Received: 31 August 2018 | Revised: 8 October 2018 | Accepted: 4 November 2018

DOI: 10.1002/jcla.22826

RESEARCH ARTICLE

WILEY

Association of the study between *LncRNA-H19* gene polymorphisms with the risk of breast cancer

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Abstract

Background: The H19 is a maternally expressed imprinted gene transcribing a long noncoding RNA (lncRNA), which has previously been reported to be involved in tumorigenesis and cancer progression. The aim of this study was to evaluate the associations between two lncRNA-H19 (rs3741219 T>C and rs217727 C>T) gene polymorphisms with the risk of breast cancer (BC).

Methods: In a case-control investigation, we evaluated 150 BC patients and 100 cancer-free subjects in East Azerbaijan Province of Iran. To assess two gene polymorphisms, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used.

Results: The genotype frequencies of two lncRNA-H19 (rs217727 C>T and rs3741219 T>C) gene polymorphisms TT + TC/CC and CC + CT/TT have not shown a statistically significant association with the risk of BC ($P = 0.065$; OR = 0.967; 95% CI, 0.938-0.996) and ($P = 0.510$; OR = 1.583; 95% CI, 0.399-6.726), respectively. In addition, our findings revealed a significant differences in allele frequencies in lncRNA-H19 rs217727 C>T polymorphism between groups ($P = 0.033$; OR = 1.985; 95% CI, 1.048-3.761).

Conclusion: Our findings suggested that rs217727 C>T polymorphism may be involved in the pathogenesis of BC, whereas rs3741219 T>C variation may not be involved in the genetic background of BC in Iranian.

KEYWORDS

breast cancer, *H19* gene, *LncRNA*, *LncRNA-H19*

1 | INTRODUCTION

Breast cancer (BC) is one of the most prominent causes of illness and death worldwide. BC is a malignant proliferation of epithelial cells that cover lacrimal ducts or lobules. Risk factors such as premenstrual meningitis, premature menopause, infertility, or age at the time of first birth may be responsible for one-third of cases of BC. With the improvement of early diagnosis and treatment regime, the mortality rate of BC significantly decreased.[1] Breast cancer is a complex disease and multifactorial process, in which a large number of epidemiological studies have been conducted to identify other risk factors for BC.[2] Previous genomic research has provided evidence to support single-nucleotide polymorphisms (SNP) in several genes associated with the risk of BC and contributed as carcinogenic agents.[3,4] The total of SNPs has been identified in cancers; nearly 10 percent were associated with a change in the amino acid sequence, while a large proportion occurred in the coding or noncoding regions.[7] This highly questionable observation led to a wide range of research into the discovery of the function of noncoding sites and roles of the cancer development. These studies have led to the identification of *lncRNA*, which was transcribed from noncoding sites and may be increased the susceptibility of

risk cancer.[8,9] The *lncRNA-H19* gene is a maternally expressed and coded a long noncoding RNA that has been reported previously involved in the tumor progression.[11]

LncRNA-H19 is a carcinogenic gene located at 11p15.5 of human chromosome, which is abnormally expressed in some types of tumors and acts as a tumor suppressor gene (TSG). According to the evidence, it suggests that genetic changes in *lncRNA-H19* play an important role in cancer development.[12,13] To date, few studies have attempted to reveal the association between *lncRNA-H19* gene polymorphism with the risk of BC.[16,17] According to the previous findings, we assume that two SNPs in *lncRNA-H19* may be related to the risk of BC in Iranian. However, the relationship between *lncRNA-H19* polymorphism and BC remained unclear. The purpose of this investigation was to examine the association between two SNPs in *lncRNA-H19* (rs3741219 T>C and rs217727 C>T) with the risk of BC.

2 | MATERIAL AND METHODS

2.1 | Patients

In case-control investigation, we recruited a convenience peripheral blood sample of 150 BC women and 100 cancer-free women, which were referral to the Tabriz International Hospital of Iran, during May 2015 to November 2017. Control group consisting of 100 healthy women without any diseases, especially chronic diseases and matched age and ethnicity, from over 2000 people, was selected. A questionnaire for women's data was filled and used. All patients were recently diagnosed with BC according to the pathological procedures.

The sample was obtained according to protocols confirmed by the ethics committee of the Tabriz University of Medical Sciences, and signed informed consent and questionnaire were received from each case. Individuals who underwent chemotherapy, radiotherapy, or proposed therapy were excluded. In addition, Ethics and Human Rights Committee in Tabriz University of Medical Sciences approved the present investigation. We have obtained 2 mL peripheral blood samples from of 100 healthy individuals and 150 patients with BC (according to inclusion and exclusion criteria) in anticoagulant tubes containing EDTA, stored at −80°C prior to DNA extraction.

2.2 | Genotyping

For determination of genotype frequencies of two *lncRNA-H19* gene polymorphisms, we used PCR-RFLP method and the following sequence of forward and reverse primers: 5′-CCCCCTGCGGCGGACGGTTG-3′ and 5′-GGCGTAATGGAATGCTTCAA-3′ for *lncRNA-H19* (rs3741219) polymorphism, and 5′-ACTCACGAATCGGCTCTGGAAGGTG-3′ and 5′-ATGTGGTGGCTGGTGGTCAACGGT-3′ for *lncRNA-H19* (rs217727) polymorphism.[16]

The PCR of *lncRNA-H19* (rs217727) gene polymorphism amplification consists of 1 μL (10 pmole) each of the primers, 2 μL genomic DNA (50 ng), 13 μL Master Mix Red 2× (Ampliqon, Odense, Denmark), and 8 μL distilled water and for *lncRNA-H19* (rs3741219) 1 μL (10 pmole) each of the primers, 1 μL genomic DNA (50 ng), 14 μL Master Mix Red 2× (Ampliqon), and 8 μL distilled water. The reaction was carried out in the final volume of 25 μL. The PCR cycle condition followed with the initial denaturation at 95°C for 5 minutes, 35 cycles for (rs3741219) and 32 cycles for (rs217727) of the PCR, consisting of denaturation at 95°C for the 20 seconds, the annealing temperature 61°C for (rs3741219) and 63°C for (rs217727) for 15 seconds, extended at 72°C for 30 seconds, and the final cycle expanded 72°C for 5 minutes. Protocol digestion was performed on the following enzymes and conditions according to the manufacturer's instructions; HhaI and RsrII (Thermo Fisher Scientific Company, Waltham, MA, USA) enzyme digestion was used for the genotyping of rs3741219 and rs217727 at 37°C for 8 hours, respectively. We obtained a PCR product with sizes of 247 and 434 bp for rs217727 and rs3741219, respectively. During product digestion, rs217727 (T allele: 247 bp, C allele: 221 + 26 bp) and rs3741219 (T allele: 342 + 92 bp, C allele: 301 + 92 + 41 bp) fragments were generated. The PCR product digested was separated on 3% agarose gel (Figures 1 and 2). We validated genotype frequencies by sequencing 10% of the examples through arbitrary selection.

2.3 | Statistical analysis

In order to determine the allele and genotype frequencies of *lncRNA-H19* in two samples, the multivariate logistic regression and chi-square test were used, respectively. In addition, deductive variables and the difference ratio (OR) and confidence interval (CI = 95%) were used to estimate the association between the *lncRNA-H19* polymorphism and probability of BC. Statistical analysis was performed by using SPSS 23.0 software package (SPSS Inc, Chicago, IL, USA). All the tests were two-sided, and a *P*-value under 0.05 was considered to be statistically significant.

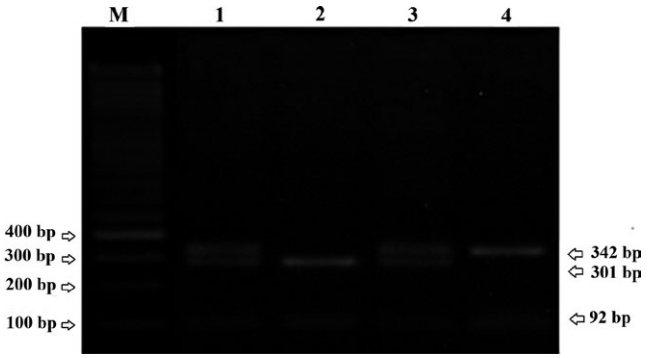

FIGURE 1 Gel electrophoresis of the PCR-RFLP products from of *lncRNA-H19* (rs3741219) gene on 3% agarose gel electrophoresis. Lanes 1 and 3: TC genotype (342, 301, 92, and 41 bp); Lane 2: CC genotype (301, 92, and 41 bp); Lane 4: TT genotype (342 and 92 bp); M: DNA size marker 100 bp

3 | RESULTS

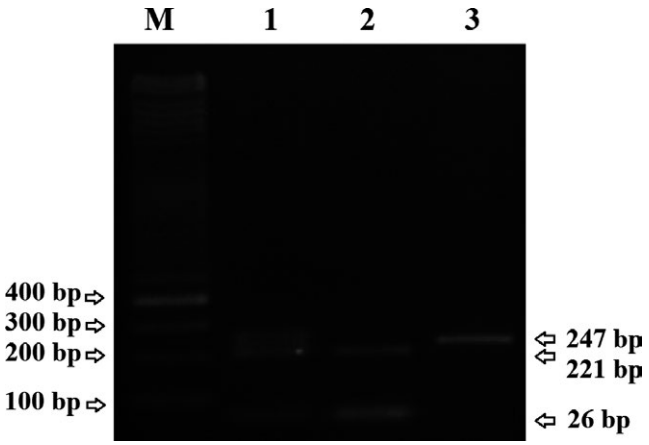

FIGURE 2 Gel electrophoresis of the PCR-RFLP products from of *lncRNA-H19* (rs217727) gene on 3% agarose gel electrophoresis. Lane 1: CT genotype (247, 221, and 26 bp); Lane 2: CC genotype (221 and 26 bp); Lane 3: TT genotype (247 bp); M: DNA size marker 100 bp

3.1 | Population characteristics

The mean age characteristics of the subjects investigated were 46.59 ± 11.18 for women with BC (range: 22-78 years) and 43.91 ± 9.99 for healthy women (range: 25-75 years). For overwhelming the influences of disturbing factors, the case and control groups were matched regarding the age and ethnicity. The genotype frequencies of *lncRNA-H19* (rs3741219 T>C) polymorphism were revealed (TT = 119, TC = 24, and CC = 7 and TT = 80, TC = 17, and CC = 3) in case and control, respectively ($P = 0.796$).

The genotype frequencies of *lncRNA-H19* (rs217727 C>T) polymorphism have shown (CC = 116, CT = 29, and TT = 5 and CC = 86, CT = 14, and TT = 0) in both groups ($P = 0.087$). However, our findings did not reveal a significant association between two SNPs of *lncRNA-H19* with the risk of BC. In our investigation, in order to assess a statistically significant difference in genotype frequencies in co-dominant, dominant, and recessive heredity models, three genotypes were analyzed in two groups. In recessive genetically model, the TT + CT/CC genotype frequencies showed a borderline association between *lncRNA-H19* (rs217727 C>T) gene polymorphisms

TABLE 1 The allele and genotype frequencies of SNPs *lncRNA-H19* in case and control subjects in three heredity models

Gene polymorphism	Case n = 150 (%)	Control n = 100 (%)	Total n = 250	OR	CI 95%		*P*-value
					Down	Up	
lncRNA-H19 (rs217727 C>T)							
Co-dominant							
CC	116 (57%)	86 (43%)	202				
CT	29 (67%)	14 (33%)	43	0.651	0.325	1.306	0.225
TT	5 (100%)	0 (—)	5	0.959	0.924	0.995	0.056
Recessive							
TT	5 (100%)	0 (—)	5	0.967	0.938	0.996	0.065
TC + CC	145 (59%)	100 (41%)	245				
Dominant							
CC	116 (57%)	86 (43%)	202	1.800	0.910	3.561	0.088
TC + TT	34 (71%)	14 (29%)	48				
Frequency of C allele	261 (58%)	186 (42%)	447	1.985	1.048	3.761	0.033
Frequency of T allele	39 (74%)	14 (26%)	53				
lncRNA-H19 (rs3741219 T>C)							
Co-dominant							
TT	119 (60%)	80 (40%)	199				
TC	24 (59%)	17 (42%)	41	1.054	0.532	2.806	0.881
CC	7 (70%)	3 (30%)	10	0.638	0.160	2.539	0.520
Recessive							
CC	7 (70%)	3 (30%)	10	1.583	0.399	6.727	0.510
CT + TT	143 (60%)	97 (40%)	240				
Dominant							
TT	119 (60%)	80 (40%)	199	1.042	0.555	1.956	0.898
CT + CC	31 (61%)	20 (39%)	51				
Frequency of T allele	262 (60%)	177 (40%)	439	1.116	0.643	1.938	0.696
Frequency of C allele	38 (62%)	23 (38%)	61				

TABLE 2 Correlation between of two SNPs *lncRNA-H19* gene with the clinicopathological parameters of BC patients

	Genotype *lncRNA-H19* rs3741219 T>C				Genotype *lncRNA-H19* rs217727 C>T			
	Normal TT	Heterozygote TC	Homozygote CC	*P*-values	Normal CC	Heterozygote CT	Homozygote TT	*P*-values
Age < 65	82	14	4	0.353	79	17	4	0.818
Age > 65	70	30	0		80	20	0	
Stage 1	78	19	3	0.585	76	20	4	0.642
Stage 2	86	8	6		79	17	4	
Stage 3	74	21	5		79	21	0	
Stage 4	81	15	4		92	0	8	

TABLE 3 The associations between two SNPs *lncRNA-H19* and ER, PR, and HER2 status of BC patients

	ER-PR			HER2		
Genotype	Negative	Positive	*P*-value	Negative	Positive	*P*-value
LncRNA-H19 rs3741219 T>C						
TT	82	82	0.835	86	78	0.185
TC	16	15	0.814	12	17	0.347
CC	2	3	0.394	2	5	0.344
TT + TC	98	97	0.394	98	95	0.344
LncRNA-H19 rs217727 C>T						
CC	82	78	0.628	73	83	0.168
CT	14	19	0.492	25	13	0.071
TT	4	3	0.772	2	4	0.483
CT + TT	18	22	0.722	27	17	0.483

with the risk of BC ($P = 0.065$; OR = 0.967; 95% CI, 0.938-0.996). In addition, our findings revealed a significant differences in allele frequencies in *lncRNA-H19* rs217727 C>T polymorphism between groups ($P = 0.033$; OR = 1.985; 95% CI, 1.048-3.761). The genotype frequencies of *lncRNA-H19* (rs217727 C>T) gene polymorphisms TC + CC/TT and CC + CT/TT did not showed a statistically significant association with the risk of BC ($P = 0.308$; OR = 1.472; 95% CI, 0.735-2.950) and ($P = 0.088$; OR = 1.800; 95% CI, 0.910-3.561), respectively (Table 1). Of note, in homozygous co-dominant model (TT vs CC), genotype frequencies showed a borderline association between *lncRNA-H19* (rs217727 C>T) gene polymorphisms with the risk of BC ($P = 0.056$; OR = 0.959; 95% CI, 0.924-0.995).

The genotype and allele frequencies of *lncRNA-H19* (rs3741219 T>C) gene polymorphism did not reveal a statistically significant difference between the two groups in three heredity models ($P > 0.05$; Table 1).

We also compared genotype frequencies for each polymorphism in case and control groups with clinicopathological parameters including, age, tumor stage (Table 2), estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) receptor status (Table 3).

4 | DISCUSSION

We examined the performance of two polymorphisms rs217727 and rs3741219 in *lncRNA-H19* on susceptibility to BC in populations in East Azerbaijan Province, Iran. To get the best information, this study looked up at the role of nucleotide changes in *lncRNA-H19* in BC carcinogenesis. Our findings revealed a significant differences in allele frequencies in *lncRNA-H19* rs217727 C>T polymorphism between groups. On this basis, it can be suggested that the presence of rs217727 C>T polymorphism poses a risk of increased BC.

According to the latest knowledge by Xia et al,[16] reported that the nucleotide changes in *lncRNA-H19* was associated with the risk of BC. The results showed that nonsignificant deviations from Hardy-Weinberg equilibrium for two polymorphisms were found among a total of 467 healthy women. Contradictory, our findings revealed that the rs217727 C>T polymorphism may be involved in BC carcinogenesis, whereas the genotyping results showed that the rs217727 was associated with a reduction in the risk of BC.

Previous studies have shown that lncRNAs can control the stages of the cell cycle, such as progression, cell death, invasion, and migration. The genetic variation in lncRNAs may alter the structures

and stability of lncRNAs and involved in carcinogenesis. Wu et al reported that the A allele compared to the rs11752942 G allele significantly improved lincRNA-uc003opf.1 by binding with microRNA-149 and affects the cellular proliferation of the esophageal cells, thereby causing cancer. They also noted that the nucleotide change in rs12325489 C to T could affect the transplant sites for miRNA-370 and affected the transcriptional activity of lncRNA-ENST00000515084 and cell proliferation of BC.[18]

The *lncRNA-H19* gene plays an important role in controlling fetal growth and development, and it is used to indicate the role of insulin-like growth factor 2 (IGF2). However, *lncRNA-H19* and IGF2 are regulated by the internal control of the gene (ICR) and most commonly used augmentation regions. In humans, the CTCF split protein binding to the ICR promotes the expression of *lncRNA-H19* from maternal alleles.[19,20] Recently, it has been shown that *lncRNA-H19* gene polymorphisms are associated with several disorders. Gao et al[21] also demonstrated that the nucleotide change in rs217727 C to T is associated with an increased risk of coronary artery disease, while the rs2067051 G to A is associated with a reduction in the risk of coronary artery disease. Hewage et al,[22] in a case-control investigation, assessed 177 patients with bladder cancer and 204 controls and reported that rs2839698 T>C was associated with a reduction in the risk of bladder cancer. In addition, findings showed a significant reduction in the bladder cancer risk in carriers of the T rs217727 allele compared with carrier C allele.

In addition, Li et al[23] have been assessed the frequencies of three *lncRNA-H19* SNPs such as rs217727, rs2735971, and rs3024270 in the 200 bladder cancer patients and 200 healthy subjects. The findings suggested that rs217727 was correlated with increased risk of bladder cancer and may be involved in the background genetics of bladder cancer susceptibility. Yuan et al[24] examined four functional SNPs in lncRNA-H19 to evaluate the influence of the risk of oral squamous cell carcinoma (OSCC) in a Chinese population. The results revealed that the two SNPs rs217727 and rs2839701 were correlated with the risk of OSCC and proposed the critical roles in genetic susceptibility to OSCC. The recent investigation was performed on the 555 lung cancer patients (LC) and 618 healthy individuals to evaluate the relationship between rs217727 polymorphisms with the susceptibility of LC. They noted that the homozygous genotype of rs217727 was notably correlated with an elevated LC risk.[25]

Yang et al[12] studied the effect of four independent *lncRNA-H19* SNPs (rs217727, rs2839698, rs3741216, and rs3741219) with gastric cancer risk in China population and showed that the T allele of rs217727 was associated with a higher risk of gastric cancer. Individuals with rs2839698 TT genotype showed a significant increase in gastric cancer susceptibility. Similarly, in the present study, we found a positive relationship between the rs217727 polymorphism and BC susceptibility. A nucleotide variation of lncRNA may be changing the structure and affects miRNA-lncRNA interaction. Increasing evidence suggests that lncRNAs can be directly regulated by miRNAs.[24] The effect of rs3741219 T>C *lncRNA-H19* gene polymorphism and interaction of miRNA-lncRNA in BC cells remained unclear, and so further studies are needed to find the mechanism. Xia et al[16] showed that the release of miR-675 with the *lncRNA-H19* prevented estrogen proliferation of ERa of cancerous cells. Furthermore, the SNPs in the *lncRNA-H19* may have a relationship with the risk of BC.

Butt et al[26] have been revealed that the T vs C allele in *lncRNA-H19* rs2107425 polymorphism decreased the risk of BC. They reported that no significant association was found between rs2107425 changes with the risk of BC in Swedish population.

In addition, Barnholtz-Sloan et al[27] assessed the relationship between *lncRNA-H19* rs2107425 changes in African American and White cases. The findings did not reveal a significant association between this polymorphism and risk of BC in African American.

Hassanzarei et al,[28] in case-control study was performed on 230 BC patients and 240 ages adjusted healthy women with no history of any cancer in Southeast Iranian population. The findings revealed an association between *lncRNA-H19* gene polymorphism and BC risk. In addition, it suggested that the nucleotide changes in *lncRNA-H19* may be considered as a potential biomarker for predisposition to BC.

Our findings involve several significant points that should be mentioned. The present investigation assessed the initial nucleotide variations of lncRNA-H19 in relationship to BC susceptibility in Azeri-Turk Iranian population. In addition, in our survey, the all individuals matched on age and the racial characteristic identical. In our investigation, we have evaluated the patient samples which all newly pathological diagnosed BC disease without obtaining any remedy regime. However, our consideration had several limitations including the analytical strength, the sample composition, and a large percentage of loss factors for some variables. In addition, we did not incorporate the effects of the *lncRNA-H19* nucleotide changes in gene expression alteration and activity. Therefore, somewhat investigations are profitable to confirm whether *lncRNA-H19* variations could influence the pathogenesis of BC.

In conclusion, our findings demonstrate that the presence of rs217727 C>T polymorphism may play crucial roles in the pathogenesis of BC, whereas rs3741219 T>C variation cannot be promoting risk of BC susceptibility.

AUTHOR CONTRIBUTIONS

Safa Abdollahzadeh and Saeid Ghorbian designed the study; Safa Abdollahzadeh and Saeid Ghorbian contributed to the sample collection; Safa Abdollahzadeh and Saeid Ghorbian performed the study; Safa Abdollahzadeh and Saeid Ghorbian analyzed the data; and Safa Abdollahzadeh and Saeid Ghorbian drafted the manuscript.

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REFERENCES

1. Even-Sapir E, Inbar M. PET in women with high risk for breast or ovarian cancer. *Lancet Oncol*. 2010;11(9):899-905.
2. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol*. 2001;2(3):133-140.
3. Bradbury AR, Olopade OI. Genetic susceptibility to breast cancer. *Rev Endocr Metab Disord*. 2007;8(3):255-267.
4. Sapkota Y, Mackey JR, Lai R, et al. Assessing SNP-SNP interactions among DNA repair, modification and metabolism related pathway genes in breast cancer susceptibility. *PLoS One*. 2014;8(6):e64896.
5. Ghorbian S, Nargesian M, Talaneh S, Asnaashar O, Sharifi R. Association of genetic variations in XRCC1 and ERCC1 genes with sporadic breast cancer. *Gene Cell Tissue*. 2018;5(2):e80166.
6. Kian R, Moradi S, Ghorbian S. Role of components of microRNA machinery in carcinogenesis. *Exp Oncol*. 2018;40(1):2-9.
7. Haemmerle M, Gutschner T. Long non-coding RNAs in cancer and development: where do we go from here? *Int J Mol Sci*. 2015;16(1):1395-1405.
8. Jendrzejewski J, He H, Radomska HS, et al. The polymorphism rs944289 predisposes to papillary thyroid carcinoma through a large intergenic noncoding RNA gene of tumor suppressor type. *Proc Natl Acad Sci USA*. 2012;109(22):8646-8651.
9. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Can Res*. 2014;74(11):2913-2921.
10. Rossi S, Sevignani C, Nnadi SC, Siracusa LD, Calin GA. Cancer-associated genomic regions (CAGRs) and noncoding RNAs: bioinformatics and therapeutic implications. *Mamm Genome*. 2008;19(7-8):526-540.
11. Noori-Daloii MR, Eshaghkhani Y. LncRNAs: new approach in cancer therapy. *Med Sci J*. 2015;25(4):249-256.
12. Yang C, Tang R, Ma X, et al. Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. *Oncotarget*. 2015;6(17):15311-15320.
13. Raveh E, Matouk IJ, Gilon M, Hochberg A. The H19 Long non-coding RNA in cancer initiation, progression and metastasis – a proposed unifying theory. *Mol Cancer*. 2015;14:184.
14. Matouk IJ, Halle D, Raveh E, Gilon M, Sorin V, Hochberg A. The role of the oncofetal H19 lncRNA in tumor metastasis: orchestrating the EMT-MET decision. *Oncotarget*. 2016;7(4):3748-3765.
15. Zhang L, Zhou Y, Huang T, et al. The interplay of LncRNA-H19 and its binding partners in physiological process and gastric carcinogenesis. *Int J Mol Sci*. 2017;18(2):450.
16. Xia Z, Yan R, Duan F, Song C, Wang P, Wang K. Genetic polymorphisms in long noncoding RNA H19 are associated with susceptibility to breast cancer in Chinese population. *Medicine*. 2016;95(7):e2771.
17. Lin Y, Fu F, Chen Y, et al. Genetic variants in long noncoding RNA H19 contribute to the risk of breast cancer in a southeast China Han population. *Onco Targets Ther*. 2017;10:4369-4378.
18. Wu HC, Zheng J, Deng JQ, et al. A genetic polymorphism in lincRNA-uc003opf.1 is associated with susceptibility to esophageal squamous cell carcinoma in Chinese populations. *Carcinogenesis*. 2013;34:2908-2917.
19. Takai D, Gonzales FA, Tsai YC, et al. Large scale mapping of methylcytosines in CTCF-binding sites in the human H19 promoter and aberrant hypomethylation in human bladder cancer. *Hum Mol Genet*. 2001;10:2619-2626.
20. Wilkin F, Paquette J, Ledru E, et al. H19 sense and antisense transgenes modify insulin-like growth factor-II mRNA levels. *Eur J Biochem*. 2000;267:4020-4027.
21. Gao W, Zhu M, Wang H, et al. Association of polymorphisms in long non-coding RNA H19 with coronary artery disease risk in a Chinese population. *Mutat Res*. 2015;772:15-22.
22. Hewage AS, Jayanthiny P, Tennekoon KH, et al. H19 rs217727 genotype and IGF-1/intron-2 dinucleotide CT repeat polymorphism are independently associated with birth weight. *Endocrine*. 2015;48:1010-1012.
23. Li Z, Niu Y. Association between lncRNA H19 (rs217727, rs2735971 and rs3024270) polymorphisms and the risk of bladder cancer in Chinese population. *Minerva Urol Nefrol*. 2018. [Epub ahead of print]. https://doi.org/10.23736/S0393-2249.18.03004-7
24. Yuan Z, Yu Y, Zhang B, et al. Genetic variants in lncRNA H19 are associated with the risk of oral squamous cell carcinoma in a Chinese population. *Oncotarget*. 2018;9(35):23915-23922.
25. Li L, Guo G, Zhang H, et al. Association between H19 SNP rs217727 and lung cancer risk in a Chinese population: a case control study. *BMC Med Genet*. 2018;19(1):136.
26. Butt S, Harlid S, Borgquist S, et al. Genetic predisposition, parity, age at first childbirth and risk for breast cancer. *BMC Res Notes*. 2012;5(1):414.
27. Barnholtz-Sloan JS, Shetty PB, Guan X, et al. FGFR2 and other loci identified in genome-wide association studies are associated with breast cancer in African-American and younger women. *Carcinogenesis*. 2010;31(8):1417-1423.
28. Hassanzarei S, Hashemi M, Sattarifard H, Hashemi SM, Bahari G. Genetic polymorphisms in long noncoding RNA H19 are associated with breast cancer susceptibility in Iranian population. *Meta Gene*. 2017;14:1-5.

How to cite this article: Abdollahzadeh S, Ghorbian S. Association of the study between *LncRNA-H19* gene polymorphisms with the risk of breast cancer. *J Clin Lab Anal*. 2019;33:e22826. https://doi.org/10.1002/jcla.22826