Association between Genetic Polymorphisms of miR-1307, miR-1269, miR-3117 and Breast Cancer Risk in a Sample of South East Iranian Women

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Abstract

Introduction: MicroRNAs (miRNAs) play an essential role in the susceptibility and development of cancer cells. Objective: Examining the dependency of breast cancer risk with genetic polymorphisms of miR-1307, miR-1269, and miR-3117 in a sample of Iranian women (southeast region). Methods: The case-control study consisted of 520 individuals (260 diagnosed BC patients, 260 healthy individuals). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used for genotyping of miR-1307 rs7911488, miR-1269 rs73239138, and miR-3117 (rs4655646 and rs7512692) polymorphisms. Results and Conclusion: This study provided evidence that miR-1307 rs7911488 polymorphism significantly reduced the risk of BC in heterozygous AG genotype, as well as dominant (AG+GG) genotype and G allele. A significant correlation was found between dominant (AA+AG) genotype, the A allele and protection against BC due to miR-1269 rs73239138 in the sample of study. In contrast, our findings suggested that AG genotype and G allele of miR-3117 rs4655646 polymorphism could increase BC’s susceptibility among the southeastern Iranian females. The miR-3117 rs7512692 variant also increased the risk of BC in codominant, dominant and recessive models, as well as the T allele. The possible dependency of miR-1307, miR-1269, and miR-3117 variants with patients’ clinicopathological characteristics and BC was also studied. It was concluded that there is a correlation between miR-3117 rs7512692 variant and tumor grade (p=0.031); also, a correlation between miR-1269 rs73239138 variant and progesterone receptor status (p=0.006). The current investigation revealed that miR-1307, miR-1269, and miR-3117 polymorphisms might play a crucial role in the Iranian population’s vulnerability to BC.

Keywords: Breast cancer- microRNA- polymorphism- cancer susceptibility

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Introduction

Breast cancer (BC), one of the most frequent carcinomas amongst women, is the second leading cancer-related cause of death in women worldwide (Bray et al., 2018). Breast cancer may occur in several parts of the breast, including lobules, ducts, and connective tissue. However, it commonly occurs in the inner lining of milk ducts or the lobules which produce milk. Out of control cell division in these tissues could invade other breast tissues and move to the lymph nodes and cause metastasis to other organs (Winer, 2001; Yu, 2019; Umami et al., 2020), including bones, lung, liver, and brain (Eckhardt et al., 2012; Vickers, 2017).

The breast cancer incidence rate ranges widely all over the world. According to GLOBOCAN 2018 report, the global average BC incidence rate was 46.3 per 100000 individuals, while Australia and New Zealand reported the highest rate (94.2) and South-Central Asia recorded the lowest rates (25.9) (Bray et al., 2018). Based on GLOBOCAN 2018, the Iranian BC incidence rate was 31.0 per 100,000 (Bray et al., 2018).

Screening of numerous BC patients demonstrated that the risk of BC might be associated with several factors, including genetic mutation, family history, lifestyle, alcohol consumption, level of estrogen and progesterone...
hormones, and physical activity (Jayasekara et al., 2016; Pizot et al., 2016; Dall and Britt, 2017; Shiyabola et al., 2017; Bertoni et al., 2019; McTiernan et al., 2019). Numerous genetic mutations might occur in the human genome, responsible for the permanent alternation in DNA or RNA sequences. A Single Nucleotide Polymorphism (SNP) is a replacement of a nucleotide at several positions in the human genome (Kitts and Sherry, 2002). Studies by Dr. Hashemi’s research team showed that there had been relationships between SNPs and different diseases, including breast cancer (Hassanzarei et al., 2017), prostate cancer (Hassanzarei et al., 2017; Sattarifard et al., 2019), lung cancer (Moazeni-Roodi et al., 2019), colorectal cancer (Hashemi et al., 2018), bladder cancer (Sadeghi-Bojd et al., 2019), nephrotic syndrome (Sadeghi-Bojd et al., 2019), nonsyndromic cleft lip (Rafighdoost et al., 2015; Rafighdoost et al., 2017; Rafighdoost et al., 2018; Rafighdoost et al., 2019), and nonalcoholic fatty liver disease (Hashemi et al., 2013).

The transcriptome of genome and tiling array studies provided evidence that over 90 percent of humans’ genomic DNA is not translated to any proteins (Non-coding RNAs), and only two percent is expected to translate into functional proteins (Rinn and Chang, 2012). According to the original transcription size, non-coding RNAs are clustered into two main groups, the small Non-Coding RNAs (shorter than 200 nucleotides), including miRNAs and snoRNAs piwiRNAs, and siRNAs; and long non-coding RNAs which contain more than 200 nucleotides (Bhan and Mandal, 2015). It is shown that miRNAs have multiple functions, including gene regulation. Matured miRNA could bind to the 3’-untranslated section (3’UTR) of specific miRNAs, which might lead to regulating gene expression (Meijer et al., 2013; Peng and Croce, 2016). miRNAs are key regulators of the human’s transcriptome and function as oncogenes or tumor suppressor genes depending on their target genes’ function. Recent evidence showed that genetic variations in miRNA genes could affect the expression, biogenesis of miRNA, or target selection, which in turn affects their target genes’ expression and the cancer progress (Hu et al., 2008; Omrani et al., 2014, Liu et al., 2016; Wang et al., 2016; Sibin et al., 2017; Wu et al., 2018). miR-1307-3p was recently recognized as a cancer-related miRNA. The studies showed that miR-1307-3p could be involved in critical biological pathways, including proliferation, differentiation, lymphocytes activation, nucleotide synthesis, and metabolism (Zhao et al., 2015; Qiu and Dou, 2017; Yang et al., 2018). The relation between miR-1307-3p and cancers, including renal cell carcinoma (RCC) (Garcia-Donas et al., 2016), ovarian cancer (Zhou et al., 2015), colorectal cancer (Tang et al., 2015) and breast cancer (Shimomura et al., 2016) has been previously reported. Furthermore, recent BC research showed that the elevated level of miR-1307-3p in serum could be used to identify the BC patients in their early stages (Shimomura et al., 2016). miR-1269 is located at human chromosome 4, and recent studies suggested that it could act as an oncomir (ono miRNA) (Yang et al., 2014; Bu et al., 2015). The correlation between miR-1269 and prostate cancer metastasis and progression of primary hepatocellular carcinoma (HCC) has been approved in recent studies (Yang et al., 2014; Bu et al., 2015). Despite all these documents, other investigations show the controversial function of mir-1269 as a tumor suppressor gene in gastric cancer (Li et al., 2017) and HCC (Xiong et al., 2015). miR-3,117 is located at human chromosome 1. The significant association between mir-3117 and many types of cancers, including colorectal cancer (Neerinx et al., 2015), HCC (Cui et al., 2017), and acute lymphoblastic leukemia (Gutierrez-Camino et al., 2018) was recently examined. No studies have investigated the susceptibility of BC risk with miR-3117 though.

In the current this investigation, the correlation between miR-3117 rs4655646, miR-3117 rs7512692, miR-1269 rs73239138, miR-1307-3p rs7911488 and the risk of BC in a sample of southeast Iranian women was evaluated.

Materials and Methods

Patients

Our population-based case-control study consists of 520 individuals, including 260 histologically confirmed BC patients and 260 age-matched population-based healthy women with no history of any type of cancer and (samples are not related to the patients of the study). The protocol of this study has been designed based on previous investigations (Danesh et al., 2018; Hashemi et al., 2018; Karami et al., 2020). The Institutional Review Board approved this study to be conducted at the Zahedan University of Medical Sciences (IR.ZAUMS.REC.1397.385). Proper consent was obtained from all participants. The genomic DNA samples were extracted using the salting-out technique and were collected in separate special tubes containing EDTA (Hashemi et al., 2013).

Genotyping

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) was used to genotype miR-1269, miR-1307, and miR-3117 genes polymorphisms. The protocol used for this research, previously used by Dr. Hashemi’s lab, is as follow (Hassanzarei et al., 2017; Payelghadr et al., 2018; Nazarian et al., 2019):

1. The volume for assembling 17 µl of the reaction solution in each PCR tube is presented in Table 1.

2. The sequences of primers used for detection of miR-1307, miR-1269 and miR-3117 polymorphisms are listed in Table 2.

3. PCR thermal cycling conditions, which were used for amplification of miR-1307, miR-1269 and miR-3117 polymorphisms, are listed in Table 3.

4. PCR products were digested with corresponding restriction endonucleases.

5. In the last pace, a UV transilluminator was used to detect and visualize the digested fragments, which were separated by agarose gel electrophoresis. Briefly, for miR-1307 rs7911488, the HhaI restriction enzyme digested the G allele and produced 18 and 176 base pair (bp) pattern, while the A allele was undigested (194 bp fragment) (Figure 1A), miR-1269 rs73239138 A allele was
Digestion by BstXI restriction enzyme and produced a 58 and 237 bp fragments, while the G allele was undigested (295 bp fragment) (Figure 1B), miR-3117 rs4655646 G allele was digested by Taq restriction enzyme and produced 39 and 143 bp fragments, while A allele was undigested (182 bp fragment) (Figure 2A), and Hpy188III restriction enzyme digested miR-3117 rs7512692 C allele and produced 21 and 136 bp fragments, while T allele was undigested (157 bp fragment) (Figure 2B).

Statistical analysis

Statistical analyses were done using SPSS 22 software. To estimate the Hardy–Weinberg equilibrium (HWE) among the controls, the χ² test was used. The correlation between the genotypes and risk of BC was measured by odds ratios (ORs) with 95% confidence intervals (Erdmann, Szymanski et al.). Unconditional logistic regression analysis was applied to assess the relationship between miR-1269, miR-1307 and miR-3117 genes polymorphisms and BC risk. The p-value of less than 0.05 was considered statistically significant.

Results

The present study included 520 participants. The study consisted of 260 females who were diagnosed with breast cancer with an age group of 48.09 ±10.59 and 260 healthy females with an age group of 46.26±10.72 recruited in the study. There was not a significant age difference between the patient and control groups (p=0.052). Frequency of alleles and genotyping of miR-1307, rs7911488, miR-1269, rs73239138, miR-3117, rs4655646 and rs7512692 polymorphisms among the study group and the control group are presented in Table 4./

Our findings show that miR-1307 rs7911488 polymorphism has significantly reduced the risk of BC in heterozygous genotype AG (OR=0.28, 95%CI=0.19-0.40, P<0.001, A/G vs A/A), dominant (OR=0.30, 95%CI=0.21-0.43, P=0.001, A/G+G/G vs A/A), and G allele (OR=0.50, 95%CI=0.38-0.67, P=0.001, G vs A). Similarly, the miR-1269 rs73239138 G>A polymorphism significantly decreased the risk of BC in dominant (OR=0.64, 95%CI=0.42-0.98, P=0.048, A/A+A/G vs G/G), and A allele (OR=0.66, 95%CI=0.45-0.93, P=0.041, A vs G).
Our investigation also showed that miR-3117 rs4655646 is a risk factor for BC in heterozygous genotype AG (OR=1.93, 95%CI=1.05-3.51, P=0.030, A/G vs A/A), and G allele (OR=2.08, 95%CI=1.20-3.62, p=0.014, G vs A). So as miR-3117 rs7512692 C>T polymorphism increased the risk of BC in C/T heterozygous genotypes (OR=4.58, 95%CI=2.87-7.44, p=0.001, C/T vs C/C) and T/T homozygous (OR=12.80, 95%CI=6.72-24.12, p<0.001, T/T vs C/C), dominant (OR=5.70, 95%CI=3.58-9.06, p<0.001, C/T+T/T vs C/C), recessive (OR=4.27, 95%CI=2.55-7.22, p<0.001, T/T vs C/C+C/T) and T allele (OR=2.75, 95%CI=2.14-3.54, p<0.001, T vs C) genetic models.

Furthermore, the correlation between the variants and clinicopathological characteristics, including age, size of the tumor, lymph node, histology, tumor grade, the status of estrogen and progesterone receptors was examined. Our results showed that there was a significant association between miR3117 rs7512692 C>T and tumor grade (p=0.031) and miR-1269 rs73239138 G>A with progesterone receptor status (p=0.006) Table 5.

Discussion

Recent investigations showed that miRNAs are involved in regulating more than 30% of the human genome (Filipowicz et al., 2008). It is suggested that miRNAs may be involved in many biological pathways, including proliferation and metastasis. However, the primary function of miRNAs has not been identified yet (Bueno et al., 2008). Several studies have shown that there is a strong correlation between abnormal expression of miRNAs and risk of BC (Qi et al., 2015; Danesh et al., 2018; Moazeni-Roodi et al., 2019). Recently, several investigations have been conducted on miR-1307, miR-1269, and miR-3117 polymorphisms to clarify the direct association of these variants in cancer susceptibility.

The association of microRNA’s such as miR-1307, miR-1269, and miR-3117 polymorphisms with risk of cancer has been demonstrated (Gan et al., 2015; Xiong et al., 2015; Cui et al., 2017; Bao et al., 2018; Wang and Zhu, 2018; Han et al., 2019).

The current investigation in this study, for the first time in Iran, has examined the possible association between miR-1307 rs7911488, miR-1269 rs73239138, miR-3117, rs4655646, rs7512692 and the risk of BC in a sample of women in southeast of Iran was studied.

Current findings proposed that the AG genotype, as well as the G allele of rs7911488 of miR-1307 polymorphism, significantly reduced the risk of BC among the sample group of southeast Iranian women. Only two studies have already investigated the impact of rs7911488 miR-1307 on cancer so far. For the first time, Tang et al., (2015) showed that miR-1307 is involved in the overexpression of Bcl2 and increasing the risk of
miR-3117 variants increased the risk of colorectal cancer, which is contradictory to our results. The contradiction between these two findings could be due to the different ethnicities of samples and cancer types being studied.

Furthermore, Qi et al., (2017) showed that *miR-1307* polymorphism is involved in capectabine-based chemotherapy in patients who were diagnosed with colon cancer. Their results showed that the response rate of capectabine-based treatment in the patients with TC genotype was the highest while CC genotype had the lowest chemotherapy response (Min et al., 2017). *miR-1269* was identified as an onco miRNA, which could act as a tumor suppressor (Bu et al., 2015). *miR-1269* is located at chromosome 4. So far, only three studies have examined the relation between *miR-1269 rs73239138* and vulnerability to cancer. In 2015, Guanying et al., (2015) observed that the AG and AA genotype of *miR-1269 rs732-39138* decreased the risk of susceptibility to HCC in the southern Chinese population (Xiong et al., 2015). In contrast to the previous findings, Pei Min et al. showed that *miR-1269 rs73239138* considerably increased the risk of HCC in the eastern Chinese population (Min et al., 2017). In 2017, the results of Wenshuai Li et al. showed that the downregulating of Zinc Finger Protein70 (ZNF70) by *miR-1269* variant rs73239138 was a protective factor against gastric cancer (Li et al., 2017). Our current results suggest that there is a significant correlation between dominant (AA+AG) genotype, the A allele and protection against BC due to *miR-1269 rs73239138* in the Iranian population.

It is important to note that the study of the correlation between polymorphisms in a specific type of cancer and a certain genotype is heavily dependent on the type of cancer as well as the ethnic population under investigation. This may cause possible contradictions among different research results.

*miR-3117* is located at human chromosome 1. The association between the development and metastasis of colorectal cancer and *miR-3117* was recently confirmed (Neerincx et al., 2015). The studies showed that overexpression of *miR-3117* could promote cell proliferation in HCC (Cui et al., 2017). Few studies have been done about researched *miR-3117* and susceptibility to cancer. No study has reported the role of *miR-3117 rs4655646* and *rs7512692* polymorphisms in cancer. Our investigations on *miR-3117* rs4655646 polymorphism showed that the AG genotype, as well as G allele, increased the risk of BC in the sample of Iranian women. Similarly, our findings suggest that *miR-3117 rs7512692* variant increased the risk of BC in CT and TT genotypes as well as T allele.

In conclusion, our findings suggest that *miR-1307 rs7911488* and *miR-1269 rs73239138* polymorphisms reduced the risk of BC in women within the southeast region of Iran. However, *miR-3117 rs4655646* and *miR-3117 rs7512692* variants increased the risk of developing BC in the sample of Iranian women. Our findings could help scientists better understand the pathways that cause the BC development of BC and possible new methods and biomarkers to predict and fight this deadly disease.
Table 5. The Association of miR-1307, miR-1269 and miR-3117 Polymorphisms with Clinicopathological Characteristics of Breast Cancer (BC) Patients

| Characteristic of patients | miR-1307 rs7911488 P-value | miR-1269 rs73239138 P-value | miR-3117 rs4655646 P-value | miR-3117 rs7512692 P-value |
|---------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Age, years                | AA  | AG  | GG  | 0.731 | 0.63 | 0.766 | 0.835 |
| ≤50                       | 91  | 55  | 7   |       |     |       |       |
| >50                       | 63  | 35  | 7   |       |     |       |       |
| Tumor size, cm            | 0.133 | 0.991 | 0.709 | 0.743 |
| ≤2                        | 34  | 17  | 0   |       |     |       |       |
| >2                        | 100 | 66  | 11  |       |     |       |       |
| Histology                 | 0.924 | 0.064 | 0.694 | 0.057 |
| Ductal carcinoma          | 0.416 | 0.094 | 0.57  | 0.031 |
| Others                    | 126 | 74  | 12  |       |     |       |       |
| Lymph node metastasis     | 0.817 | 0.619 | 0.362 | 0.123 |
| No                        | 75  | 43  | 8   |       |     |       |       |
| Yes                       | 56  | 37  | 5   |       |     |       |       |
| Grade                     | 0.416 | 0.094 | 0.57  | 0.031 |
| I                         | 16  | 12  | 51  |       |     |       |       |
| II                        | 66  | 36  | 34  |       |     |       |       |
| III+IV                    | 51  | 5   | 4   |       |     |       |       |
| Stage                     | 0.155 | 0.368 | 0.67  | 0.299 |
| I                         | 9   | 5   | 0   |       |     |       |       |
| II                        | 69  | 38  | 3   |       |     |       |       |
| III                       | 36  | 25  | 5   |       |     |       |       |
| IV                        | 16  | 11  | 5   |       |     |       |       |
| Estrogen receptor status  | 0.556 | 0.082 | 0.593 | 0.655 |
| Positive                  | 99  | 54  | 7   |       |     |       |       |
| Negative                  | 47  | 30  | 6   |       |     |       |       |
| Progesterone receptor status | 0.834 | 0.006 | 0.187 | 0.082 |
| Positive                  | 94  | 51  | 8   |       |     |       |       |
| Negative                  | 50  | 32  | 5   |       |     |       |       |
| HER2 status               | 0.392 | 0.371 | 0.279 | 0.562 |
| Positive                  | 43  | 29  | 6   |       |     |       |       |
| Negative                  | 103 | 55  | 7   |       |     |       |       |

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Author Contribution

Sahel Sarabandi: preparation of the project’s proposal, sample collection and doing experiments on the bench (qPCR, genotyping).

Hedieh Sattarifard: preparation of the first draft of the manuscript, and statistical analysis of data, and preparation of the tables and figures for the manuscript.

Mohammad Kiumarsi: preparation of the first draft of the paper, preparation of the second draft with Hedieh considering English development.

Shima Karami: sample preparation and doing benchwork with Sahel.

Mohsen Taheri and Gholamreza Bahari: co-supervision of students (Shima, Sahel) after Professor Hashemi passed away. They also gave scientific advice to Hedieh and Mohammad during manuscript preparation.

Professor Mohammad Hashemi: the primary supervisor of the project and co-designed the project with Dr. Saeid Ghavami. He was the primary supervisor of Shima and Sahel and finalized the proposal and arranged with the clinician to collect the samples and prepare the grant to support the project.

Dr. Saeid Ghavami: the leader of the team, did the final proofread of the manuscript (scientific language), interpreted the results with students, co-design the project with Professor Hashemi, and proofread the thesis extracted from the project.
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