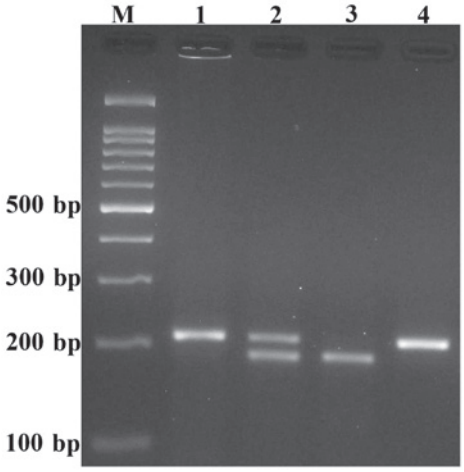

Figure 1. Image of the pri-miR-34b/c rs4938723 T>C polymorphism using the polymerase chain reaction restriction fragment length polymorphism method. The C allele was digested by the *Nmu*CI restriction enzyme and produced a 26- and 186-base pair (bp) pattern, while the T allele was undigested (212-bp fragment). M, DNA marker; lanes 1 and 4, TT; lane 2, TC; lane 3, CC.

The genotype of the polymorphism in the controls and cases were in Hardy-Weinberg equilibrium (χ^2=3.49, P=0.061 and χ^2=0.227, P=0.624, respectively).

Associations between the variant and clinicopathological characteristics. The association between the pri-miR-34b/c rs4938723 variant and clinicopathological characteristics, including age, body mass index (BMI), tumor size, tumor stage, tumor grade, lymph node metastasis, estrogen and progesterone receptors (ER and PgR), and human epidermal growth factor receptor 2 (HER2) are shown in Table II. The results showed a significant association between the pri-miR-34b/c rs4938723 variant and grade, PgR and HER2 status of BC patients (P<0.05). No significant association was identified between the rs4938723 polymorphism and age, BMI, tumor size, lymph node metastasis, stage and histological type of BC patients (P>0.05).

Discussion

The present study investigated the impact of the pri-miR-34b/c rs4938723 polymorphism on the BC risk in a sample of the Iranian population. The data showed that the rs4938723 variant of pri-miR-34b/c was not associated with the risk of BC population. By contrast, a significant association was identified between the pri-miR-34b/c rs4938723 genotypes and clinicopathological characteristics, such as grade, PgR and HER2 status (P<0.05). In agreement to this finding, Bensen *et al* (32) identified no significant association between the pri-miR-34b/c

Table I. Association of the pri-miR-34b/c rs4938723 T>C polymorphism and risk of breast cancer.

pri-miR-34b/c rs4938723	Case, n (%)	Control, n (%)	OR (95% CI)	P-value
Codominant				
TT	125 (47.5)	100 (45.2)	1.00	-
TC	115 (43.7)	106 (48.0)	0.87 (0.60-1.26)	0.506
CC	23 (8.7)	15 (6.8)	1.22 (0.61-2.47)	0.600
Dominant				
TT	125 (47.5)	100 (45.2)	1.00	-
TC+CC	138 (52.5)	121 (54.8)	0.91 (0.64-1.31)	0.648
Recessive				
TT+TC	240 (91.3)	206 (93.2)	1.00	-
CC	23 (8.7)	15 (6.8)	1.32 (0.67-2.59)	0.498
Overdominant				
TT+CC	148 (56.3)	115 (52.0)	1.00	-
TC	115 (43.7)	106 (48.0)	0.84 (0.59-1.21)	0.361
Allele				
T	365 (69.4)	306 (69.2)	1.00	-
C	161 (30.6)	136 (30.8)	0.99 (0.75-1.31)	0.986

OR, odds ratio; CI, confidence interval.

rs4938723 variant and risk of BC, and reported that this polymorphism was associated with BC survival (CC vs. TT+TC: hazard ratio, 0.57; 95% CI, 0.37-0.89; P=0.01).

Recently, Chen *et al* (26) performed a case-control study and revealed that pri-miR-34b/c rs4938723 significantly increased the risk of papillary thyroid carcinoma (PTC). In addition, a significant upregulation of pri-miR-34b was observed in PTC patients. Zhu *et al* (23) found no significant association between the pri-miR-34b/c rs4938723 variant and esophageal squamous cell carcinoma (ESCC) in Kazakh patients in northwest China. However, Zhang *et al* (24) reported that pri-miR-34b/c rs4938723 significantly decreased the risk of ESCC in Chinese populations.

It has been reported that the potentially functional SNP rs4938723 in the promoter region of pri-miR-34b/c increased the risk of hepatocellular carcinoma (HCC) in Chinese and Korean populations (19,35). However, the results of a meta-analysis performed by Liang *et al* (31) did not support an association between the rs4938723 variant and HCC risk. A meta-analysis performed by Liu *et al* (36) reported a significant association between the rs4938723 variant and cancer risk. Subsequent to stratifying by ethnicity and cancer type, the CT genotype of rs4938723 was significantly associated with an increased cancer risk in the Asian population, and the C allele and CT genotype significantly increased the risk of HCC, but the rs4938723 CT genotype significantly decreased the risk of colorectal cancer. Yi *et al* (37) conducted a meta-analysis and identified that the pri-miR-34b/c rs4938723 TC heterozygote increased the overall cancer risk. However, the CC genotypes of rs4938723 were associated with an increased HCC risk but also with a decreased colorectal cancer risk (37). Tao *et al* (29) found no significant association between the hsa-miR-34b/c rs4938723 polymorphism and overall cancer risk. Furthermore, subgroup analysis suggested that the variant CT genotypes were associated with an increased risk of HCC compared with the wild-type TT genotype. However, the CC/TT genotype decreased the risk of colorectal cancer compared with TT genotype.

A meta-analysis performed by Ji *et al* (25) showed that the pri-miR-34b/c rs4938723 variant significantly decreased the risk of digestive tract cancer. Pan *et al* (27) reported that the CT and CT/CC genotypes of the miR-34b/c rs4938723 were associated with a significantly decreased risk of gastric cancer compared with the TT genotype. It has been shown that the pri-miR-34b/c rs4938723 C allele may increase the susceptibility to renal cell carcinoma by decreasing the activity of pri-miR-34b/c promoter (30).

The results of a previous meta-analysis indicated that the pri-miR-34b/c rs4938723 polymorphism may decrease the susceptibility to colorectal cancer (28). A meta-analysis performed by Wang *et al* (38) suggests that the pri-miR-34b/c rs4938723 polymorphism may be associated with the risk of cancer, including nasopharyngeal cancer, osteosarcoma and renal cell cancer. Tong *et al* (39) reported that the rs4938723 variant significantly decreased the risk of Chinese childhood acute lymphoblastic leukemia.

There is no clear explanation for the controversy of the results regarding the impact of the pri-miR-34b/c rs4938723 variant on different types of cancer. Ethnicity, genetics and/or environmental factors, as well as gene-diet interaction, may interact in diverse modes to either increase or decrease the risk of various types of cancers in different areas.

In conclusion, no significant association was identified between pri-miR-34b/c rs4938723 polymorphism and the risk of BC. However the present findings indicate that this variant may be associated with clinicopathological characteristics.

Table II. Correlation between the miR-34b/c rs4938723 T>C genotypes and clinical characteristics of breast cancer patients.

	miR-34b/c rs4938723 T>C genotypes			
Variables	TT	CT	CC	P-value
Age, years				0.535
≤50	63	68	14	
>50	56	46	9	
Mean BMI ± SD, kg/m^2	25.8±3.2	25.6±3.3	26.4±2.5	0.489
Tumor size, cm				0.453
≤2	44	34	9	
>2	72	76	13	
Lymph node metastasis status, n				0.848
Yes	34	30	5	
No	44	43	9	
Grade, n				0.028
I	17	23	5	
II	74	56	7	
III+IV	16	21	8	
Stage, n				0.941
I	21	20	2	
II	44	44	10	
III	34	28	7	
IV	19	18	3	
Histology, n				0.890
Ductal carcinoma	85	72	16	
Other	29	36	7	
Estrogen receptor, n				0.004
Positive	65	67	21	
Negative	46	35	1	
Progesterone receptor, n				0.007
Positive	58	72	16	
Negative	53	28	6	
HER2, n				0.031
Positive	56	64	7	
Negative	61	45	16	

BMI, body mass index; SD, standard deviation; HER2, human epidermal growth factor receptor 2.

Population-based studies with larger sample sizes of different ethnicities and long-term follow-up are required to confirm this finding.

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