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Role of *MRE11* in DNA damage repair pathway dynamics and its diagnostic and prognostic significance in hereditary breast and ovarian cancer

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Abstract

Background DNA damage repair pathway genes are key components for maintaining genomic stability and are mainly associated with hereditary breast and ovarian cancer.

Methods The present study aimed to investigate the gene expression profile of DNA damage repair pathway genes, including *BRCA1*, *BRCA2*, *ATM*, *TP53*, *CHEK2*, *MRE11*, *RAD50*, *BARD1*, *PALB2*, and *NBN,* in hereditary breast and ovarian cancer patients using quantitative real-time PCR.

Results The study showed significant upregulation of most DNA damage repair genes in HBOC patients compared to controls, except *MRE11*, which was downregulated. Receiver operating characteristic (ROC) curve analysis revealed that *MRE11* ($p < 0.001$), *BRCA1* ($p < 0.001$), *BRCA2* ($p < 0.001$), and *PALB2* ($p < 0.001$) can be used as potential diagnostic biomarkers for hereditary breast and ovarian cancer. Spearman correlation analysis showed that *RAD50* was significantly associated with the *BRCA1/2* mutation status ($p = 0.05$). Furthermore, bivariate analysis revealed a strong positive correlation between *BARD1* gene expression and the expression of *BRCA1*, *PALB2,* and *NBN* genes. Kaplan–Meier survival analysis showed that reduces expression of the *MRE11* gene was associated with better overall survival.

Conclusions The study findings may lead to a better understanding of the molecular mechanisms underlying hereditary breast and ovarian cancer, suggesting its role as a potential diagnostic and prognostic marker.

Keywords Hereditary breast and ovarian cancer, DNA damage repair, Peripheral blood, Real time PCR, *BRCA1*, *BRCA2*

Introduction

The escalating prevalence of breast cancer (BC) in India is a significant concern, with nearly 60% of cases diagnosed at an advanced stage. This increase in BC incidence is attributed to various factors, including delayed healthcare-seeking behavior and challenges in early detection [1, 2]. Hereditary breast and ovarian cancer (HBOC) is a significant issue worldwide, with studies indicating that 5–10% of all breast cancer patients are genetically predisposed to cancers due to inherited genetic mutations in specific genes such as *BRCA1* and *BRCA2*. The burden of breast and ovarian cancers

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among Indian women is substantial, with breast cancer being the most prevalent [3, 4]. According to NCCN guidelines, pathogenic *BRCA1/2* variants significantly increase cancer risk worldwide. The lifetime breast cancer penetrance ranges from 41 to 90%, with cumulative risks of 72% for *BRCA1* and 69% for *BRCA2* by age 80. The cumulative ovarian cancer risk by age 70 is higher in *BRCA1* carriers (48.3%) than in *BRCA2* carriers (20.0%), with pathogenic variants detected in 3.8%–14.5% and 4.2%–5.7% of invasive ovarian cancer cases, respectively [5].

Beyond *BRCA1* and *BRCA2*, the NCCN guidelines include non-BRCA genes in gene panels for HBOC, such as *TP53*, *PTEN*, *CDH1*, *ATM*, *CHEK2*, and *PALB2*. These genes are associated with an increased risk of breast and ovarian cancer, emphasizing the importance of comprehensive genetic testing [5]. *BRCA1* and *BRCA2* are tumor suppressor genes that play critical roles in maintaining genomic integrity by inducing DNA double-strand breaks (DSB) via homologous recombination repair (HRR) [3]. In addition, DNA repair pathways maintain genetic stability through repair of DNA damage caused by endogenous or exogenous agents, and dysregulation of these pathways is associated with cancer progression [6, 7]. Various tumor suppressor genes facilitate DNA damage in DNA Damage repair (DDR) pathway, including *ATM*, the *MRE11-RAD50-NBN* (MRN) complex, *CHEK2*, *BARD1*, *BRCA1*, *BRCA2*, and *RAD51*. These genes identify DNA breaks, activate cell cycle checkpoints, and enable DNA repair mechanisms by maintaining genomic integrity [8]. *BARD1* is a crucial partner of *BRCA1* for its stability in vivo, and germline *BARD1* mutations have been reported in families with breast and ovarian cancer, highlighting other DNA repair genes [9]. Similar to *BARD1*, *PALB2* serves as a partner and localizer of *BRCA2*, engaging with both *BRCA1* and *BRCA2*, and participating in homologous recombination repair processes. Pathogenic mutations in *PALB2* are associated with an increased risk of developing breast and ovarian cancer, similar to mutations in *BRCA1* and *BRCA2* [10].

Moreover, the cell cycle checkpoint kinases *CHEK2* is downstream substrate of *ATM*, which act as the "central transducers" of the DDR by phosphorylating and stabilizing *TP53*. It is important for regulating checkpoints properly and activation of DNA repair mechanism [6, 11, 12]. Given its pivotal function in DDR, disruption of the *ATM-CHEK2-TP53* complex may result in genomic instability, heightening the susceptibility to cancer development, and is hypothesized to be a barrier against cancer initiation [13, 14]. The expression patterns of DNA repair genes provide significant prognostic and predictive insights into various molecular subtypes of breast cancer. Specifically, certain genes, such as *ATM* and *TOP2 A*, have been correlated with patient outcomes and responses to treatment [15].

In addition to *ATM-CHEK2-TP53*, the MRN complex regulates the DNA damage response due to DSB, replication fork collapse, telomere dysfunction, and viral invasion [16, 17]. *MRE11* serves as a vital constituent of the MRN complex involved in DSB repair. The nuclease activity of *MRE11* is crucial for initiating *ATM* activation in response to DSBs. Additionally, the MRN complex facilitates the resection of DSB ends and promotes repair through HRR when non-homologous end joining (NHEJ) is stalled, with *MRE11* nuclease activity playing a pivotal role in driving these events [18, 19]. Aberrant expression of MRN complex proteins, particularly in familial breast cancer and triple-negative tumors, correlates with high-grade tumors and poorer patient survival. Germline mutations in *MRE11* have been proposed as novel candidate for susceptibility to breast cancer in non-*BRCA1/2* families [20].

These genes play a critical role in preserving genome integrity and mutations in these genes can increase the risk of tumorigenesis. Understanding the molecular mechanisms underlying *BRCA1* and *BRCA2* in maintaining genome stability is imperative to added precise therapies and interventions for individuals susceptible to HBOC. DNA repair pathways, especially *BRCA1* and *BRCA2*, play crucial roles in HBOC. Targeting these genes is promising for enhancing treatment and patient outcomes [8, 21]. Moreover, the DDR pathway has emerged as a valuable diagnostic and therapeutic target in breast and ovarian cancers [22, 23]. DNA repair proteins and DDR gene expression in peripheral blood show promise as minimally invasive biomarkers for early detection and prognosis [24]. Their role in genomic stability, immune interactions, and therapeutic response highlights their potential in personalized cancer treatment [25]. In our previous study, we identified pathogenic mutations in *BRCA1*, *BRCA2*, *BRIP1*, *TP53*, *ATM*, and *PALB2*, with *BRCA1/2* mutations being the primary contributors to hereditary breast and ovarian cancers in our cohort [4]. To further understand the role of DDR pathway genes in our population, we investigated the expression profiles of DDR pathway genes in hereditary breast and ovarian cancer patients.

Materials and methods

Sample collection

This study enrolled 63 patients with HBOC and 41 age-, sex-, and ethnically matched healthy controls without a family history of cancer. All the participants provided written informed consent. This study was approved by the Institutional Ethical Committee and Institutional Review Board of the Gujarat Cancer and Research

Table 1 List of Gene-Specific Primers Used for Real-Time PCR

Gene		Primer sequence (5′— 3′)	Amplicon length (bp)	Ref. or gene Accession no
β-ACTIN	F	ATTGGCAATGAGCGGTTC	70	NM_001101.5 [26]
	R	CGTGGATGCCACAGGACT		
BRCA1	F	CTGAAGACTGCTCAGGGCTATC	155	NM_007294.4 [27]
	R	AGGGTAGCTGTTAGAAGGCTGG		
BRCA2	F	AGCCCTTTGAGAGTGGAAGTG	70	NM_000059.4
	R	TGAGACCATTCACAGGCCAA		
ATM	F	CTCTGAGTGGCAGCTGGAAGA	129	NM_000051.4
	R	TTTAGGCTGGGATTGTTCGCT		
TP53	F	GGAGCCGCAGTCAGATCCTAG	100	NM_000546.6 [28]
	R	CAAGGGGGACAGAACGTTG		
CHEK2	F	CCCAAGGCTCCTCCTCACA	81	NM_007194.4 [29]
	R	AGTGAGAGGACTGGCTGGAGTT		
MRE11	F	CTTGTACGACTGCGAGTGGA	285	NM_005591.4 [30]
	R	TTCACCCATCCCTCTTTCTG		
RAD50	F	GCGGAGTTTTGGAATAGAGGAC	185	NM_005732.4 [31]
	R	GAGCAACCTTGGGATCGTGT		
BARD1	F	TGCAGCCAAGAATGGGCATGTG	145	NM_000465.4
	R	CTTCTCTGGTAGCAGCAATAGCG		
PALB2	F	ATTGTGAACCACTTTTGCCAACT	130	NM_024675.4
	R	TTTTGATGACGACTTTTCTTCCCTT		
NBN	F	ATGGAGGCCATATTTCCATGAC	152	NM_002485.5 [32]
	R	CAAGCAGCCAGAACTTGGAAG		

Institute. The exclusion criteria included secondary primary malignancies, other hormonal illnesses, HIV/HBsAg/HCV-positive status, and pregnancy. Clinical data, including age, sex, disease site, TNM stage, and histopathological findings, were obtained from the Medical Records Department. Patients were followed up for a minimum of three years for survival analysis.

RNA extraction and cDNA synthesis

Total RNA was extracted from Peripheral Blood cells (PBCs) samples using a QIAamp RNA Blood Mini Kit (QIAGEN, Germany). The extracted RNA was quantified using a Qubit 3.0 fluorometer (Thermo Fisher Scientific, US). cDNA was synthesized from 1 µg of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied BioSystems, Thermo Fisher Scientific, US) in a 20 µl reaction volume, according to the manufacturer's instructions. The synthesized cDNA was stored at − 80 °C until further use.

Quantitative real-time PCR (qPCR)

Gene expression analysis of DDR pathway genes was performed by quantitative PCR (qPCR). Target genes included *BRCA1*, *BRCA2*, *ATM*, *TP53*, *CHEK2*, *MRE11*, *RAD50*, *BARD1*, *PALB2*, and *NBN*. *β-ACTIN* was used as the housekeeping gene. The primers used for the amplification are listed in Table 1.

The qPCR reaction included 50 ng of cDNA sample, 0.2 µmol of primer, and QuantiNova™ SYBR® Green PCR (2X) Master Mix, and was performed on an AriaMx Real-Time PCR System. Cycling conditions involved heat activation at 95 °C for 2 min, followed by denaturation at 95 °C for 5 s, annealing/extension at 60 °C for 10 s for 40 cycles, and a melt curve analysis from 65 °C to 95 °C.

Data analysis

Relative mRNA expression levels of target genes were calculated using the $2^{-\Delta\Delta Ct}$ method [33]. Melt curve analysis confirmed the presence of a single intact PCR product, indicating specific amplification without non-specific products.

Statistical analysis

To assess the normality of the data, the Kolmogorov–Smirnov test was performed using SPSS v27.0 software. If the *p*-value was less than 0.05, indicating non-normality, the non-parametric Mann–Whitney *U* test was employed for data analysis. The data are shown as the mean of the Fold change values to represent differential gene expression, patients having gene expression > 1.5-Fold-change value were considered to be up-regulated and patients

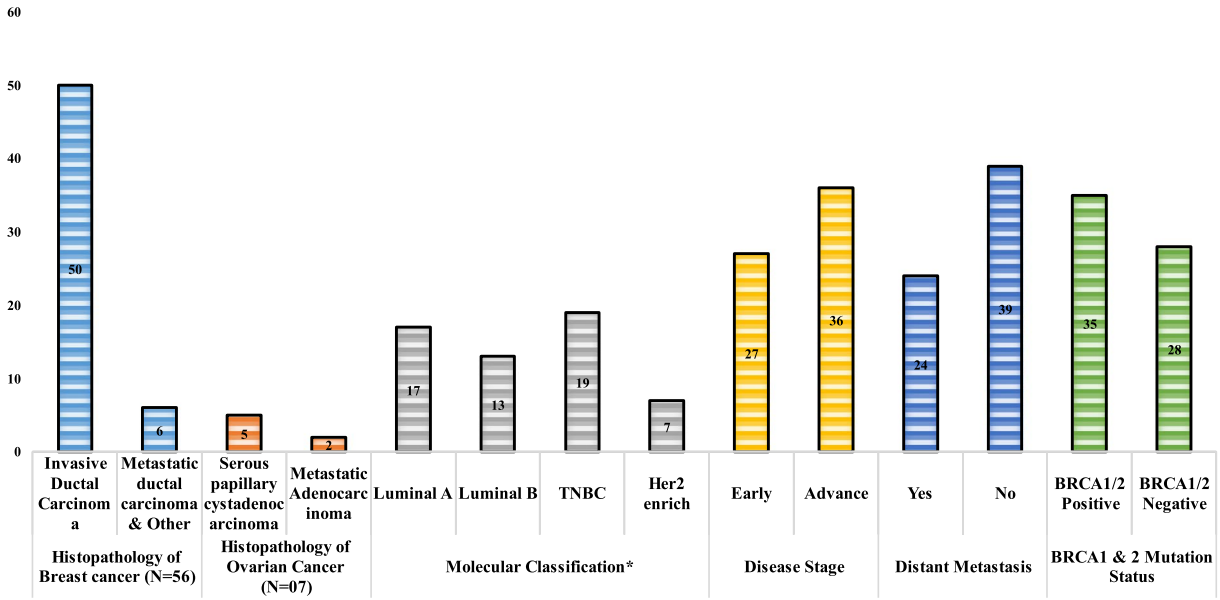

Fig. 1 Clinical and pathological details of HBOC patients.*Excluded Ovarian Cancer patients

having gene expression < 1.5-Fold change values were considered to be down-regulated. Furthermore, receiver operating characteristic (ROC) curve analysis was conducted using MedCalc software version 20 to develop a combination model of genes identified as potential biomarkers, demonstrating their diagnostic capabilities. Pearson's chi-square test was used to examine the correlation between various clinicopathological parameters and gene expression. Kaplan–Meier analyses were conducted to determine patient survival rates, with statistical significance considered at a p-value below 0.05 for the tests. The gene correlation matrix and cluster analysis of the normalized gene expression values for each sample were plotted using SRplot [34].

Results

Clinical and pathological features of HBOC patients

The present study analyzed the clinicopathological characteristics of 63 patients with HBOC. The median age at diagnosis was 45 years (range: 24–64), with 54.14% of the patients had early onset cancer. Most patients (88.89%) had breast cancer and 60.32% were postmenopausal. The majority of patients had a family history of breast cancer (66.67%), followed by those with a history of ovarian cancer, combined breast and ovarian cancer, and/or other early-onset cancers. Histologically, invasive ductal carcinoma was the most common breast cancer subtype (79.37%), while serous papillary cystadenocarcinoma was the predominant ovarian cancer subtype (7.94%). The breast cancer molecular subtypes were Luminal A (28.57%), Luminal B (20.63%), triple-negative (30.16%), and HER2-enriched (11.11%). Moreover, the majority of patients presented with advanced-stage disease (57.14%) compared to early-stage disease (42.86%), and distant metastases were observed in 38.10% of the cohort. More than half of the patients (55.56%) had pathogenic variants in the *BRCA1* or *BRCA2* genes (Fig. 1).

Differential gene expression of DDR pathway genes in HBOC Patients

In total, 63 HBOC blood samples were analyzed for gene expression by qPCR. Mann–Whitney *U* test revealed that the majority of DDR pathway genes exhibited significantly different expression levels between HBOC patients and healthy controls. Significant upregulation of *BRCA1* ($p < 0.0001$), *BRCA2* ($p < 0.0001$), *ATM* ($p < 0.0001$), *TP53* ($p < 0.0001$), *CHEK2* ($p < 0.0001$), *PALB2* ($p < 0.0001$), *NBN* ($p < 0.0001$), *RAD50* ($p < 0.0001$), and *BARD1* ($p < 0.0001$) was observed in PBCs from HBOC patients compared to controls (Fig. 2A). In contrast, *MRE11* ($p < 0.0001$) was significantly downregulated in HBOC patients compared to controls. Additionally, the cluster gram revealed a distinct pattern of DDR gene expression between HBOC patients and controls. (Fig. 2B).

Receiver operating characteristic (ROC) curves analysis of DDR pathway genes

ROC) curve analysis was employed to evaluate the diagnostic power of biomarkers to distinguish between HBOC patients and controls. Besides *ATM*, all the

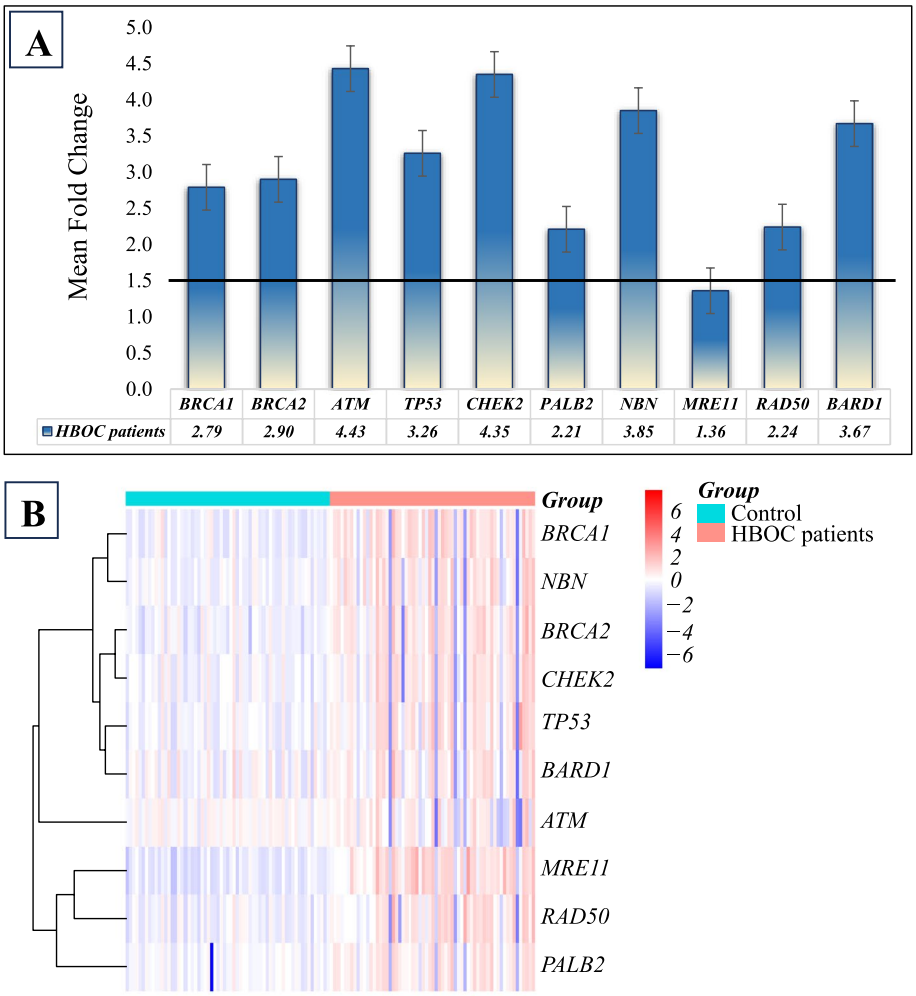

Fig. 2 Expression of DDR Pathway genes in HBOC patients. **A** The bar graph illustrates differential expression analysis of DDR pathway genes, with values representing the mean Fold Change ± SEM in HBOC patients compared to controls (**B**) Cluster gram of DDR Gene expression in HBOC patients and controls

genes of the DDR pathway significantly discriminated between HBOC patients and controls, most notably *MRE11* with an Area Under Curve (AUC) of 0.911 (95% CI, 0.847–0.955), *BRCA1* with an AUC of 0.819 (95% CI, 0.740–0.882), *BRCA2* with an AUC of 0.808 (95% CI, 0.728–0.872), and *PALB2* with an AUC of 0.805 (95% CI, 0.726–0.871). Moreover, ROC analysis of the other genes did not show a great discriminatory capacity (AUC < 0.80) (Table 2). The AUC, sensitivity, and specificity of the gene are plotted and shown in Fig. 3(A) and (B).

Correlation of DDR pathway genes with clinicopathological parameters

According to the results of the Pearson correlation analysis, the expression of *RAD50* ($\chi^2 = 3.823$, $p = 0.051$, $r = 0.246$) was significantly associated with *BRCA1/2* mutation status. A significant positive correlation was found

Table 2 AUC, sensitivity and specificity of DDR pathway genes

Gene Name	AUC	95% CI	Sensitivity	Specificity	*p* value
MRE11	0.911	0.847 to 0.955	82.5	98.4	< 0.001
BRCA1	0.819	0.740 to 0.882	68.3	95.2	< 0.001
BRCA2	0.808	0.728 to 0.872	81.0	81.0	< 0.001
PALB2	0.805	0.726 to 0.871	81.0	77.8	< 0.001
RAD50	0.770	0.687 to 0.840	53.9	96.8	< 0.001
CHEK2	0.763	0.680 to 0.835	69.8	85.7	< 0.001
NBN	0.755	0.671 to 0.827	68.3	87.3	< 0.001
TP53	0.746	0.661 to 0.819	69.8	82.5	< 0.001
BARD1	0.654	0.564 to 0.737	74.6	60.3	0.002
ATM	0.545	0.454 to 0.634	33.3	95.2	0.411

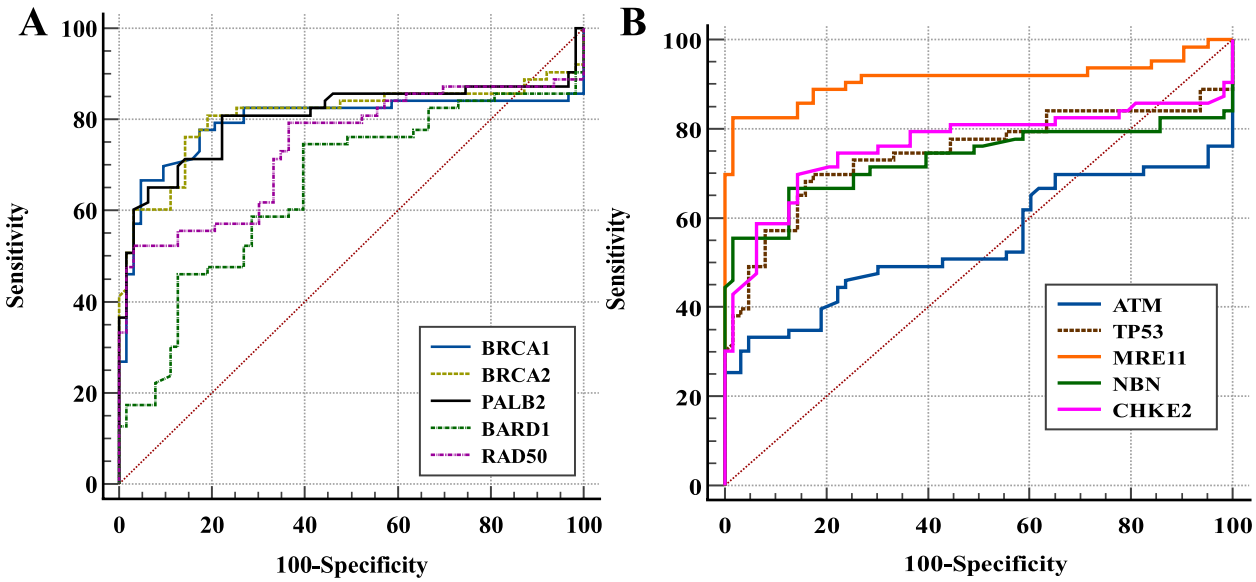

Fig. 3 Receiver operating characteristic (ROC) curves of DDR pathway genes in HBOC patients. **A** ROC curves for *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, and *RAD50* (**B**) ROC curves for *ATM*, *TP53*, *MRE11*, *NBN*, and *CHEK2*, illustrating their sensitivity and specificity to assess their diagnostic performance in HBOC patients. Area under the curve (AUC) values were calculated to evaluate the predictive accuracy of each gene in HBOC patients

between a family history of cancer and the expression of *TP53* ($\chi^2 = 8.767$, $p = 0.033$, $r = 0.013$) and *CHEK2* ($\chi^2 = 8.617$, $p = 0.035$, $r = 0.106$). Conversely, a family history of cancer was significantly negatively associated with the expression of *PALB2* ($\chi^2 = 7.672$, $p = 0.053$, $r = -0.045$), *RAD50* ($\chi^2 = 17.116$, $p < 0.001$, $r = -0.060$), and *BARD1* ($\chi^2 = 14.085$, $p = 0.003$, $r = -0.007$). Furthermore, *MRE11* expression ($\chi^2 = 5.114$, $p = 0.024$, $r = 0.430$) was significantly and positively associated with the histopathological diagnosis of breast cancer. The expression levels of other DDR pathway genes, including *BRCA1*, *BRCA2*, *NBN*, *ATM*, and *BARD1*, were not significantly associated with any of the clinicopathological parameters analyzed in the HBOC cohort.

An inter correlation of DDR pathway genes

Bivariate correlation analysis was conducted to explore the relationships between the expression levels of various DDR pathway genes in HBOC patients. Pearson correlation coefficients between the fold-change values of these genes were calculated and are presented in Fig. 4. According to the results of Pearson correlation analysis, *BRCA1* expression showed a strong positive correlation with *NBN* ($r = 0.854$, $p < 0.01$) and *BARD1* ($r = 0.816$, $p < 0.01$). *BRCA2* expression was highly positively correlated with *CHEK2* expression ($r = 0.889$, $p < 0.01$). *TP53* was strongly positively correlated with *BARD1* ($r = 0.934$, $p < 0.01$) and strongly correlated with *PALB2* ($r = 0.743$, $p < 0.01$). *PALB2* showed a strong positive correlation with *NBN* ($r = 0.825$, $p < 0.01$) and *NBN* was strongly correlated with *BARD1* ($r = 0.845$, $p < 0.01$). These strong positive correlations suggest potential co-regulation or shared pathways among the key DDR genes in HBOC. However, *ATM* exhibited the weakest and least significant associations with other DDR pathway genes.

Overall survival (OS) analysis of DDR pathway genes

Univariate survival analysis using the Kaplan–Meier method was performed on 63 HBOC patients with ≥36 months of follow-up to assess the prognostic significance of DDR pathway gene expression. Survival probabilities were calculated based on dichotomized expression levels (high vs. low) for each gene, and log-rank tests were used to evaluate differences between the groups. Low *MRE11* expression correlates with better survival, whereas high *MRE11* expression is linked to shorter overall survival (log rank = 8.901, $p = 0.003$) (Fig. 5). The mean survival time of patients with upregulated *MRE11* had a mean survival time of 30.0 months, whereas those with downregulated *MRE11* had a mean survival of 34.81 months. No other DDR genes were found to be significantly associated with overall survival in patients with HBOC.

Discussion

The DDR pathway is crucial for HBOC development. This complex network in cells coordinates the discovery, signaling, and fixing of different DNA damage types, such as DSBs single-strand breaks and DNA crosslinks [35]. The DDR pathway functions well in maintaining healthy genes and preventing cancer changes [11].

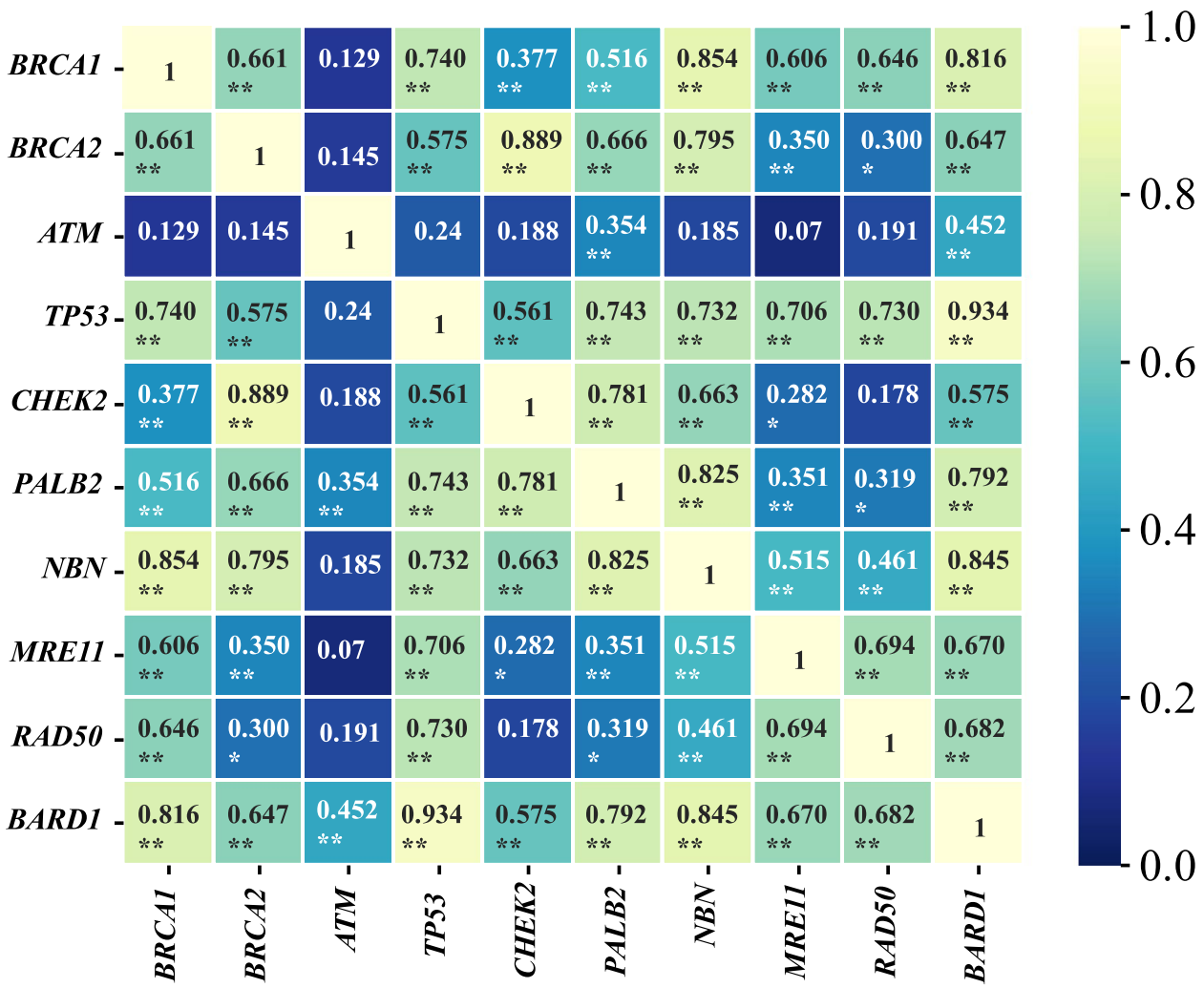

Fig. 4 Inter correlation of DDR pathway genes in HBOC patients. *$p < 0.05$, **$p < 0.01$

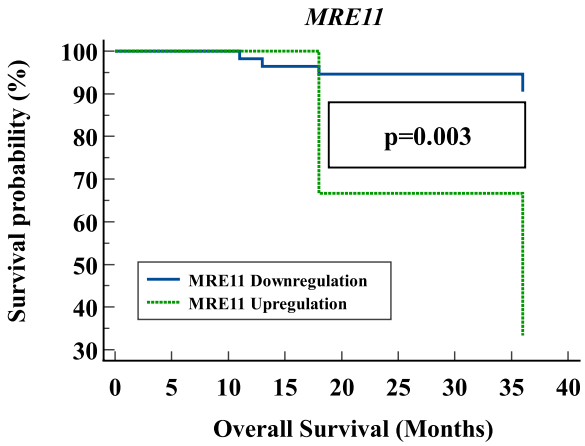

Fig. 5 Kaplan–Meier univariate survival analysis of *MRE11* in HBOC patients

HBOC is mainly caused by inherited mutations/alterations in *BRCA1* and *BRCA2*, which are important components of the DDR system. These tumor suppressor genes help to repair DNA through HR, and sudden malfunctions can cause gene instability, which can lead to cancer changes and tumor growth [36]. In addition to *BRCA1* and *BRCA2*, changes in other DDR genes such as *TP53*, *PALB2*, and *ATM* are also associated with HBOC risk [35].

ATM is a key kinase activated by DSBs, which initiates the genome maintenance pathway. The MRN complex, which is the primary sensor that detects and signals the presence of DSBs, activates the DDR pathway cascade [37]. Additionally, *ATM* induces the phosphorylation of *CHEK2* and *TP53* to control cell cycle arrest at the G1/S checkpoint and facilitates DNA repair, which can eventually induce senescence or apoptosis [36]. Other genes of the DDR pathway, such as *RAD51*, *RAD52*, *PALB2 (a*

BRCA2 binding partner), and *BARD1 (a BRCA1* localization partner), play crucial roles in HR-mediated DNA repair mechanism, and defects in these genes can contribute to genomic instability [38].

Moreover, DDR genes form complex regulatory networks with the HRR and NHEJ pathways to maintain genomic stability. Within the HRR pathway, *BRCA1* and *BRCA2* form functional complexes with *RAD51*, enabling precise repair of DNA double-strand breaks [39, 40]. Upstream regulation occurs through the *ATM/ATR* signaling cascade, where *ATM*-mediated phosphorylation modifies various targets, including *BRCA1* and *TP53*, following DSB detection [41]. Emerging research highlights that compromised function in these pathways creates vulnerabilities that can be targeted therapeutically, as demonstrated by PARP inhibitor efficacy in BRCA-deficient tumors [42, 43]. The synergistic nature of DDR pathways is evident through studies showing that simultaneous *ATM* and *TP53* dysfunction leads to more rapid tumor development than isolated mutations in either pathway [14, 44]. Therefore, elucidating the role of DDR pathway genes in HBOC will provide an understanding of the molecular mechanisms related to these genes and aid in the development of tailored therapies for HBOC.

The current study aimed to assess the mRNA expression levels of key DDR pathway genes in the PBCs of HBOC patients compared to healthy controls. Several studies have shown the utility of conducting mRNA expression or transcriptome analysis from PBCs as a non-invasive approach to detect gene expression patterns with high sensitivity and reliable diagnostic performance [45, 46]. Moreover, various studies have shown that gene expression in PBCs reflects early breast cancer development, supporting its use in early detection [47–49]. Additionally, mRNA expression levels of DNA repair and methylation-related genes in PBCs have been associated with cancer risk [50, 51]. The findings of our study indicate that the mRNA expression of most key DDR pathway genes, including *BRCA1*, *BRCA2*, *ATM*, *TP53*, *CHEK2*, *RAD50*, *BARD1*, *PALB2*, and *NBN*, were significantly upregulated in the PBCs of HBOC patients compared to healthy controls. Conversely, the expression of *MRE11* was significantly downregulated in the PBCs of HBOC patients compared to healthy controls. Our findings indicate a significant upregulation of DDR pathway genes in HBOC patients, which contrasts with the expected DDR deficiency typically associated with HRR defects. This upregulation may reflect a compensatory response to persistent genomic instability, where increased DDR gene expression in peripheral blood could be an attempt to counteract DNA damage [24, 52]. Similar patterns have been reported in other malignancies, where systemic DDR activation is linked to immune signaling and stress response pathways [25, 53]. Moreover, some studies have shown the upregulation of *BRCA1* and *BRCA2* in breast and ovarian cancers, which aligns with our findings [54–56]. According to Panera, N et al., 2022, *TP53* upregulation along with *BRCA1*and *BRCA2* is important for prognosis and therapeutic response in breast cancer patients [45]. Apart from *BRCA1/2*, various studies have supported the upregulation of the MRN complex, which includes *MRE11*, *RAD50,* and *NBN* genes in different malignancies [57, 58]. However, Poncet et al., 2008 found downregulation of *MRE11* and *RAD50* in B-chronic lymphocytic leukemia patients, which aligns with our findings [59]. *MRE11* deficiency leads to spontaneous chromosomal breaks and genome aberrations, contributing to cellular senescence and increased cancer risk [60]. Furthermore, several studies have shown that *ATM* expression is downregulated in breast cancer, which may contribute to the optimal response to PARP inhibitor treatment [61, 62]. However, *ATM* gene expression varies across different cancer types, *ATM* mRNA expression is significantly higher in colorectal cancer [63] and cisplatin-resistant lung cancer cells [64]. In addition to breast cancer, DDR pathway genes have been associated with various hereditary cancer syndromes such as pancreatic, colon, and gastric cancers [65]. Tumor suppressor genes like *TP53*, play key roles in immune regulation, apoptosis, and inflammation, leading to detectable systemic changes in PBMCs. These changes may reflect immune activation, tumor-host interactions, or systemic inflammation, supporting the rationale for analyzing TSG expression in blood [66, 67]. Emerging evidence suggests that primary tumors influence peripheral blood early by shedding neoplastic cells, serves as a non-invasive approach to investigating cellular heterogeneity, resistance mechanisms, and therapeutic targets in cancer [68, 69]. However, further validation using tumor tissue expression analysis, cfDNA profiling, or functional assays is necessary to determine whether this observed upregulation is a biological adaptation or a potential diagnostic biomarker for HBOC.

In our study, we found a significant positive correlation between a family history of cancer and the mRNA expression of *TP53* and *CHEK2*. However, a family history of cancer was significantly negatively associated with *PALB2*, *RAD50*, and *BARD1* expression levels. In contrast, Kurian et al., 2021 found that mutations in breast cancer susceptibility genes, including *TP53*, *CHEK2*, *PALB2*, *RAD50*, and *BARD1*, were not associated with family cancer history [70]. Furthermore, mRNA expression of *RAD50* was significantly associated with *BRCA1/2* mutation status. In contrast, *BRCA1*-associated cancers have lower nuclear *RAD50* expression [71]. In *BRCA* wild-type ovarian cancers, *RAD50* deletion was

associated with better overall survival and progression-free survival and could be used as a prognostic marker and linked to a better response to PARP inhibitor therapy [72]. Additionally, the present study revealed a positive correlation between *MRE11* expression and invasive ductal carcinoma (IDC), whereas Alblihy A et al., 2022 noted high *MRE11* expression was associated with high-grade, advanced-stage serous cystadenocarcinoma [17]. In the present study, no statistically significant correlation was observed between the expression levels of other DDR pathway genes, such as *BRCA1*, *BRCA2*, *NBN*, *ATM*, and *BARD1*, and any of the clinicopathological characteristics analyzed in the present study. Comparably, Harahap et al., 2018 showed no statistically significant association between the mRNA expression of *BRCA1* and clinicopathological parameters such as estrogen receptor, progesterone receptor, and *KI 67* expression [73]. A study by Alblihy A et al., 2022 found **a** strong positive correlation between *MRE11*, *RAD50,* and *NBN* in ovarian cancer [17]. In contrast, we found that the mRNA expression of *NBN* was strongly and positively correlated with the expression of *BRCA1, PALB2,* and *BARD1*. In addition, we found that *CHEK2* expression was strongly associated with *BRCA2* expression, and that *BARD1* expression was positively correlated with *BRCA1* expression. E3 ubiquitin ligase activity of *BARD1* and *BRCA1* heterodimers facilitates their interaction with other DDR proteins via the HR [74].

Furthermore, ROC curve analysis indicated that the mRNA expression of most DDR pathway genes, mainly *MRE11*, *BRCA1*, *BRCA2,* and *PALB2,* could significantly discriminate between HBOC patients and controls. Herein, the AUC value of these DDR pathway genes showed potential utility as sensitive and specific markers in HBOC patients and can be used as diagnostic markers. A study by Ge O et al., 2021 found similar observations in different malignancies, which showed that higher expression of *PALB2* in Pancreatic ductal adenocarcinoma could be an additional diagnostic marker [75]. According to Li L et al., 2024**,** a significant difference in the expression of *BRCA1* was observed between *BRCA*-associated breast cancer tissue and normal breast cells, which may act as a predictive marker in the disease [76]. Yang, C et al., 2017 reported that there were no studies have specifically identified the role of *MRE11* expression could be diagnostic marker in breast cancer [77]. It is interesting to note that reduced *MRE11* expression has been associated with better prognosis in various cancers, which showed that loss of *MRE11* may act as a tumor suppressor and increased genomic instability [78, 79]. Furthermore, loss of *MRE11* can enhance sensitivity of cancer cells to DNA damaging agents like radiation therapy and PARP inhibitors [80]. We found a significant correlation between reduced *MRE11* expression was associated with better survival, while higher *MRE11* expression was associated with poor overall survival. Our finding suggesting its potential role as a prognostic marker for various cancers, including HBOC. In addition, we did not find any significant correlations between other DDR pathway genes and OS. While, *MRE11* expression is strongly associated with overall survival and functions as a prognostic marker in various cancers, such as Colorectal Cancer [81], Gastric Cancer [82], Bladder Cancer [83], and Ovarian cancer [17]. For instance, patients with genetic mutations and comprehensive testing (e.g., NGS) can be used to identify pathogenic variants, with functional validation assessing their impact on DDR pathways. Targeted therapies, such as PARP inhibitors for *BRCA1/2* mutations and risk assessment with genetic counselling, can provide precise diagnosis, early detection, and personalized treatment strategies [84]. Due to the low prevalence of HBOC, this study was conducted in modest sample size, ensuring statistical robustness through data normalization test and various statistical analysis. Despite the modest sample size, significant trends were observed, warranting further validation in larger cohorts.

The key findings of the current study show upregulation of all DDR genes except *MRE11* expression. DDR gene upregulation is linked to cellular responses to DNA damage, whereas *MRE11* loss is associated with homologous recombination deficiency (HRD) and compromised DNA repair. Mutations in *BRCA1/2*, the main drivers of HBOC, may elevate breast cancer risk. Additionally, high MRN complex expression is associated with poor prognosis, treatment resistance, and poor therapeutic response in various cancers. However, Future investigations will utilize comprehensive gene panels and RNA sequencing analysis to expand upon these findings. This approach will enable the identification of additional biomarkers and genetic variants, while providing detailed transcriptomic data. The resulting insights will advance our understanding of HBOC development and reinforce the clinical relevance of the DDR pathway genes. Subsequent investigations have integrated these technological platforms to validate and extend the present observations.

Conclusion

The study emphasizes the fundamental role of the DDR pathway in the pathogenesis of HBOC, highlighting the upregulation of key DDR genes in HBOC patients. *MRE11* Expression may serve as a diagnostic and prognostic marker for HBOC. These findings contribute to a better understanding of the molecular mechanisms underlying HBOC and suggest potential diagnostic markers and prognostic targets. Due to modest sample

size, further studies with larger cohorts may shed light on their functional implications and highlight their potential as diagnostic or prognostic markers in HBOC.

Abbreviations

BC	Breast Cancer
HBOC	Hereditary breast and ovarian cancer
DSB	DNA double-strand breaks
HRR	Homologous recombination repair
DDR	DNA Damage repair
PBCs	Peripheral Blood Cells
NHEJ	Non-homologous end joining
qPCR	Quantitative Real-Time PCR
ROC	Receiver operating characteristic
AUC	Area Under Curve
OS	Overall survival
IDC	Invasive ductal carcinoma
PFS	Progression free survival
HRD	Homologous recombination deficiency

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Authors' contributions
B.T. and F.S. designed the computational framework and analysed the data. B.T. carried out the implementation and wrote the manuscript with input from both authors. F.S. reviewed the data and oversaw overall direction and planning to shape the research, analysis, and manuscript. Both authors read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The present study was approved by The Institutional Review Board Committee (IRB) of The Gujarat Cancer & Research Institute (EC/BHR/10/2022) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

Consent for publication
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Competing interests
The authors declare no competing interests.

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