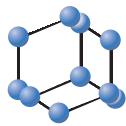


RESEARCH ARTICLE

BENTHAM
SCIENCE

The Relationship between Pre-miR-3131 3-bp Insertion/Deletion Polymorphism and Susceptibility and Clinicopathological Characteristics of Patients with Breast Cancer



Mahsa Azizi¹, Nahid Rahimi¹, Gholamreza Bahari^{2,*}, Seyed Mehdi Hashemi³ and Mohammad Hashemi^{1,4}

¹Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran;

²Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran;

³Department of Oncology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran; ⁴Genetics of Non-communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

Abstract: Aims: This study aimed at examining the effect of 3-bp pre-miR-3131 insertion/deletion (ins/del) polymorphism on Breast Cancer (BC) risk.

Objectives: Totally 403 women including 199 BC patients and 204 women who have no cancer were included in this case-control study. Genotyping of miR-3131 3-bp ins/del polymorphism was performed by mismatch PCR-RFLP method.

Methods: The findings expressed that the pre-miR-3131 3-bp ins/del variant was not related to the risk of BC in all genetic tested models. While, the ins/del genotype was related to late onset BC (OR=2.53, 95%CI=1.27-4.84, p=0.008).

Results: Pooled results from the meta-analysis indicated to that the pre-miR-3131 ins/del is related to with an increased risk of cancer in heterozygous (OR=1.26, 95%CI=1.06-1.51, p=0.01), dominant (OR=1.33, 95%CI=1.14-1.54, p=0.0002), and allele (OR=1.24, 95%CI=1.06-1.45, p=0.006) genetics models.

Conclusion: It is concluded that, our findings did not support a relationship between pre-miR-3131 ins/del polymorphism and the risk of BC. While, this variant was significantly related to late onset BC. Combined results of this study with previous studies indicated that this polymorphism increased the risk of cancer. More studies in a study with larger population with variety of ethnicities are required to verify our findings.

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1. INTRODUCTION

Breast Cancer (BC) is one of the most common cancers among women in the world. It is reported for 24.2% of all new cancer cases and 15% of all cancer deaths globally among female in 2018 [1]. The etiology of BC is inadequately understood; although genetic, environmental and lifestyle risk factors have been related to the incidence of BC. Mounting evidence indicated that genetic forms in microRNAs (miRNAs) are involved in BC development and progression [2-7].

MicroRNAs are short (19-23 nucleotides), non-coding, single-stranded RNA molecules that regulate post-translational genes expression by degradation or translation prohibiting of target mRNA [8-10]. MiRNAs are key regulators of the human transcriptome and function as oncogenes or tumor suppressor genes depending on the function of their target genes [11-14].

Increasing evidence shows that genetic variations in miRNA genes can change the expression, biogenesis of miRNA, or target selection thus affecting their target genes' expression and cancer development [3, 7, 11, 15-17]. Small insertions and deletions (Indels) variations are one of the most genetic alterations that change the human traits and diseases [18-21].

*Address correspondence to this author at the Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran; Tel: +9854 33295722; E-mails: r_b_1333@yahoo.com; ghbahari@zaums.ac.ir

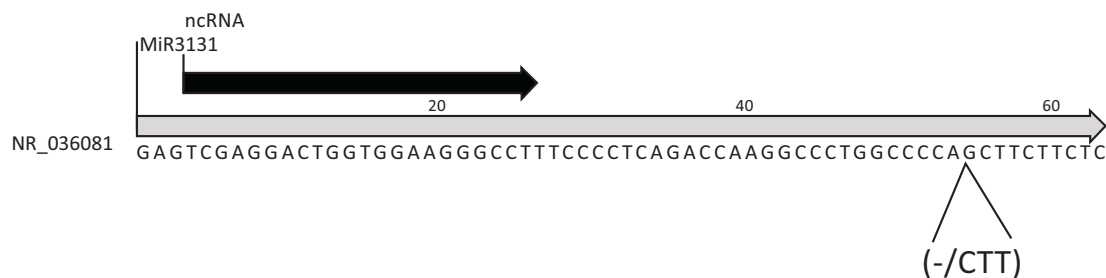


Fig. (1). Schematic representation of 3-bp ins/del (rs57408770) polymorphism in the 3' end of miR-3131.

Pre-miR-3131 is mapped to chromosome 2 in the intron 2 of IHH (Indian Hedgehog) gene. A 3-bp ins/del (rs 57408770) polymorphism is placed in the 3' end of miR-3131 (Fig. 1). Although, the precise molecular mechanism of miR-3131 in cancer development remains mostly unidentified. It has been reported that miR-3131 operates as a proto-oncogene in Hepatocellular Carcinoma (HCC) [11]. The 3-bp ins/del polymorphism affects the expression of miR-3131 [11]. Limited studies examined the effect of 3-bp ins/del (rs57408770) polymorphism in pre-miR-3131 on cancer [11, 22]. To the best of our knowledge, there is no data about the role of pre-miR-3131 3-bp ins/del polymorphism on BC development. Therefore, this study aimed at examining the relationship between pre-miR-3131 3-bp ins/del polymorphism and BC susceptibility in a sample of the southeast Iranian population.

2. MATERIALS AND METHODS

This case-control study was conducted on 199 BC female patients and 204 women without cancer as control group. The enrolment process and study design have been previously described [23, 24]. Ethics approval for recruitment was obtained from review board of Zahedan University of Medical Sciences, and all subjects provided the written informed consent. Extraction of genomic DNA from whole blood was achieved by salting out method. Extracted DNA was stored at -20°C until analysis.

2.1. Genotyping

As previously mentioned, genotyping of miR-1313 rs57408770 polymorphism was done by mismatch PCR-RFLP method [22]. The primer sequences of forward and reverse were 5'-CTGTGCAGCTGACTCTGAGAAGACG-3' and 5'-TATTGGCTCCTAGGAAGGCTGAGT-3', respectively. 1 μl of genomic DNA (100 ng/ μl), 1 μl of each primers (10 μM), 7 μl 2X master mix (GeNet Bio, Korea) and 10 μl of nuclease free water was added in each 0.20 ml PCR reaction tube. Amplification was performed with an initial denaturation at 95°C for 6 min, followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 65°C for 30 s, extension at 72°C for 30 sec, with a final extension step of 72°C for 5 min. The amplification product was digested by AluI (New England BioLabs, Beverly, MA) restriction enzyme and resolved by electrophoresis in 2.5% agarose gel. The del allele remained undigested (191 bp), while the ins allele were digested and produced two fragments of 171 and 20 bp.

2.2. Bioinformatics Analysis

We examined whether the 3-bp ins/del polymorphism affect secondary structure by quantifying Minimum Free Energy (MFE) change of miR-3131.

2.3. Statistical Analysis

All statistical analyses were performed by statistical package SPSS 22 software. Independent sample t-test and χ^2 test were used for contentious and categorical data, respectively. Unconditional logistic regression analysis was used to test the relationship between miR-3131 3-bp ins/del variant and BC risk. *P*-value below 0.05 was considered statistically significant.

2.4. Quantitative Analysis

We also conducted a meta-analysis by combining our results with those from previous studies. Searching electronic databases enabled us to identify eligible case-control studies. We calculated the Combined Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for five genetic models to estimate the relationship between the miR-3131 3-bp ins/del polymorphism and the risk of overall cancer. The significance of the combined OR was measured by the Z-test and $P < 0.05$ is considered to be statistically significant. Review Manager version 5.3 software was used to perform the statistical analyses.

3. RESULTS

3.1. Association Findings

This study included 199 BC patients with a mean age of 48.39 ± 11.08 years and 204 women who have no cancer with a mean age of 48.49 ± 10.51 years. There is no significant difference between the groups in term of age ($p = 0.924$).

Table 1 shows the genotypes and allele frequencies of miR-3131 rs57408770 polymorphism in BC cases and controls. The results showed that the ins/del polymorphism was not related to the risk of BC in heterozygous (OR=1.31, 95%CI= 0.84-2.05, $p=0.254$ ins/del vs. del/del), homozygous (OR=0.92, 95%CI=0.55-1.56, $p=0.792$, ins/ins vs. del/del), dominant (OR=0.83, 95%CI=0.77-1.70, $p=0.550$, ins/del+ins/ins vs. del/del), recessive (OR=0.57, 95%CI=0.52-1.36, $p=0.543$, ins/ins vs. ins/del+del/del and allele (OR=1.01, 95%CI=0.75-1.35, $p=0.999$, ins vs. del) genetic models.

Table 2 shows the relationship between rs57408770 polymorphism and clinicopathological characteristics, such as

Table 1. The genotype and allele frequencies of 3-bp I/D (rs57408770) polymorphism of pre-miR-3131 in breast cancer patients and controls.

Polymorphism	Breast Cancer n (%)	Controls n (%)	OR (95%CI)	P
Codominant				
del/del	94 (47.2)	103 (50.5)	1.00	-
ins/del	68 (34.2)	57 (21.1)	1.31 (0.84-2.05)	0.254
ins/ins	37 (18.6)	44 (28.4)	0.92 (0.55-1.56)	0.792
Dominant				
del/del	94 (47.2)	103 (50.5)	1.00	-
ins/del+ins/ins	105 (52.8)	101 (49.5)	0.83 (0.77-1.70)	0.550
Recessive				
del/del+ins/del	162 (81.4)	160 (71.6)	1.00	-
ins/ins	37 (18.6)	44 (28.4)	0.57 (0.52-1.36)	0.534
Allele				
del	256 (64.3)	263 (64.5)	1.00	-
ins	142 (35.7)	145 (35.5)	1.01 (0.75-1.35)	0.999

Table 2. Association of 3-bp indel (rs57408770) polymorphism of pre-miR-3131 with clinicopathological characteristics of Breast Cancer (BC) patients.

Characteristic of Patients	3-bp Indel			P
	DD	ID	II	
Age, years				0.021
≤50	43	17	12	-
>50	51	51	25	-
Tumor size, cm				0.458
≤2	29	27	11	-
>2	58	39	26	-
Histology				0.811
Ductal carcinoma	63	48	24	-
Others	27	18	12	-
Lymph node metastasis				0.817
No	23	15	11	-
Yes	54	43	24	-
Grade				0.379
I	13	11	4	-
II	42	37	16	-
III+IV	15	10	11	-

(Table 2) contd...

Characteristic of Patients	3-bp Indel			P
	DD	ID	II	
Stage				0.895
I	14	11	5	-
II	34	21	16	-
III	25	22	10	-
IV	17	14	6	-
Estrogen receptor status				0.660
Positive	53	44	23	-
Negative	33	20	12	-
Progesterone receptor status				0.594
Positive	48	41	21	-
Negative	38	23	14	-
HER2 status				0.504
Positive	45	33	14	-
Negative	46	33	22	-

age, tumor size, grade, stage, pathological type, lymph node metastasis, estrogen receptor status, progesterone receptor status and HER2 status. The findings expressed that rs57408770 polymorphism was only related to late onset BC so that the ins/del genotypes increased the risk of BC in age>50 years compared to Age ≤50 years (OR=2.53, 95%CI=1.27-4.84, p=0.008).

3.2. Bioinformatics Findings

The complete RNA sequence of miR-3131 (Accession: NR_036081.1) was used to measure the impact of 3-bp ins/del polymorphism on the RNA structure (Fig. 2). The free energy of the thermodynamic ensemble for deletion and insertion are -30.19 kcal/mol and -29.99 kcal/mol, respectively.

3.3. Meta-analysis Results

Combined analysis of data showed that miR-3131 3-bp ins/del polymorphism significantly augmented the risk of overall cancer in heterozygous (OR=1.26, 95%CI=1.06-1.51, p=0.01), dominant (OR=1.33, 95%CI=1.14-1.54, p=0.0002), and allele (OR=1.24, 95%CI=1.06-1.45, p=0.006) genetics models (Fig. 3).

4. DISCUSSION

Intensive transcriptome sequencing has discovered non-coding RNAs (ncRNAs), which report about 98% of the whole genome [25, 26]. The ncRNAs can be classified into miRNAs, small interfering RNAs (siRNAs), antisense RNAs (asRNAs), and lncRNAs [27, 28]. They play a key role in various biological functions by regulating the gene expression [29].

MiRNAs function as tumor suppressors or oncogenes and dysregulation of miRNAs are involved in the initiation and progression of cancer [30-34]. Small insertions and deletion (indels) variations in human genome could be functionally key sites and potentially affect human traits and diseases [11, 18, 22]. Many studies have been conducted on the relation between polymorphisms in miRNAs and cancer development [3, 7, 17, 35-40]. To our knowledge, this is the first study that examines the effect of miR-3131 3-bp ins/del polymorphism on of BC susceptibility. Our finding showed that there is no significant relationship between pre-miR-3131 ins/del variant and BC susceptibility. On the other hand, we observed that this variant was significantly related to the late onset BC. Wang *et al.* [11] reported that the insertion allele is significantly related to the risk of Hepatocellular Carcinoma (HCC). Moreover, their findings showed that 3-bp ins/del polymorphism may affect the miR-3131 expression. Hashemi *et al.* [22] have found that 3-bp ins/del polymorphism is related to the risk of Prostate Cancer (PCa), but this polymorphism was not related to clinicopathological characteristics of PCa patients. Shen *et al.* [41] have reported that the level of miR-3131 was up-regulated 92-folds in treated HepG2 cells with Ganoderma lucidum polysaccharide, indicating that miR-3131 may play a significant role in the proliferation and differentiation of HCC cells.

We examined the effect of 3-bp ins/del polymorphism on miR-3131 RNA stability. The results indicated that ins/del polymorphism affect the stability of RNA. The analysis of free energy of RNA structure shows that the deletion allele structure is more stable than that of insertion allele (-30.19 kcal/mol for deletion and -29.99 kcal/mol for insertion, respectively).

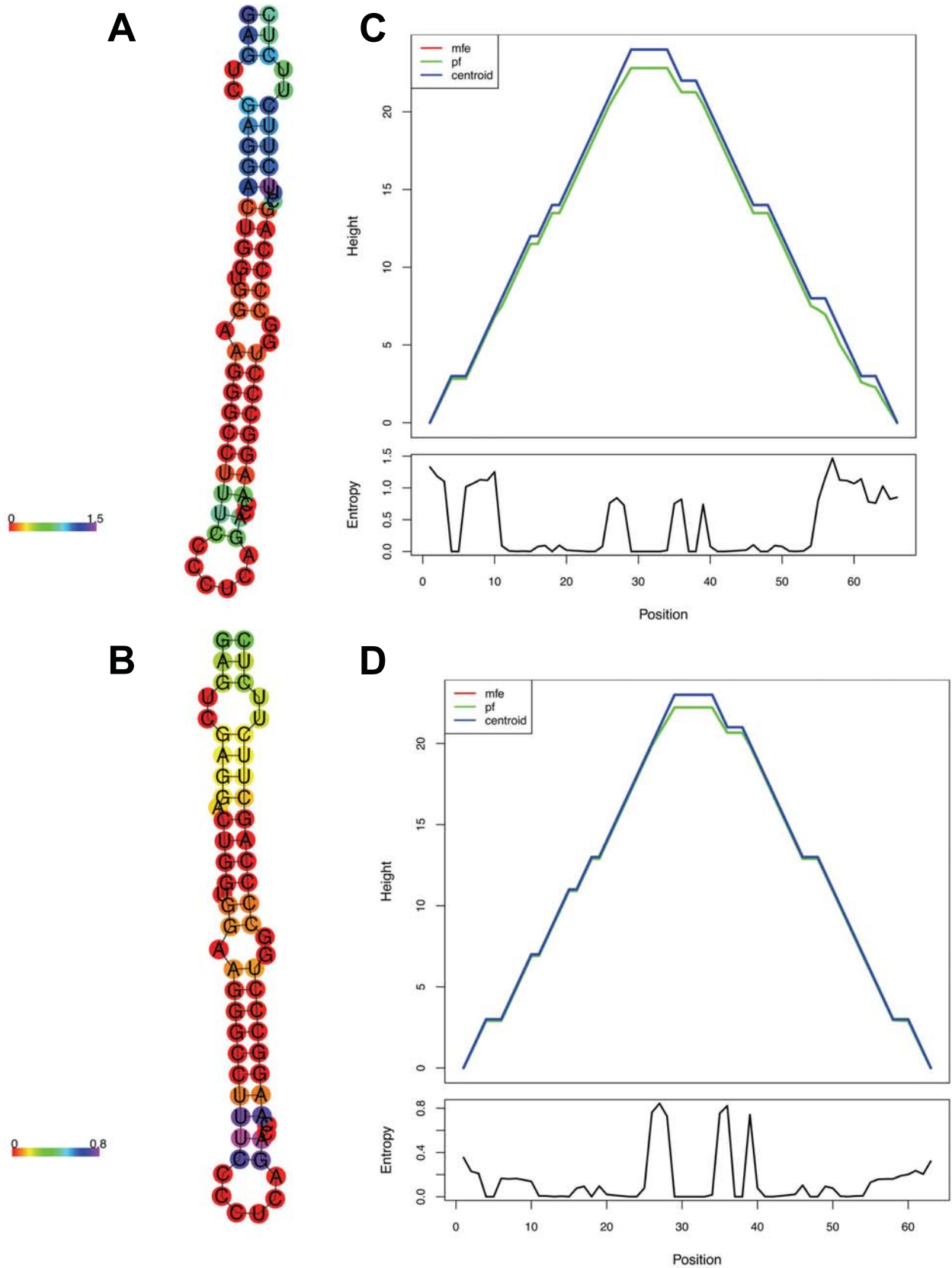


Fig. (2). The effect of 3-bp ins/del (rs57408770) polymorphism in the 3' end of miR-3131 on mRNA folding structure by RNAfold (**A**, ins; **B**, del; **C** and **D** mountain plot of ins and del that indicate the MFE structure, the thermodynamic ensemble of RNA structures, the centroid structure and positional entropy for each position). The free energy of the thermodynamic ensemble for ins and del is -29.99 kcal/mol and -30.19 kcal/mol, respectively.

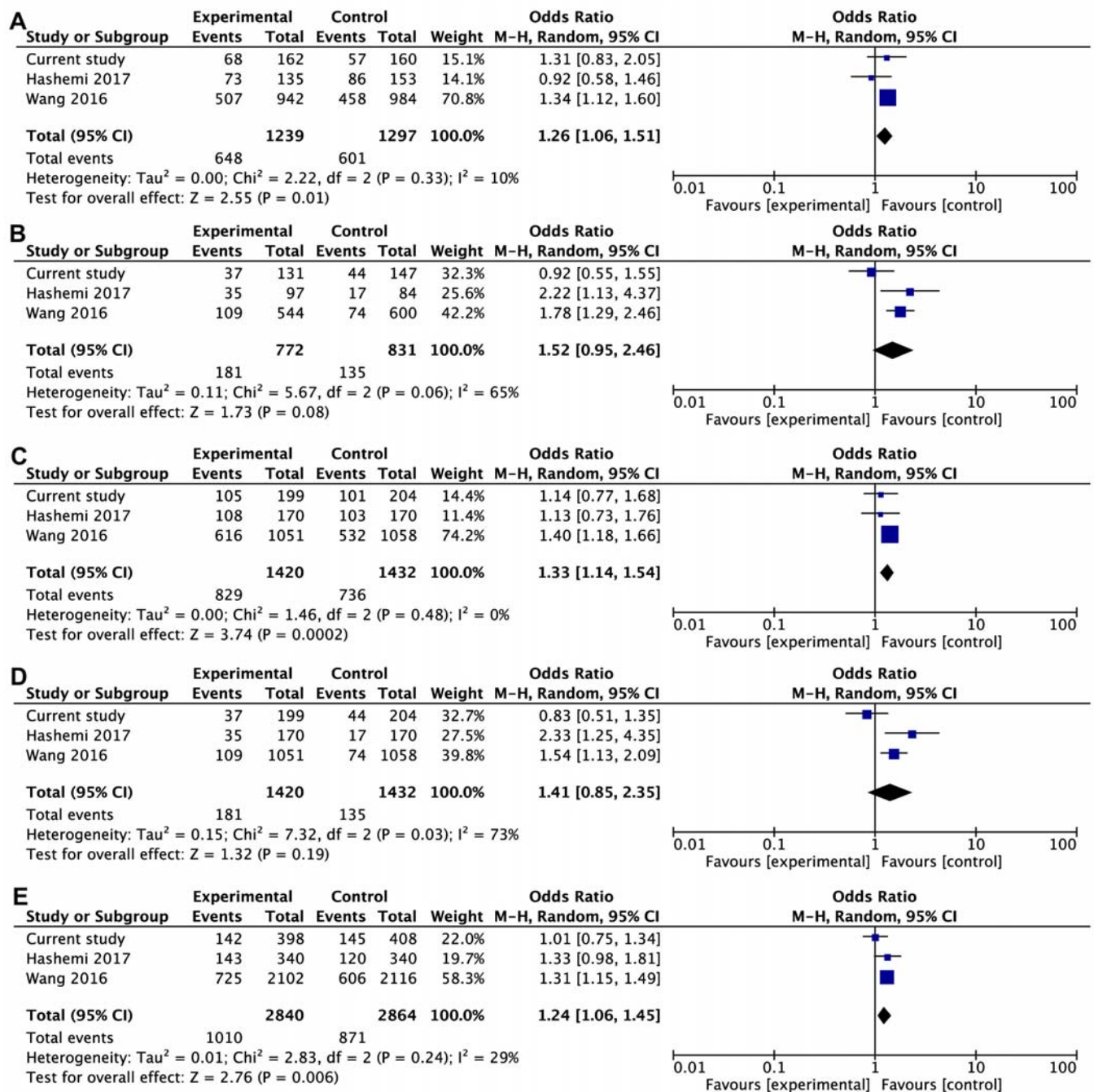


Fig. (3). The Forest plot for association between miR-3131 3-bp ins/del polymorphism and cancer susceptibility for (A), ins/del vs. del/del (B), ins/ins vs. del/del (C), ins/del+ins/ins vs. del/del (D), ins/ins vs. ins/del+del/del (E), and ins vs. del.

The findings of combined analysis showed a relationship between miR-3131 3-bp ins/del polymorphism and increased the risk of cancer development.

Activation of oncogenes and inactivation of tumor suppression genes is one of the hallmarks of cancer.

miRNAs are small non-coding RNA molecules that regulate gene expression by binding to the in 3'-untranslated regions (UTR) of target certain mRNAs [42, 43]. Polymorphisms within miRNAs sequences affecting miRNA expression and/or miRNA-target pair sites [44]. Genetic polymor-

phisms in miRNAs have been shown to be involved in the initiation and progression of several cancers [5, 35, 45, 46]. It has been proposed that miR-3131 may act as a protooncogene in HCC [11]. The expression level of miR-3131 in HCC tissues was significantly higher than those in the paired non-cancerous tissues. It has been shown that 3-bp indel polymorphism within miR-3131 is functional and affect the expression of mature miR-3131. The expression level of miR-3131 was significantly higher in insertion allele than the deletion allele [11].

CONCLUSION

In conclusion, our findings showed no significant association between pre-miR-3131 3-bp ins/del polymorphism and female BC development in a sample of Southeast Iranian population. A combined analysis expressed that this variant increased the risk of overall cancer. More studies with different ethnicities and larger sample sizes seek to verify the findings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from Zahedan University of Medical Sciences, Zahedan, Iran, approval number (IR.ZAUMS.REC.1396.296).

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. All reported human were experimented in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the *Helsinki Declaration* of 1975, as revised in 2008 (<http://www.wma.net/en/20activities/10ethics/10helsinki/>).

CONSENT FOR PUBLICATION

Written informed consent was taken from each individual.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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