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ORIGINAL ARTICLE

Homozygous T172T and Heterozygous G135C Variants of Homologous Recombination Repairing Protein *RAD51* are Related to Sporadic Breast Cancer Susceptibility

Mazhar Salim Al-Zoubi[1,2] · Chiara Maria Mazzanti[1] · Katia Zavaglia[1] · Mohammad Al Hamad[1,4] · Ivana Armogida[1] · Michael P. Lisanti[3] · Generoso Bevilacqua[1]

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Abstract Breast cancer (BC) is the most common cancer and the second leading cause of death among women worldwide. Only 10% of BC cases have been related to genetic predisposition. Rad51, a homologous recombination (HR) protein plays an important role in HR in meiosis and repairing DNA double-strand breaks. Expression of *RAD51* may be a predictive biomarker in certain types of cancers. The exact mechanisms involved in the regulation of *RAD51* expression are not fully understood, but certain transcription factors have been suggested to be the tuning mechanism of its expression. In this study, we propose that polymorphisms in the 5′-UTR promoter region of the *RAD51* gene are prognostic factors for BC development. Direct sequencing of 106 samples from sporadic BC patients and 54 samples from a control group was performed. FFPE samples were the choice of sample collection, which might be a limitation of our study. Homologous variant T172T alone was found to be significantly associated with BC risk (OR 3.717, 95% CI 2.283–6.052, $p < 0.0001$). On the other hand, heterozygous G135C did not show

✉ Mazhar Salim Al-Zoubi
mszoubi@yu.edu.jo

[1] Division of Surgical, Molecular, and Ultrastructural Pathology, Pisa University Hospital, University of Pisa, Pisa, Italy

[2] Department of Biological Sciences, Faculty of Science, Yarmouk University, Irbid 211-63, Jordan

[3] Manchester Breast Centre & Breakthrough Breast Cancer Research Unit, Paterson Institute for Cancer Research, Manchester Academic Health Science Centre, School of Cancer, Enabling Sciences and Technology, University of Manchester, Manchester, UK

[4] Department of Pathology and Laboratory Medicine, University of Dammam, Dammam, Saudi Arabia

any significant relationship with risk of sporadic BC (OR 1.598, 95% CI 0.5638–4.528, $p > 0.05$). Moreover, both variants; homozygous T172T and heterozygous G135C together; showed a significant relationship with sporadic BC susceptibility.

Keywords *RAD51* · UTR-5′ · 135 G>C · T172T · Breast cancer · SNP

Introduction

Breast cancer (BC) is the most common cancer with the exception of non-melanoma skin cancer and the second leading cause of death among women in the United States. In 2012, 226,870 new cases of breast cancer are expected to be diagnosed in women in the U.S. (Siegel et al. 2012). In Italy, 47,200 cases of breast cancer had been detected in 2005 (Piscitelli et al. 2009). Only 10% of breast cancer cases have been demonstrated to be related to genetic predisposition, which is attributable to the inheritance of mutations in a single gene, such as BRCA1 and BRCA2 (Ford et al. 1998). Furthermore, 37% of BRCA1 and BRCA2 mutation carriers will develop breast cancer, moreover, the risk of breast cancer development in BRCA1 and BRCA2 mutation carriers' increases up to 80% by age 70 (Easton et al. 1995; Struewing et al. 1997; Thorlacius et al. 1998). Discovering mutations in other genes associated with breast cancer might be a helpful tool to develop new treatment options for breast cancer.

Rad51 is a RecA homologous recombinase in eukaryotes, which is essential for the homologous recombination (HR) process either in meiosis or for repairing DNA double-strand breaks (DSBs) (Masson and West 2001; Baumann and West 1998). With the other similar family members, Rad51 is involved in the search of the homologous intact duplex, DNA pairing and strand exchange (Shinohara and Ogawa 1995; Baumann et al. 1996; Arnaudeau et al. 2001). In normal cells, Rad51 interacting proteins have been suggested to tune the expression of Rad51 recombinase (Richardson 2005; Thacker 2005; Raderschall et al. 2002; Maacke et al. 2000; Xia et al. 1997; Richardson et al. 2004).

Rad51 family recombinases have been intensively studied to reveal their role in cancer development by estimating levels of expression, mutations and polymorphisms (Klein 2008; Silva et al. 2010; Pooley et al. 2008; Winsey et al. 2000; Gaudet et al. 2009; Schneider et al. 2008; Lee et al. 2005; Auranen et al. 2005; Zoubi 2015). Rad51 has been demonstrated to be elevated in a number of tumor cell lines (Xia et al. 1997; Arnaudeau et al. 1999). Whether, overexpression of *RAD51* in cells stimulates HR (Arnaudeau et al. 1999; Maacke et al. 2000; Martin et al. 2007; Vispe et al. 1998) or reduces HR (Arnaudeau et al. 2001), it may potentially lead to chromosome rearrangements (Klein 2008; Lundin et al. 2003). However, *RAD51* may not to be an oncogene because it may be an essential gene, redundant gene, and/or independent of the BRCA1/BRCA2 tumor suppressor pathway (Schmutte et al. 1999).

RAD51 expression levels have been correlated with increased invasiveness in breast cancer (Maacke et al. 2000), aggressiveness in prostate cancers, in both sporadic and BRCA germline mutation-associated cancers (Mitra et al. 2009). However, the mechanisms leading to *RAD51* overexpression in cancer cells are not entirely understood. But transcriptional regulation in the promoter region is believed to play the major role in *RAD51* transcription. For instance, the tumor suppressor protein p53 interacts indirectly with response elements at the *RAD51* core promoter and with the Rad51 protein to inhibit both its expression and activity (Arias-Lopez et al. 2006; Linke et al. 2003). Interestingly, Hasselbach et al. have observed significantly enhanced promoter activity of the *RAD51* gene by substituting G for C and T at the polymorphic positions +135 (rs1801320) and +172 (rs1801321), respectively (Hasselbach et al. 2005).

RAD51 genetic variants, 135 and 172 at the 5′-UTR, have been studied in BC and other cancers (Antoniou et al. 2007; Zhou et al. 2011; Gao et al. 2011; Yu et al. 2011; Sun et al. 2011; Ding et al. 2009; Michalska et al. 2015). Variant 135-C allele has been found to be significantly associated with high risk of breast cancer development and low risk of ovarian cancer development among BRCA1/2 carriers (Wang et al. 2001). Another study has showed that the G135C polymorphism is associated with a higher risk of breast cancer development in BRCA2 carriers, but not in BRCA1 carriers or non-carriers (Kadouri et al. 2004). Moreover, the G135C polymorphism has been found to increase the risk of familial BC in women less than 50 years old at diagnosis (Jara et al. 2007). This field remains controversial and variants in all exons of *RAD51* gene have been studied and no variants were associated with development of familial breast cancer (Lose et al. 2006; Gal et al. 2006; Blasiak et al. 2003; Brooks et al. 2008; Kuschel et al. 2002). Besides, the homozygous T172T variant has been associated non-significantly with Thyroid Cancer (Bastos et al. 2009). Inversely, a protective effect of T172T homozygous variant allele has been found in SCCHN patients particularly in P53 homozygous Arg72Arg (Lu et al. 2007). Moreover, *RAD51* 135 C but not 172 T allele has been associated with reduced risk for AML, suggesting that this variant in the *RAD51* gene may modulate genetic predisposition to AML (Rollinson et al. 2007).

Meta-analysis studies have showed elevated risk for breast cancer associated with the homologous G135C polymorphism among BRCA2 mutation carriers (Antoniou et al. 2007; Zhou et al. 2011; Gao et al. 2011). However, it has been shown that non-BRCA1/2 mutation carriers are also at the risk of breast cancer development (Yu et al. 2011). On the other hand, a meta-analysis study has suggested that the *RAD51* G135C polymorphism is a low-penetration risk factor for developing breast cancer (Sun et al. 2011). SNPs of *RAD51* interacting proteins have also been suggested to work in parallel with *RAD51* SNPs to determine breast cancer susceptibility (Ding et al. 2009).

In the current case–control study, we set out to study the relationship between G135C (rs1801320) and G172T (rs1801321) variants and the risk of sporadic breast cancer.

Fig. 1 Sequence histogram of part of 5′-UTR region of *RAD51* gene. **a** Homozygous variant G135G is ▶ indicated by *black arrow*. **b** Heterozygous variant G135C is indicated by *black arrow*. **c** Homozygous variant C135C is indicated by *black arrow*. **d** Homozygous variant G172G is indicated by *black arrow*. **e** Heterozygous variant G172T is indicated by *black arrow*. **f** Homozygous variant T172T is indicated by *black arrow*

Methods and Techniques

Patients and Samples

One hundred and six paraffin embedded tissue blocks (FFPE) were collected randomly from two different populations of sporadic BC female patients; thirty-three samples were collected from Italian breast cancer patients (Santa Chiara Hospital, Pisa-Italy) and seventy-three samples were collected from Jordanian breast cancer patients (King Abdullah University Hospital, Ramtha-Jordan). A control group of fifty four blood samples were collected from Italian female population without a diagnosis of breast cancer. All BC samples were collected from sporadic cases with no family history or BRCA mutations.

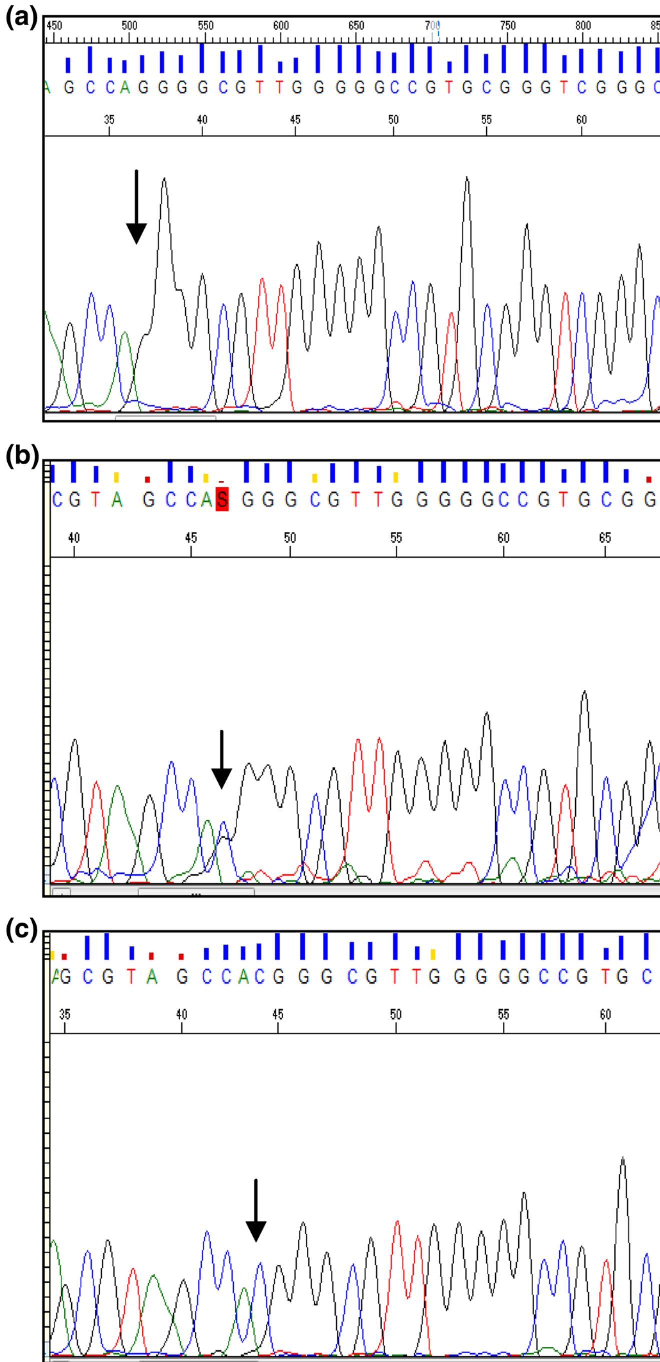
DNA Extraction

Ten um thickness of 4 sections of FFPE samples were de-paraffinized by two steps of xylene for 5 min each, followed by centrifugation for 5 min on maximum speed (16.100X). Removing of xylene from the pellet is performed by two steps of absolute ethanol cleaning; by incubation for 5 min each step and centrifugation on maximum speed. Ethanol is evaporated by air dry under the chemical cabinet for 20–30 min. Genomic DNA from tumor tissues and corresponding control samples was prepared using a Qiagen DNeasy kit (Qiagen, Germany).

PCR Amplification and Sequencing

PCR amplifications targeting the *RAD51* gene area of interest was performed using two pairs of primer based on the *RAD51* sequence obtained from the National Center for Biotechnology Information (NCBI). Primer pairs were chosen to amplify 5′-UTR region that includes the targeted polymorphisms (Forward Primer: 5′-AGCTGGGAACTGCAACTCAT-3′, reverse primer: 5′-CGCCTCACACACT-CACCTC-3′). PCR amplification was performed in 30 μl reaction volumes that contained 75 mM Tris–HCl, 1.5 mM MgCl2, 50 mM KCl, 20 mM $(NH_4)_2SO_4$, 0.2 mM of each primer and 1 U of Taq DNA polymerase. PCRs were done under the following cycling conditions: an initial 7 min of denaturation at 95°C followed by 45 cycles for 45 s each at 94, 59, and at 72°C for 1 min, and a single final extension step for 10 min at 72°C.

Direct DNA sequencing was performed using Big Dye Terminator (Ver. 3.1) kit (Applied Biosystems, USA). Samples were run on an ABI Prism Genetic Analyzer system 3130xl (Applied Biosystems, USA).



(a)
450 500 550 600 650 700 750 800 850
A G C C A G G G G C G T T G G G G G C C G T G C G G G T C G G G C
35 40 45 50 55 60
(b)
C G T A G C C A S G G G C G T T G G G G C C G T G C G G
40 45 50 55 60 65
(c)
A G C G T A G C C A C G G G C G T T G G G G C C G T G C
35 40 45 50 55 60

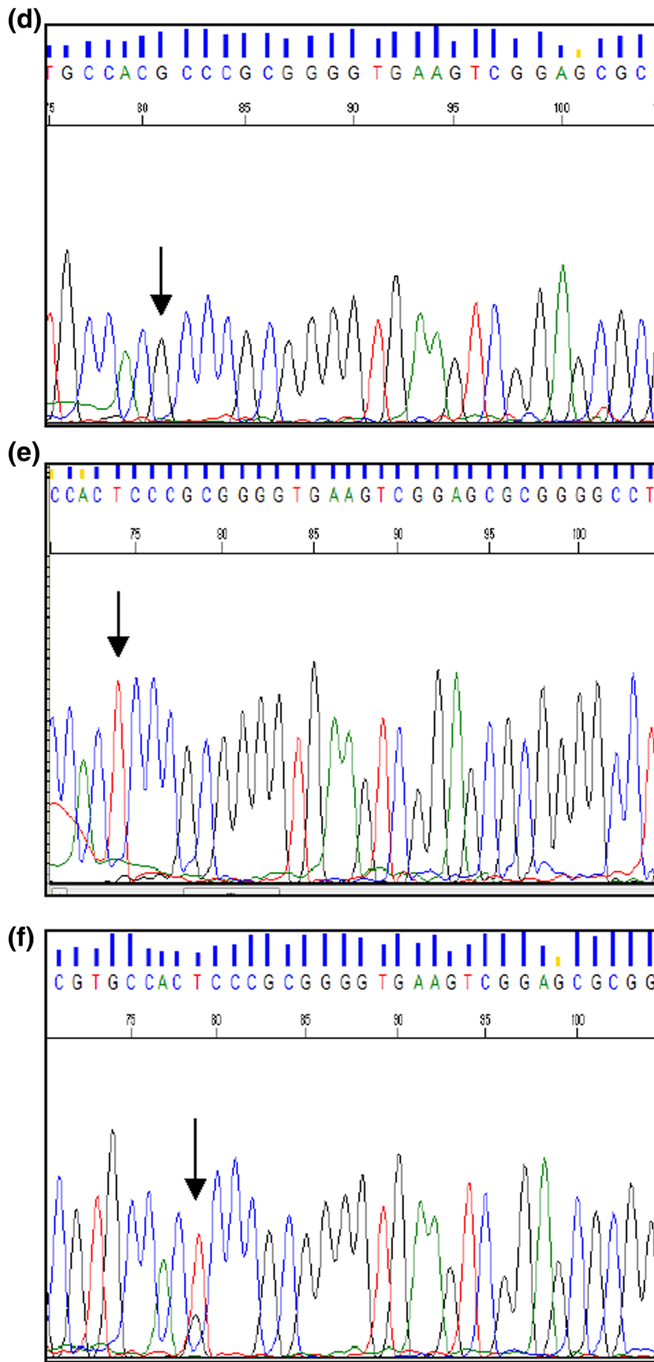


Fig. 1 continued

Statistical Analysis

Fisher's exact test analysis was used for the calculation of p value, odds ratio (OR), and 95% confidence interval (CI) and Hardy–Weinberg Equilibrium (HWE) evaluation. GraphPad Prism-6 software was used for statistical analysis, $p < 0.05$ was considered significant.

Results

Direct sequencing of the 5′-UTR promoter region of *RAD51* gene shows the position of variant G135G(Fig. 1a), variant G135C (Fig. 1b), and variant C135C (Fig. 1c). Out of 106 patients, 92 tumor samples have Homozygous G135G alleles, representing 86.8% of the total cases, while the other polymorphisms were represented as follows; variant G135C and C135C, 13 (12.3%) and 1 (0.9%), respectively, (Table 1). On the other hand, 49 control samples out of 54 were homozygous for variant G135G (90.7%) while the other variants G135C and C135C were 5 (9.3%) and 0 (0.0%), respectively. Statistical analysis of these variants in the patient and control group did not show any significant relationship between this variant (G135C) and breast cancer susceptibility in both or either population, which is consistent with some studies (Fig. 2a).

Histogram sequencing of the 5′-UTR promoter region of *RAD5* gene showed the position of variant G172G (Fig. 1d), variant G172T (Fig. 1e), and variant T172T (Fig. 1f). Out of 106 patients, 22 tumor samples have Homozygous G172G alleles, representing 20.8% of the total cases, while the other polymorphisms were represented as the following; variant G172T and T172T, 14 (13.2%) and 70 (66%), respectively, (Table 2). On the other hand, 17 control samples out of 54 were Homozygous for variant G172G representing 31.5% of the control group. While the other variants G172T and T172T were 29 (53.7%) and 8 (14.8%), respectively. A highly significant association was found between this polymorphism (T172T) and breast cancer susceptibility ($p < 0.001$) (Fig. 2b). In order to rule out the possibility of an association between the two variants T172T or G135C and breast cancer susceptibility, we analyzed the polymorphisms by dividing the groups into T172T or G135C carriers against the all other variants (G172T or G172G or G135G) carriers. T172T or G135C carriers showed stronger a relationship with breast cancer susceptibility in comparison with the control group (Fig. 3) ($p = 0.0001$).

Table 1 Percentage distribution of G135G, G135C, and C135C polymorphisms in breast cancer (BC) cases and control group, showing no significant difference between breast cancer cases and control group

SNP	Tumors	(%)	Control	(%)	
G135G	92	86.8	49	90.7	OR 1.598
G135C	13	12.3	5	9.3	95% CI 0.5638–4.528
C135C	1	0.9	0	0.0	$p > 0.05$
Total	106	100	54	100	

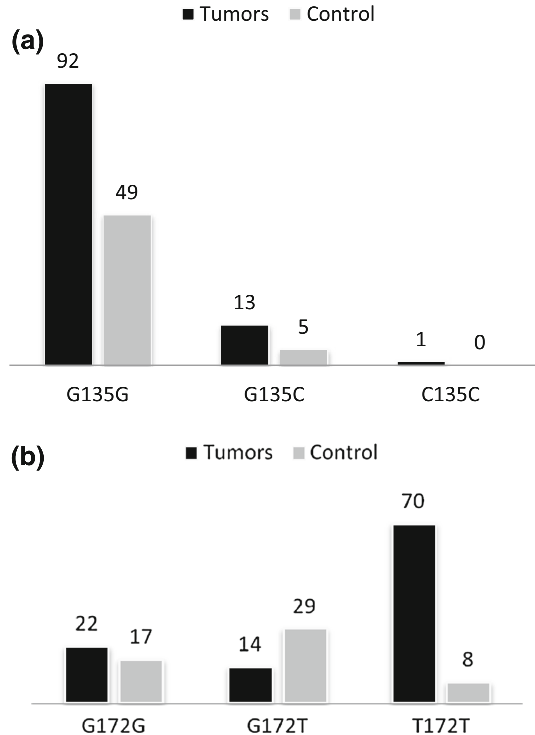


Fig. 2 **a** Frequencies of G135G, G135C, and C135C polymorphisms in breast cancer BC cases and control group, there is no significant difference between breast cancer (*Black*) and control group (*Gray*). **b** Frequencies of G172G, G172T, and T172T polymorphisms in breast cancer (BC) cases versus control group, a significant value have been found between BC (*Black*) and control group (*Gray*)

Our data showed that all cases from two different populations have a significant association between Homozygous T172T polymorphism in *RAD51* promoter region and breast cancer susceptibility. Moreover, each population, Jordanian or Italian cancer cases showed the same significant value for Homozygous T172T polymorphism in the *RAD51* gene. In the 73 Jordanian breast cancer cases, 46/73 (63%), 10/73 (14%), and 17/73 (23%) have T172T, G172T, and G172G polymorphisms, respectively. While the Italian cancer cases have the following polymorphism distribution: 24/33 (73%), 4/33 (12%), and 5/33 (15%) for T172T, G172T, and G172T polymorphisms, respectively. The Italian population of cancer cases showed the same significant association for increased risk of breast cancer among homozygous T172T carriers.

Discussion

Homologous recombination is a crucial process for DNA double-strand break DSB repairing mechanisms, RAD51 a recA homologous protein in eukaryotes is a key player that promotes homologous pairing and strand exchange (Masson and West 2001; Baumann and West 1998). *RAD51* expression has been associated with BC and other cancers. However, the mechanism of *RAD51* expression is not fully understood. Nevertheless, transcriptional regulation in the promoter region is

Table 2 Percentage distribution of G172G, G172T, and T172T C135C polymorphisms in breast cancer (BC) cases and control group, showing a significant difference between breast cancer cases and control group ($p < 0.001$)

SNP	Tumors	(%)	Control	(%)	
G172G	22	20.8	17	31.5	OR 3.717
G172T	14	13.2	29	53.7	95% CI 2.283–6.052
T172T	70	66.0	8	14.8	$p < 0.0001$
Total	106	100	54	100	

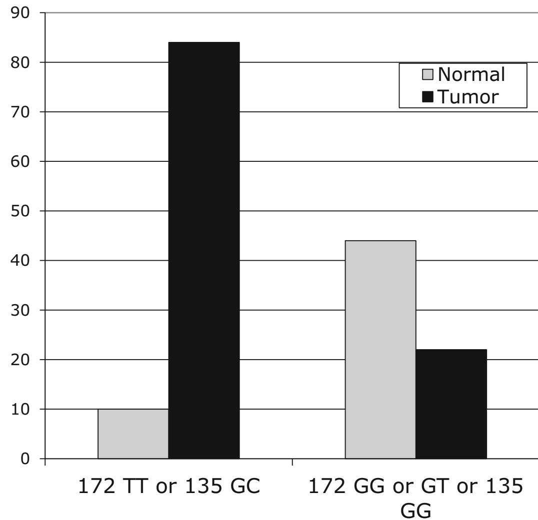


Fig. 3 Frequencies of T172T or G135C polymorphisms against the all other wild type genotypes (G172G, G172T and G135G) in breast cancer (BC) cases (*Black*) versus control group (*Gray*), a significant difference is found between BC (*Black*) and control group (*Gray*), $p = 0.0001$

believed to play the major role in *RAD51* transcription (Arias-Lopez et al. 2006; Linke et al. 2003). Moreover, promoter activity of the *RAD51* gene has been activated by substituting G for C and T at the polymorphic positions +135 (rs1801320) and +172 (rs1801321), respectively (Hasselbach et al. 2005).

Our results did not find any significant association between G135C variant and BC risk, which is consistent with previous results (Lose et al. 2006; Gal et al. 2006; Blasiak et al. 2003; Brooks et al. 2008; Kuschel et al. 2002). However, other studies have shown significant impact of G135C polymorphism in the development of BC among BRCA carriers and less than 50 years old females (Wang et al. 2001). Age group and familial BC could modify the impact of 135-C allele.

On the other hand, we found a highly significant association between T172T homozygous variant and the risk of sporadic BC. Our findings are very consistent with recent results (Michalska et al. 2015). Previous studies did not show any significant association between G172T variant and BC susceptibility due to some technical approach or out of focus research. Most of the previous studies used RFLP technique for the G135C polymorphism. We used direct sequencing to evaluate the

polymorphic variants at 5′-UTR of *RAD51* gene. Nevertheless, SNPs of *RAD51* interacting proteins have also been suggested to work in parallel with *RAD51* SNPs to determine breast cancer susceptibility (Ding et al. 2009).

In current study, the analysis was performed on entire tumor tissue which includes cancerous and normal stromal cells. Therefore, the genotypes of (rs1801320) and (rs1801321) could be uncertain what exactly the source of the polymorphic variation. Collection of peripheral blood samples would be the best choice for such study; even though it was very difficult to collect peripheral blood samples from our selected population because of many obstacles related to availability of the patients. The other choice could be by laser capture micro-dissection procedure which is not available. Consequently, FFPE samples were the choice of sample collection, which might be a limitation of our study. Nevertheless, our results will increase the interest in the types of samples that should be collected from cancer patients for future studies.

In conclusion, we suggest 5′-UTR variants, G135C and T172T together, to be associated with sporadic BC susceptibility. Our results showed a highly significant association between 172T and 135C haplotype and BC risk. More studies are recommended to reveal the relationship between these variants and breast cancer risk. Only one functional study demonstrated the enhancement of *RAD51* gene expression by substitution C and T at positions 135 G and 172 G, respectively. Biochemical studies are also needed to understand the effect of these polymorphisms on gene function and expression (Hasselbach et al. 2005).

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Compliance with Ethical Standards

Conflicts of interest No potential conflicts of interest were disclosed.

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