Research Article

Association of XRCC3, XRCC4, BAX, and BCL-2 Polymorphisms with the Risk of Breast Cancer

Emre Ozoran,1 Fadime Didem Can Trabulus,2 Duygu Erhan,3 Bahadir Batar,4 and Mehmet Guven3

1Department of General Surgery, School of Medicine, Koc University, Istanbul, Turkey
2Department of General Surgery, Bahcesehir University Faculty of Medicine, Istanbul, Turkey
3Department of Medical Biology, Cerrahpasa School of Medicine, Istanbul University Cerrahpasa, Istanbul, Turkey
4Department of Medical Biology, Tekirdag Namik Kemal University School of Medicine, Tekirdag, Turkey

Correspondence should be addressed to Emre Ozoran; ozoran@gmail.com

Received 20 April 2021; Revised 6 December 2021; Accepted 20 December 2021; Published 14 March 2022

Academic Editor: Pranshu Sahgal

Copyright © 2022 Emre Ozoran et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Breast cancer is the most common malignancy in women. Genetic risk factors associated with breast cancer incidence have been identified. Aims. This study is aimed at determining the association of XRCC3 Thr241Met (rs861539), XRCC4 G(-1394) T (rs6869366) DNA repair and BAX G(-248) A (rs4645878), and BCL2 C(-938) A (rs2279115) apoptotic gene polymorphisms with breast cancer. Materials and Methods. Genetic analysis was performed using peripheral blood samples. Gene polymorphisms were detected by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. 175 patients and 158 healthy controls were enrolled in the study. Results. Breast cancer risk was 5.43 times more in individuals with AA genotype of Bax G(-248) A (rs4645878) (P = 0.002). The risk of metastasis was 11 times with this genotype. It was associated with 6 times more risk of having a tumor larger than 2 cm. The risk of breast cancer was 2.77 times more in individuals carrying the Met/Met genotype of XRCC3 Thr241Met (rs861539) (P = 0.009). The risk of having advanced clinical stage (stage III+IV) with the Met/Met genotype was 4 times more increased. No relationship with breast cancer was found with XRCC4 G(-1394) T (rs6869366) and BCL2 C(-938) A (rs2279115) gene polymorphisms. Conclusion. Multicenter trials using subjects with genetic variations are needed to establish the relationship between breast cancer and single gene polymorphism.

1. Introduction

Breast cancer is one of the most common malignancies seen in women and one of the leading reasons of cancer-related mortality in developed countries. The lack of clear knowledge about the molecular mechanisms responsible for the development of breast cancer empowers the need for detailed and all round studies on this subject. Although its etiology is not clearly known, several genetic risk factors related to the high incidence have been defined. Studies have suggested that DNA repair and apoptosis mechanisms could have a role in the development of breast cancer. It has been reported that DNA repair and apoptosis gene polymorphisms could affect breast cancer risk [1, 2].

DNA repair mechanisms play major roles in the sustainability of genomic integrity. Various types of DNA damages have been repaired with various types of DNA repair mechanisms. DNA double-strand breaks could result from factors like free radicals of endogenous origin, exogenous chemicals, and ionizing radiation [3]. Mammal cells have established two different pathways for the repair of DNA double-strand breaks, homologous recombination (HR) and non-homologous end joining (NHEJ). Epidemiological studies have shown that DNA double-strand breaks are a risk factor in the development of breast cancer [4]. These findings, put the genes responsible for DNA double-strand break repair important candidates for further studies.

Aiding in preserving the stability of the chromosome, X-ray repair cross-complementing group 3 (XRCC3) gene is
enrolled the HR pathway [5]. The product protein is enrolled in preserving the stability of the chromosome and in case of DSBs mending the DNA damage. XRCC3 gene has been mapped at 14q32.3 of the human chromosome. XRCC3 protein interacts with Rad51 during the repair process of DNA double-strand breaks aiding in the sustainability of DNA [6]. The X-ray cross-complementing group 4 (XRCC4) is an important component of NHEJ. XRCC4 gene has been mapped at 5q13-q14 of the human chromosome. XRCC4 protein forms a complex interacting with DNA ligase IV in the repair process of DNA double-strand breaks [7]. This complex is responsible for the ligation step of NHEJ repair. Single-nucleotide polymorphisms (SNPs) occurring in the XRCC3 and XRCC4 genes could enhance the injury caused by the unrepaired DNA damage leading to inclination to malignancy.

Apoptosis is programmed cell death at physiologic and pathologic circumstances. The disruptions in the apoptotic pathways could lead to development of cancer by affecting cellular hemostasis [8]. Apoptotic process is regulated by several proapoptotic or antiapoptotic proteins. Bcl-2 is a proapoptotic protein while Bax is an antiapoptotic protein. The levels of these two proteins are important indicators in the rate of apoptosis. BCL-2 gene has been mapped at 18q21.3 in the human chromosome. BCL-2 C(-938) A polymorphism at the promoter region of BCL-2 gene is the most common polymorphism. This polymorphism has been associated with predisposition to breast cancer [6, 9]. BAX gene has been mapped at 19q13.3. BAX G(-248) A polymorphism at the promoter region of the Bax gene has been associated with decreased Bax expression [10]. Many studies showed that BAX G(-248) A polymorphism has been associated with the risk of several cancers [11–13].

In our study, we investigated the relationship between breast cancer risk and genetic variations in DNA repair [XRCC3 Thr241Met and XRCC4 G(-1394) T] and apoptosis [BAX G(-248) A and BCL2 C(-938) A] pathways. Our results could aid in linking the presence of gene polymorphism with clinical findings.

### 2. Methods

#### 2.1. Study Population

The study population consisted of 175 female patients with breast cancer who admitted to the breast disease outpatient clinic of Istanbul Education and Research Hospital. The control group consisted of 158 women with the same demographic status as the disease group. The demographical information of the patients was obtained by one on one interviews. Histopathological diagnosis and data were obtained with the permission of the Pathology Department. The distributions of clinical characteristics of the patients are shown in Table 1.

The study was approved by the ethics committee of Istanbul Education and Research Hospital. The funding for genetic analysis was provided by the Education and Planning Committee of the same hospital. Genetic analysis was performed in Department of Medical Biology, Cerrahpasa School of Medicine, Istanbul University-Cerrahpasa.

#### 2.2. Extraction of DNA and Genotyping Analysis

Blood samples were taken into vacuumed, sterile K3-EDTA tubes (2 ml), and stored at −20°C until analysis. At the day of analysis, total genomic DNAs were prepared using DNA isolation kit (High Pure PZR Preparation Template kit, Roche Diagnostics GmbH, Mannheim, GE) according to the manufacturer’s instructions.

Genotyping of XRCC3 Thr241Met [14], XRCC4 G(-1394) T [15], BAX G(-248) A [16], and BCL2 C(-938) A [17] was determined by using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. PCR was initially performed to determine the
polymorphic regions using suitable primers. Each PCR was performed in a total volume of 25 μl reaction mixture containing 100 ng DNA, 1 X PCR buffer (with KCl), 0.04 mM dNTPs, 0.04 U Taq DNA polymerase, 10 pmol forward and reverse primers, and variable amount of H₂O. The PCR conditions were presented in Table 2. PCR products were further subjected to digestion with restriction enzymes (Table 3). The PCR products were visualized by electrophoresis through a 3% agarose gel. The relative size of the PCR products was determined through comparison of the migration of a 50–1000 bp DNA molecular weight ladder (Invitrogen, Grand Island, NY, USA). In the event of any conflicts, the genotypes were repeated.

2.3. Statistical Analysis. Mean and standard deviations (SDs) were shown as continuous variables. Student’s t-test was used in portraying the differences among two continuous variables. Chi square (χ²) or Fischer’s exact test (two sided) were utilized in evaluation the genotypes and alleles, and test for deviation of genotype distribution from Hardy–Weinberg equilibrium (HWE). P values of <0.05 were considered statistically significant. The odds ratio (OR) and their 95% confidence intervals (CIs) were calculated to estimate the strength of the association. The data were analyzed using Statistical Package for the Social Sciences (SPSS; version 18.0).

3. Results

Our study consisted of 175 patients and 158 healthy controls. Patients (53 ± 12 years, range from 21 to 84 years) and controls (54 ± 9 years, range from 25 to 85 years) were not different in terms of age (P = 0.44). Smoking rate was 35% in the patients and 37% in the controls. Smoking status was not significantly different between patients and controls (P = 0.81).

The distributions of the XRCC3 Thr241Met, XRCC4 G(-1394) T, BAX G(-248) A, and BCL2 C(-938) A genotypes were in accordance with the HWE among the cases and controls.

In the analysis of BAX G(-248) A gene polymorphism, homozygote expression (AA genotype) of BAX-248A allele was associated with 5 times increased risk of breast cancer (OR = 5.43, 95% CI = 1.70–15.84; P = 0.002). BAX-248 AA genotype was seen in 3% of the control group and 14% of the patients. The frequency of the G allele was 69% in the patients and 74% in the controls. The frequency of the A allele was 31% in the patients and 36% in the controls. The difference was not statistically significant (Table 4). In the analysis of XRCC3 Thr241Met polymorphism, women with homozygote expression (Met/Met genotype) of 241Met allele had three times increased risk of breast cancer (OR = 2.77, 95% CI = 1.26–6.11; P = 0.009). XRCC3 241 Met/Met genotype was seen in 9% of the controls and 19% of the patients. The frequency of the XRCC3 241Thr allele was 55% in the patients and 65% in the controls. The frequency of the XRCC3 241Met allele was 45% in the patients and 35% in the controls. These results were not statistically significant (Table 4). No such significant difference between groups was observed for neither the genotypes nor the alleles of BCL2 C(-938) A and XRCC4 G(-1394) T polymorphisms (Table 4).

We investigated the association between the clinical characteristics of the patients and XRCC3 Thr241Met, XRCC4 G(-1394) T, BAX G(-248) A, and BCL2 C(-938) A genotypes. The BAX G(-248) AA genotype defined as the risk genotype was associated with metastatic status (P = 0.02) and tumor size (P = 0.02). Patients with AA genotype had 4 times increased risk of having metastasis (OR: 10.8, 95% CI: 1.40–82.7). The patients with the AA genotype had 6 times increased risk of having tumor sizes more than 2 cm (OR: 6.1, 95% CI: 1.2–30.0). In addition, XRCC3 241 Met/Met genotype defined as the risk genotype was associated with clinical stage (P = 0.02). Patients with Met/Met genotype had 4 times increased risk of being clinical stage III + IV (OR: 3.85, 95% CI: 1.20–12.7). On the other hand, XRCC4 G(-1394) T and BCL2 C(-938) A gene polymorphism and all of the disease parameters did not have any statistically significant relationship. Also, we did not find any significant relationship between XRCC3 Thr241Met, XRCC4 G(-1394) T, BAX G(-248) A, and BCL2 C(-938) A polymorphisms and the ER/PR/HER2 and triple negative status of the patients (P > 0.05, data not shown).

4. Discussion

We investigated the relationship between the risk of breast cancer and XRCC3 Thr241Met, XRCC4 G(-1394) T, BAX G(-248) A, and BCL2 C(-938) A gene polymorphisms. These genes code for the proteins enrolled in DNA injury repair and apoptosis which are important processes in carcinogenesis. Several studies addressed the polymorphisms on these genes. The results from the previous studies show variations. The genetic differences endemic in a geographical area could be one of the reasons. The frequency of genetic variants associated with a gene polymorphism in a particular population is an important determinant of the breast cancer risk. Thus, differences in the incidence of variant alleles associated with a polymorphism among societies may lead to different results. The genes we studied encode proteins registered in DNA damage repair and apoptosis, which are important processes in carcinogenesis and breast cancer.

| Program | Cycle | Time | Temperature (°C) |
|---------|-------|------|-----------------|
| Initial denaturation | 1 | 4 min | 94 |
| Denaturation | 30 s | 94 |
| Annealing | 16 | 30 s | 68–53 |
| Extension | 1 min | 72 |
| Denaturation | 30 s | 94 |
| Annealing | 30 s | 55 |
| Extension | 1 min | 72 |
| Final extension | 1 | 5 min | 72 |
| Cooling | Indefinite | Indefinite | 4 |
The polymorphisms we have studied regarding these genes are polymorphisms that have been found to be related to different parameters and cancer risk in various cancers but have not been studied in the Turkish population.

In our study, women with homozygote BAX-248A allele (AA genotype) had 5 times more risk of developing breast cancer. In addition, status of metastasis and tumor size was associated with this genotype. These findings were similar with the study of Kholoussi et al. [18]. They found that presence of heterozygote variant BAX-248A allele (GA genotype) was associated with higher grade (grade 3 or more), T2 status and having lobular disease. Similar results were obtained in homozygote and heterozygote BAX-248A variant alleles (GA genotype+AA genotype), thus making BAX-248A variant allele as the "risk allele".

The relationship between BAX G(-248) A gene polymorphism and clinical parameters in different types of cancer has been studied previously with various different results. Wang et al. studied the effects of BAX G(-248) A gene polymorphism and survival in gastric cancer patients receiving postoperative chemotherapy. In their study, having at least one variant genotype in BAX G(-248) A was associated with

### Table 3: PCR and RFLP procedures and expected products of XRCC3 Thr241Met, XRCC4 G(-1394) T, Bax G(-248) A, and BCL2 C(-938) A genes.

| Genes          | Primers (forward and reverse) | PCR product | Restriction enzyme | Restriction products                  |
|----------------|-------------------------------|-------------|--------------------|---------------------------------------|
| XRCC3 Thr241Met| 5′-GCTGGTGAAGTGACAGTCCAAAAC-3′, 5′-TGCAACGGTCGGGTCTTCTT-3′ | 456 bp      | Nla III (37°C)     | Thr/Thr: 316 + 140 bp Met/Met: 211 + 140 + 105 bp |
| XRCC4 G(-1394)T| 5′-AGAGGCCGCAATCCACCTTT TG-3′, 5′-AGTATTAGGCGCTTCTGAGG-3′ | 257 bp      | Mbo II (37°C)      | GG: 165 + 92 bp TT: 257 bp            |
| Bax G(-248) A  | 5′-CTATTAGGCTGGATTTGAGCG-3′, 5′-GCTGGGATGGTTGTGGTGA-3′ | 109 bp      | Msp I (37°C)       | GG: 89 + 20 bp AA: 109 bp             |
| BCL2 C(-938) A | 5′-CTGCCTTCAATTTATCCAGCA-3′, 5′-GGCCTGAGATGAATTACA-3′ | 262 bp      | Bcc I (37°C)       | CC: 154 + 108 bp AA: 262 bp          |

### Table 4: Distribution of XRCC3 Thr241Met, XRCC4 G(-1394) T, Bax G(-248) A, and BCL2 C(-938) A genotypes among the controls and patients.

| Genotype/allele | Controls, n(%) | Patients, n(%) | P value | OR (95% CI) |
|-----------------|----------------|----------------|---------|-------------|
| BX A(-248) A     |                |                |         |             |
| GG              | 80 (51)        | 92 (53)        | 0.12    | 0.68 (0.42–1.10) |
| GA              | 74 (47)        | 58 (33)        | 0.002   | 5.43 (1.70–15.84) |
| AA              | 4 (3)          | 25 (14)        | 0.90    | 0.92 (0.50–1.72) |
| BCL2 C(-938) A  |                |                |         |             |
| CC              | 33 (21)        | 52 (30)        | 0.06    | 0.56 (0.31–1.01) |
| CA              | 76 (48)        | 68 (39)        | 0.32    | 0.71 (0.38–1.32) |
| AA              | 49 (31)        | 55 (31)        | 0.85    | 0.85 (0.47–1.54) |
| XRCC3 Thr241Met |                |                |         |             |
| Thr/Thr (CC)    | 61 (39)        | 52 (30)        | 0.38    | 1.27 (0.77–2.10) |
| Thr/Met (CT)    | 83 (52)        | 90 (51)        | 0.009   | 2.77 (1.26–6.11) |
| Met/Met (TT)    | 14 (9)         | 33 (19)        | 0.19    | 1.51 (0.82–2.79) |
| XRCC4 G(-1394)T |                |                |         |             |
| GG              | 24 (15)        | 32 (18)        | 0.98    | 1.05 (0.55–2.05) |
| GT              | 66 (42)        | 93 (53)        | 0.10    | 0.55 (0.28–1.10) |
| TT              | 68 (43)        | 50 (29)        | 0.36    | 0.45         |
| G allele frequency | 0.36          | 0.35          | 0.25    | 0.68 (0.37–1.26) |
| T allele frequency | 0.64          | 0.55          |         |             |
increase in the recurrence risk and poorly affecting survival [19]. Gu et al. studied the relationship of BAX G(-248) A gene polymorphism and hematological toxicity in patients with advanced stage small cell lung cancer receiving platinum based chemotherapy. They showed that BAX G(-248) A gene polymorphism did not affect survival [20].

The analysis we conducted on XRCC3 Thr241Met polymorphism portrayed that, homozygote expression of 241Met allele (241Met/Met) was associated with 3 times increased risk of developing breast cancer. This genotype was also associated with clinical stages of III + IV. Chai et al. performed a meta-analysis on XRCC3 Thr241Met gene polymorphism and breast cancer arriving at similar results as our study. In that study having 241 Met/Met genotype in XRCC3 Thr241Met gene polymorphism was reported as a risk factor for breast cancer especially in the Asian population [11, 21]. Qureshi et al. studied the effects of XRCC3 (Thr241Met) gene polymorphism and breast cancer, and their results were similar with our study [22]. In their study 241Met/Met genotype was associated with 1.5 times increased risk of developing breast cancer. Similar results as our study were obtained by Jara et al., who studied the effects of XRCC3 Thr241Met gene polymorphism and breast cancer [23]. It was shown that XRCC3 241Met allele carriers had increased risk of developing breast cancer. Smith et al.'s study on the relationship with breast cancer patients and healthy controls was in parallel with our study, finding to relationship with XRCC3 Thr241Met gene polymorphism and breast cancer [24]. On the other hand, in the study by Romanowicz et al. investigating the relationship between DNA repair gene polymorphisms and breast cancer; XRCC3 Thr241Met gene polymorphism was not associated with the risk of breast cancer [25]. The relationship between XRCC3 Thr241Met gene polymorphism and breast cancer was not studied previously. Nonetheless, Ji et al. showed that XRCC3 Thr241Met gene polymorphism did not have an effect on response to chemotherapy treatment and overall survival in osteosarcoma patients [26].

In our study, no statistically significant relationship was found between XRCC4 G(-1394) T gene polymorphism and breast cancer. In the study of Chiu et al., on the other hand, homozygote or heterozygote expression of -1394T allele increased the risk of breast cancer. The difference between this study and our study could result from the difference in the incidence of the variant allele [30]. While the incidence of these variant allele as homozygote was 0% in that study, and it was 43% in our study. In their meta-analysis Zhou et al. showed the relationship with this polymorphism and breast cancer [31]. Romanowicz et al. [25] and Saadat M and Saadat S [32] did not find a relationship with this polymorphism and breast cancer in parallel with our study.

Apoptosis and DNA repair are important processes establishing the road leading to cancer development. The proteins utilized during these process play important roles. Gene polymorphisms have key roles in the activity of these proteins. The risks and roles of these polymorphisms and their relationship with clinical parameters have been shown in the literature. Our study has shown that these polymorphisms have significant roles in the development of breast cancer, studying four different gene polymorphisms in the Turkish population for the first time. While we found a relationship only between BAX G(-248) A and XRCC3 Thr241Met between the onset or risk of the disease and the polymorphisms we studied, we found a relationship only between the XRCC3 Thr241Met polymorphism in terms of the severity of the disease.

Data Availability

The data is available upon request.

Ethical Approval

Local ethical council approved the study.

Consent

Written informed consents were obtained from every patient and controls.

Disclosure

The results involved in this study was presented as an oral presentation at the 6th UTSAK International Medicine and Health Sciences Researches Congress 10–11 April 2021- Ankara, Turkey.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors’ Contributions

Emre Ozoran drafted the manuscript and gathered of data. Fadime Didem Can Trabulus is in involved in the study conception design and drafting of the manuscript. Duygu Erhan, Bahadır Batar, and Mehmet Guven contributed in
the for the analysis and interpretation of data and drafting of the manuscript.

Acknowledgments

This work was supported as part of a surgery residency thesis by Istanbul Training and Research Hospital. This research has been funded by Istanbul Education & Research Hospital as part of a residency thesis.

References

[1] S. Gochhait, S. I. A. Bukhari, N. Bairwa et al., “Implication of BRCA2 -26G>A 5’ untranslated region polymorphism in susceptibility to sporadic breast cancer and its modulation by p53 codon 72 Arg>pro polymorphism,” *Breast Cancer Research*, vol. 9, no. 5, p. R71, 2007.

[2] D. G. Tang and A. T. Porter, “Target to apoptosis: a hopeful weapon for prostate cancer,” *Prostate*, vol. 32, no. 4, pp. 284–293, 1997.

[3] L. F. Brown, B. Berse, R. W. Jackman et al., “Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer,” *Human Pathology*, vol. 26, no. 1, pp. 86–91, 1995.

[4] G. Gasparini, E. Bonoldi, C. Gatti et al., “Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma,” *Journal of the National Cancer Institute*, vol. 89, no. 2, pp. 139–147, 1997.

[5] J. Thacker, “The RAD51_ gene family, genetic instability and cancer,” *Cancer Letters*, vol. 219, no. 2, pp. 125–135, 2005.

[6] H. Kurumizaka, S. Ikawa, M. Nakada et al., “Homologous-pairing activity of the human DNA-repair proteins Xrcc2, Xrcc3, Rad51C,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 10, pp. 5538–5543, 2001.

[7] R. Xue, Y. Peng, B. Han, X. Li, Y. Chen, and H. Pei, “Metastasis suppressor NME1 promotes non-homologous end joining of DNA double-strand breaks,” *DNA Repair (Amst)*, vol. 77, pp. 27–35, 2019.

[8] R. C. Bargou, P. T. Daniel, M. Y. Mapara et al., “Expression of the bcl-2 gene family in normal and malignant breast tissue: low bax-alpha expression in tumor cells correlates with resistance towards apoptosis,” *International Journal of Cancer*, vol. 60, no. 6, pp. 854–859, 1995.

[9] C. Binder, D. Marx, L. Binder, A. Schauer, and W. Hiddemann, “Expression of Bax in relation to Bcl-2 and other predictive parameters in breast cancer,” *Annals of Oncology*, vol. 7, no. 2, pp. 129–133, 1996.

[10] C. M. Perou, S. S. Jeffrey, M. van de Rijn et al., “Distinctive gene expression patterns in human mammary epithelial cells and breast cancers,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 16, pp. 9212–9217, 1999.

[11] M. Alam, T. Kashyap, P. Mishra, A. K. Panda, S. Nagini, and R. Mishra, “Role and regulation of proapoptotic Bax in oral squamous cell carcinoma and drug resistance,” *Head & Neck*, vol. 41, no. 1, pp. 185–197, 2019.

[12] A. T. Fernandes, N. P. Rocha, E. Vendrame et al., “Polymorphism in apoptotic BAX (-248G>a) gene but not in anti-apoptotic BCL2 (-938C>a) gene and its protein and mRNA expression are associated with cervical intraepithelial neoplasia,” *Apoptosis*, vol. 20, no. 10, pp. 1347–1357, 2015.

[13] S. Dholariya, R. Mir, M. Zuberi et al., “Potential impact of (rs 4645878) BAX promoter -248G>a and (rs 1042522) TP53 72Arg>pro polymorphisms on epithelial ovarian cancer patients,” *Clinical & Translational Oncology*, vol. 18, no. 1, pp. 73–81, 2016.

[14] J. Wang, Y. Zhao, J. Jiang et al., “Polymorphisms in DNA repair genes XRCC1, XRCC3 and XPD, and colorectal cancer risk: a case-control study in an Indian population,” *Journal of Cancer Research and Clinical Oncology*, vol. 136, no. 10, pp. 1517–1525, 2010.

[15] C. Y. Yen, S. Y. Liu, C. H. Chen et al., “Combination of polymorphisms of four DNA repair genes XRCC1, XRCC2, XRCC3, and XRCC4 and their association with oral cancer in Taiwan,” *Journal of Oral Pathology & Medicine*, vol. 37, no. 5, pp. 271–277, 2008.

[16] K. Chen, Z. Hu, L. E. Wang et al., “Single-nucleotide polymorphisms at the TP53-binding or responsive promoter regions of BAX and BCL2 genes and risk of squamous cell carcinoma of the head and neck,” *Carcinogenesis*, vol. 28, no. 9, pp. 2008–2012, 2007.

[17] I. Hadji Salem, F. Kamoun, N. Louhiichi, M. Trigui, C. Triki, and F. Fakhfakh, “Impact of single-nucleotide polymorphisms at the TP53-binding and responsive promoter region of BCL2 gene in modulating the phenotypic variability of LGMD2C patients,” *Molecular Biology Reports*, vol. 39, no. 7, pp. 7479–7486, 2012.

[18] N. M. Kholoussi, S. E. H. el-Nabi, N. N. Esmaiel, N. M. Abd el-Bary, and A. F. el-Kased, “Evaluation of Bax and Bak gene mutations and expression in breast cancer,” *BioMed Research International*, vol. 2014, Article ID 249372, 9 pages, 2014.

[19] X. Wang, Y. Lin, F. Lan et al., “BAX and CDKN1A polymorphisms correlated with clinical outcomes of gastric cancer patients treated with postoperative chemotherapy,” *Medical Oncology*, vol. 31, no. 11, p. 249, 2014.

[20] S. Gu, Q. Wu, X. Zhao et al., “Association of CASP3 polymorphism with hematologic toxicity in patients with advanced non-small-cell lung carcinoma treated with platinum-based chemotherapy,” *Cancer Science*, vol. 103, no. 8, pp. 1451–1459, 2012.

[21] F. Chai, Y. Liang, L. Chen, F. Zhang, and J. Jiang, “Association between XRCC3 Thr241Met polymorphism and risk of breast cancer: meta-analysis of 23 case-control studies,” *Medical Science Monitor*, vol. 21, pp. 3231–3240, 2015.

[22] Z. Qureshi, I. Mahjabeen, R. M. Baig, and M. A. Kayani, “Correlation between selected XRCC2, XRCC3 and RAD51 gene polymorphisms and primary breast cancer in women in Pakistan,” *Asian Pacific Journal of Cancer Prevention*, vol. 15, no. 23, pp. 10225–10229, 2014.

[23] L. Jara, K. Dubois, D. Gaete et al., “Variants in DNA double-strand break repair genes and risk of familial breast cancer in a South American population,” *Breast Cancer Research and Treatment*, vol. 122, no. 3, pp. 813–822, 2010.

[24] T. R. Smith, M. S. Miller, K. Lohman et al., “Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer,” *Cancer Letters*, vol. 190, no. 2, pp. 183–190, 2003.

[25] H. Romanowicz, L. Pyziak, F. Jabloński, M. Bryś, E. Forma, and B. Smolarsz, “Analysis of DNA repair genes polymorphisms in breast cancer,” *Pathology Oncology Research*, vol. 23, no. 1, pp. 117–123, 2017.
[26] W. P. Ji and N. B. He, "Investigation on the DNA repaired gene polymorphisms and response to chemotherapy and overall survival of osteosarcoma," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 1, pp. 894–899, 2015.

[27] C. J. Searle, I. W. Brock, S. S. Cross, S. P. Balasubramanian, M. W. R. Reed, and A. Cox, "A BCL2 promoter polymorphism rs2279115 is not associated with BCL2 protein expression or patient survival in breast cancer patients," *Springerplus*, vol. 1, no. 1, 2012.

[28] N. Zhang, X. Li, K. Tao et al., "BCL-2 (-938C > a) polymorphism is associated with breast cancer susceptibility," *BMC Medical Genetics*, vol. 12, no. 1, 2011.

[29] P. B. Meka, S. Jarjapu, S. K. Vishwakarma et al., “Influence of BCL2-938 C>a promoter polymorphism and BCL2 gene expression on the progression of breast cancer,” *Tumour Biology*, vol. 37, no. 5, pp. 6905–6912, 2016.

[30] C. F. Chiu, H. C. Wang, C. H. Wang et al., “A new single nucleotide polymorphism in XRCC4 gene is associated with breast cancer susceptibility in Taiwanese patients,” *Anticancer Research*, vol. 28, no. 1a, pp. 267–270, 2008.

[31] L. P. Zhou, H. Luan, X. H. Dong, G. J. Jin, D. L. Ma, and H. Shang, “Association of functional polymorphisms of the XRCC4 gene with the risk of breast cancer: a meta-analysis,” *Asian Pacific Journal of Cancer Prevention*, vol. 13, no. 7, pp. 3431–3436, 2012.

[32] M. Saadat and S. Saadat, “Susceptibility to breast cancer and intron 3 ins/Del genetic polymorphism of DNA double-Strand break repair gene XRCC4,” *Journal of Medical Biochemistry*, vol. 34, no. 4, pp. 409–413, 2015.