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RAD51-UTR HAPLOTYPE GENETIC POLYMORPHISMS AND SUSCEPTIBILITY TO BREAST CANCER IN WOMEN FROM JORDANIAN POPULATION

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***Background*: Genetic predisposition to breast cancer (BC) has been extensively explored to achieve an enhanced understanding of the biology of BC. Targeting candidate genes to screen different genetic variants such as *RAD51* gene that plays a critical role in DNA repair pathways including the double-strand break repair system is an important task. *Aim:* To study several single nucleotide polymorphisms (SNPs) within RAD51-UTR gene and to find their relationship with BC risk and prognosis among Jordanian females. *Materials and Methods:* In this case-control study, DNA sequencing technique was used to screen SNPs within the untranslated region (UTR) of RAD51 in 206 cases and 185 controls and the resulting data were statistically analyzed using different types of genetic analyses. Patients' clinical and pathological features were obtained from their medical records to perform genotype-phenotype association analysis. *Results:* Our findings show a significant association between both SNPs rs528590644, rs1801320 and BC risk ($p = 0.016$). We estimated the correlation between many of BC prognostic factors and BC risk, and we found an association between rs1801321 and age at first menstruation ($p = 0.032$) in addition to a strong correlation between age at BC diagnosis and rs1801320 ($p = 0.008$). *Conclusion:* RAD51-UTR polymorphisms may be involved in BC development and progression.**

***Key Words*: breast cancer, RAD51-UTR, prognosis, DNA repair pathway.**

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Breast cancer (BC) is a multifactorial disease associated with several factors responsible for its development and progression such as smoking, oxidative stress, pregnancy status, radiation exposure, behavior, diet, and stress [1]. A combination of these environmental and patient-related factors can cause DNA damage and genomic alterations, which may lead to BC development usually when the DNA repair system is altered. Homologous recombination (HR) proteins play a crucial role in maintaining DNA integrity under many environmental genotoxic factors [2, 3]. Genetic impairments within critical genes that play a specific role in carcinogenesis-related functions may influence BC development or progression. DNA repairing pathways are the foremost defense mechanisms against genomic instability and DNA damage [4]. Failure of DNA repair system may shift the cell fate to cancer development rather proceeding to apoptosis. For instance, mutations in *BRCA1* and *BRCA2* are associated with BC occurrence in around 10% of total cases. Therefore, alterations in other DNA repairing proteins have been proposed to be associated with the development of many cancers including BC. Mutations, in particular, single nucleotide polymorphisms (SNPs) are the most investigated genetic variants in the human genome to seek a clear vision of the correlation between these variants and malignancies including BC [5, 6].

DNA double-strand breaks (DSBs) occur naturally during cell division or may be caused by environmental exposure [7]. DSB repair mechanism is a fundamental process to maintain the genome integrity and to detect the DSBs that lead to promoting carcinogenesis [8, 9]. Exposing genes that are involved in HR pathway of DSBs repair to the field of study may provide understanding for the biology of cancer [10]. Variants within different genes including *ATM*, *BRIP1*, *CHEK2,* and *XRCC2* have been identified as BC inherited risk genetic variants [11–13].

Also, *RAD51* has been recently in the spotlight as a key protein that plays a critical role in HR by mediating the synopsis of the two homologous strands [14–16]. *RAD51* gene is located on 15q15.1 and comprises nine coding exons [17]; any change in the genetic components of this gene could lead to a significant alteration in the expressed proteins, which may affect the DSBs repair pathway [18].

rs1801320 is a significant variant located in 5′ untranslated region (5′UTR) of the *RAD51* gene and involves the substitution of G to C at position 135. It has been suggested that this polymorphism manipulates mRNA stability of *RAD51* which in turn affects the DNA repair pathway and subsequently induces tumor formation [19]. In addition to rs1801320, the contribution of *RAD51* polymorphisms to BC has been

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Abbreviations used: BC – breast cancer; DSBs – DNA double-strand breaks; ER – estrogen receptor; HER2 – human epithelial receptor 2; HR – homologous recombination; PCR – polymerase chain reaction; PR – progesterone receptor; SNP – single nucleotide polymorphism; UTR – untranslated region.

explored [20]. Many epidemiological studies investigated the role of *RAD51* in BC development and progression [17, 21, 22]. Interestingly, these studies have shown disparities in the findings, possibly due to the heterogeneity of the studied cohorts [19, 23–26].

The purpose of this study is to investigate the correlation between SNPs within the 5′-UTR region within *RAD51* gene and BC risk. Furthermore, we aim to clarify the association between a group of clinicopathological features of BC and the screened polymorphisms in *RAD51*.

MATERIALS AND METHODS

Study cohort. In this study, 206 female BC patients in addition to 185 matched healthy individuals were recruited as study subjects from the Jordanian Royal Medical Services hospital. All the participants were randomly selected from Jordanian Arab descent. Ethical approval was obtained from the Intuitional Review Board at Jordan University of Science and Technology with the ethical code number (32/104/2017). Written informed consents were obtained for each volunteer. Descriptive data about patients including demographic, clinical, and pathological information were collected from patients' medical records at Jordanian Royal Medical Services.

DNA extraction. Blood sample (5 ml) was withdrawn from each participant and DNA was extracted using the DNA Purification KitWizard® Genomic (Promega, USA). The extracted DNA was then tested for quality and quantity validation using gel electrophoresis and Nano-Drop ND-1000 UV-Vis Spectrophotometer (BioDrop, UK).

PCR and DNA sequencing. Polymerase chain reaction (PCR) was performed to amplify the 5′-UTR within *RAD51* gene using *s*pecific sets of primers; F -5′-AGCTGGGAACTGCAACTCAT-3 and R-5′-CGCCTCACACACTCACCTC-3 [27]. Briefly, 3 µL of the extracted genomic DNA plus 4 µL of primers were added to 12.5 µL of 2X ready to use PCR master mix from New England Biolabs (*Taq* 2X Master Mix, USA) with nuclease-free water to reach the volume of 25 µL.

The DNA sequencing was performed as previously published by Al-Eitan *et al*. [28] using the genetic analyzer (3130x1, Applied Biosystems, USA) according to the BigDyeTerminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA). Subsequently, the chromatograms of the sequenced DNA were visualized using Chromas Pro software v.1 (USA) and compared to a reference sequence (Ensembl ID: ENSG00000178568) using Ensembl genome browser (*http://www.ensembl.org/index. html*).

Statistical analysis. Hardy — Weinberg equilibrium equation (Court lab — HW calculator) was used to calculate the genotypic and allelic frequencies. The genetic association was estimated using Pearson's chi-square test. In addition, genetic association using different genetic models was performed using SNPSTAT software (version 2.11 of Bioconductor). Pearson's chi-square and ANOVA tests were also used to estimate the phenotype-genotype correlation. In this study, *p*-value was considered as statistically significant only if less than 0.05. The Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS, Inc., USA) was used to conduct the statistical analysis.

RESULTS

Candidate SNPs of RAD51 and their association with BC. Table 1 illustrates the selected polymorphisms within *RAD51*-UTR. In this study, four out of the seven SNPs that have been screened were polymorphic. The genotype and allele frequencies for the screened polymorphisms of *RAD51* are also summarized in Table 1. Remarkably, the variant allele (C) of rs528590644 was not detected among patients, while it accounted for 1% among controls and the minor allele (G) of rs530836900 was not observed among controls except for individual cases. Furthermore, the homozygous variant allele (TT) distribution among cases (26.3%) was significantly higher than among controls (14.3%) of rs1801320. Our findings revealed that both polymorphisms rs528590644 and rs1801320 were associated with BC with the same *p*-value ($p = 0.016$). However, neither rs530836900 nor rs1801321 were in correlation with BC in this study (Table 1).

In addition, a genetic association test using different genetic models was performed to clarify the relationship between *RAD51* polymorphisms and BC. As Table 2 shows, only rs1801320 and rs1801321 were applicable for this test. Our findings revealed that none of the investigated models showed significant association with BC except for the co-dominant and recessive models of rs1801320 ($p = 0.015$ and 0.0038, respectively) (Table 2).

Haplotype analysis. Haplotypes resulted from *RAD51*-UTR polymorphisms (rs1801321, rs1801320, rs530836900, and rs528590644) are demonstrated in Table 3. The table shows haplotype variant frequencies in case and control. The haplotype analysis in this study revealed a significant association between GTCA haplotype and BC risk, $p = 0.005$ (Table 3).

Genotype-phenotype analysis. In this study group of clinical and pathological features of BC being characterized and tested for correlation with *RAD51*-UTR polymorphisms, most of these features are prognostic and predictive factors for BC. Table 4 illustrates these parameters and their association with *RAD51* SNPs. We found an association between rs1801321 and age at first menstruation ($p = 0.032$), in addition to a strong correlation between age at BC diagnosis and rs1801320 ($p = 0.008$). However, there was no relationship between rs530836900 and any of the investigated clinical factors (Table 4).

Moreover, Table 4 summarizes the pathological parameters of BC and their relationship with *RAD51*-UTR variants. Common and critical factors for BC prognosis such as progesterone (PR) and estrogen receptor (ER) status and human epithelial

Table 1. Genetic association between *RAD51*-UTR candidate SNPs and BC

Gene	SNP ID	Allele/Genotype	Cases (206)	Controls (185)	Chi-square	*p*-value*
RAD51-UTR	rs528590644	A	424 (100%)	363 (99%)	5.797	0.016*
		C	0	5 (1%)		
		AA	212 (100%)	179 (97.3%)	5.835	0.016*
		AC	0	5 (2.7%)		
	rs530836900	C	396 (99.5%)	366 (100%)	1.844	0.174
		G	2 (0.5%)	0		
		CG	2 (1%)	0	1.84	0.398
		CC	198 (99%)	183 (100%		
	rs1801321	C	54 (13.4%)	45 (12.4%)	0.148	0.700
		G	350 (86.6%)	317 (87.6%)		
		CC	3 (1.5%)	4 (2.2%)		
		CG	48 (23.8%)	37 (20.5%)	0.833	0.659
		GG	151 (74.7%)	140 (77.3%)		
	rs1801320	T	189 (46.8%)	139 (38.4%)	5.482	0.019*
		G	215 (53.2%)	223 (61.6%)		
		TT	53 (26.3%)	26 (14.3%)		
		TG	83 (41%)	87 (48.1%)	8.225	0.016*
		GG	66 (32.7%)	68 (37.6%)		

Note: *significant difference.

Table 2. Genetic association between *RAD51*-UTR polymorphisms and BC using different genetic models

Gene	SNP ID	Category test	*p*-value*
RAD51-UTR	rs1801320	Co-dominant: common Hz (GG) *vs* Het (GT) *vs* Rare Hz(TT)	0.015*
		Dominant; Common Hz (GG) *vs* Het and Rare Hz (GT+TT)	0.320
		Recessive: Common Hz and Het (GG+GT) *vs* Rare Hz (TT)	0.003*
		Over dominant: Common Hz and Rare Hz (GG+TT) *vs* Het (GT)	0.170
	rs1801321	Co-dominant: common Hz (GG) *vs* Het (GC) *vs* Rare Hz(CC)	0.660
		Dominant; Common Hz (GG) *vs* Het and Rare Hz (GC+CC)	0.550
		Recessive: Common Hz and Het (GG+GC) *vs* Rare Hz (CC)	0.600
		Over dominant: Common Hz and Rare Hz (GG+CC) *vs* Het (GC)	0.430

Note: *significant difference.

Table 3. Haplotype analysis of *RAD51*-UTR polymorphisms

Haplotype RAD51-UTR (rs1801321, rs1801320, rs530836900 and rs528590644)	Frequency of block	Frequency ratio (case: control), %	Odd ratio (95%) CI	*p*-value
GGCA	0.4462	0.3976: 0.5021	1.0	NA
GTCA	0.4184	0.4641: 0.3659	0.65 (0.48–0.88)	0.0058*
CGCA	0.1215	0.1333: 0.1069	0.63 (0.39–1.03)	0.067
Global haplotype association *p*-value: 0.0067				

Note: *significant difference.

Table 4. Association of *RAD51*-UTR SNPs with clinicopathological characteristics of BC patients

Clinical characteristics	rs1801321 (GG *vs* CG *vs* CC) *p*-value	rs1801320 (TT *vs* TG *vs* GG) *p*-value	rs530836900 (CC *vs* CG) *p*-value
Body mass index**	0.621	0.848	0.408
First pregnancy (age)**	0.910	0.579	0.520
Age at BC diagnosis**	0.645	0.008***	0.487
Allergy*	0.498	0.501	0.098
Age at first menstruation**	0.032***	0.722	0.516
Breastfeeding status*	0.375	0.833	0.473
Age at menopause**	0.261	0.837	0.476
Family history*	0.169	0.577	0.482
Co-morbidity*	0.910	0.335	0.291
Smoking*	0.653	0.512	0.533
Pathological characteristics			
Progesterone receptor*	0.884	0.051	0.311
Estrogen receptor*	0.923	0.240	0.587
HER2*	0.964	0.499	0.986
IHC profile (L.A *vs* L.B *vs* T.N)	0.931	0.413	NA
Tumor differentiation grade*	0.871	0.083	0.461
Axillary lymph nodes*	0.245	0.143	0.306
Tumor stage*	0.860	0.509	0.770
Histology classification*	0.669	0.906	0.370
Tumor size**	0.236	0.919	0.402
Lymph node involvement*	0.298	0.694	0.646

Note: *genotype-phenotype association *p*-value using Pearson Chi-squared test; **genotype-phenotype association *p*-value using ANOVA test. L.A: luminal A; L.B: luminal B; T.N: triple negative; ***significant difference.

receptor 2 (HER2) were included. In this current study, no association was disclosed between any of these pathological factors and the investigated polymorphisms of *RAD51*-UTR.

The heterogeneity of molecular markers (PR, ER, and HER2) which are known as immunohistochemistry (IHC) profile was also studied. Considering that data was available for only 124 patients, Table 4 shows three different types of BC according to IHC profiles: luminal A; ER(+) and /or PR(+) plus HER(–), luminal B: ER(+) and /or PR(+) plus HER(+) and T.N: triple negative ER(–) and PR(–) plus HER(–). However, we did not

detect any association between BC types and *RAD51*-UTR polymorphisms (Table 4).

DISCUSSION

A malfunction in DNA repair mechanics is the starting point for cancer development [29]. DSB is a reliable repair system responsible for genome integrity and stability [30]. Correspondingly, genetic alteration within a functional gene that plays a key role in DSB repair pathway may lead to cancer development including BC [31]. *RAD51* is one of the important genes that participate in the DSB repair system [32–35].

In this study, four polymorphic SNPs have been screened in BC female patients and matched healthy subjects. We investigated the association between *RAD51*-UTR polymorphisms and BC as well as the clinical and pathological prognosis parameters.

Genetic association analyses in this study indicated a significant association between both polymorphisms (rs528590644, rs1801320) and BC risk while the other two SNPs were not in correlation with BC. Our findings showed that the distribution of rs528590644 variant allele (C) was only distributed among controls but not among cases in contrast to the common allele (A) distribution. In light of these results, we propose the (A) allele of rs528590644 within *RAD51*-UTR as an increased risk variant for BC among Jordanian females. Concerning rs1801320, we suggest that both variant allele (T) and homozygous variant (TT) genotype are implicated in BC development and progression in Jordanian women. Haplotype analysis was conducted in this study to show the combined effects of *RAD51*-UTR on BC risk. Significantly, we propose that GTCA haplotype is linked with BC susceptibility.

Furthermore, the influence of *RAD51*-UTR polymorphisms on BC prognosis was explored. In this work, we detect an association between rs1801321 and age at first menstruation in addition to a correlation between age at BC diagnosis and rs1801320. Therefore, we propose that *RAD51* variants may interfere with BC prognosis. However, we did not find any connection between *RAD51* polymorphisms and the investigated pathological factors.

Several studies investigated candidate polymorphisms within the *RAD51* gene and how they could be correlated to BC development and progression [24, 36–38]. However, inconsistent findings among ethnic groups and within the same population have been revealed. In accordance to this study, Sekhar *et al.* [39] stated that homozygous substitution (CC) of 135 G > C polymorphism within *RAD51* increases the risk of BC significantly. In contrast, Korak *et al.* [19], Sliwinski *et al.* [40], and Synoweic *et al.* [41] did not find any association between BC risk and *RAD51* 135G > C polymorphism. Le Calvez-Kelm *et al.* [26] also screened *RAD51* for rare variants in 1.330 early-onset BC cases in addition to 1.123 controls and reported no significant disease-related genetic variant.

Despite the independent role of *RAD51* in tumorigenesis, it has been known to interact with other genes such as *BRCA*1/2 for HR repair. In this regard, the impact of *RAD51* variants among BC *BRCA*1/2 mutation carriers on BC risk has been also explored, both studies by Lose *et al.* [17] and Rapakko *et al.* [22] reported no association between *BRCA1* and *BRCA2*-negative BC and *RAD51 variation.* Nevertheless, RAD51 has been found to be involved in the triple negative BC me-

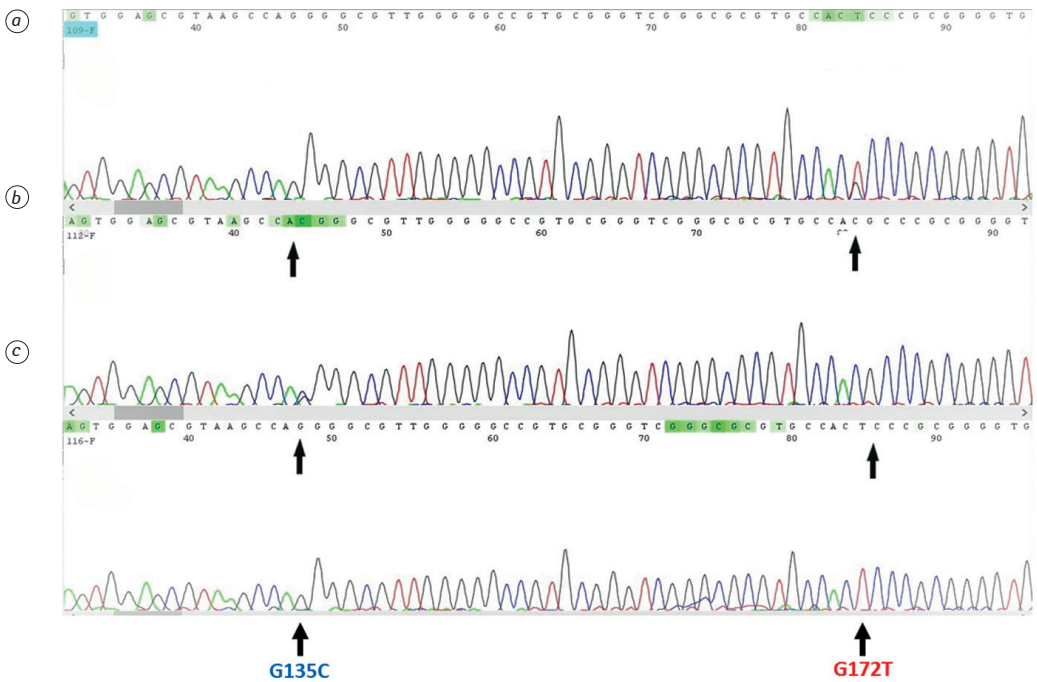

Figure. A representative chromatogram of the 5'UTR region in the *RAD51* gene: *a* — representing sample with GG genotype for G135C variant and GT genotype for G172T variant; *b* — representing sample with GC genotype for G135C variant and GG genotype for the G172T variant; c — representing sample with GG genotype for the G135C variant and TT genotype for the G172T variant

tastasis [42, 43]. And RAD51 targeting have shown a promising BC treatment option [44, 45].

In conclusion, we propose that genetic alteration of *RAD51* may influence its vital function and correspondingly influence tumor formation including BC. Moreover, *RAD51* polymorphisms may be involved in poor prognosis of BC. Comprehensive studies including protein and mRNA research are needed to reveal the precise role of *RAD51* rare variants on BC progression and development for better understanding of BC biology that may lead to new therapeutic regimens which in turn increase the survival rates worldwide.

CONFLICT OF INTEREST DISCLOSURES

All authors declare no conflict of interest.

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ГЕНЕТИЧНИЙ ПОЛІМОРФІЗМ ГАПЛОТИПУ RAD51-UTR ТА СХИЛЬНІСТЬ ДО РАКУ МОЛОЧНОЇ ЗАЛОЗИ У ЖІНОК З ЙОРДАНСЬКОЇ ПОПУЛЯЦІЇ

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Стан питання: Генетична схильність до раку молочної залози (РМЗ) широко вивчалася для досягнення більш глибокого розуміння біології РМЗ. Пошук генів-кандидатів для скринінгу різних генетичних варіантів, таких як ген *RAD51*, який відіграє важливу роль у репарації ДНК, включаючи систему репарації дволанцюгових розривів, є важливим завданням. ***Мета:*** Дослідити кілька однонуклеотидних поліморфізмів (SNP) у гені *RAD51*-UTR і виявити їх взаємозв'язок з ризиком розвитку РМЗ і прогнозом серед йорданських жінок. ***Матеріали та методи.*** У цьому дослідженні «випадок-контроль» метод секвенування ДНК використовувався для скринінгу SNP в нетрансльованій ділянці (UTR) RAD51 у 206 випадках і 185 контрольних зразках. Отримані дані були статистично проаналізовані з використанням різних методів генетичного аналізу. Інформація про клінічні та патологічні характеристики пацієнтів була отримана з їх медичних карт і використана для проведення аналізу асоціації генотип-фенотип. ***Результати:*** Отримані результати вказують на значний зв'язок між обома SNP rs528590644, rs1801320 і ризиком розвитку РМЗ (p = 0,016). Ми оцінили кореляцію між багатьма прогностичними факторами РМЗ і ризиком РМЗ і виявили зв'язок між rs1801321 і віком першої менструації (p = 0,032), а також сильну кореляцію між віком на момент встановлення діагнозу і rs1801320 (p = 0,008). ***Висновок:*** Поліморфізми *RAD51*-UTR можуть відігравати роль у розвитку та прогресії РМЗ.

Ключові слова: рак молочної залози, *RAD51*-UTR, прогноз, шляхи репарації ДНК.