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ORIGINAL ARTICLE

Expression Profiling of *TP53*, *BAX*, and *BCL2* Genes in Histologically Confirmed Breast Carcinoma Using Quantitative Real-Time PCR

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ABSTRACT:

Background: Disruption of genes that play a role in the regulation of apoptosis, both DNA-damage responses and mitochondrial cell death, can influence breast carcinoma progression. The objective of this study was to compare the expression of *TP53*, *BAX*, and *BCL2* between histologically confirmed breast carcinoma and non-malignant tissues and to check the clinicopathological associations. **Methods:** A case-control analysis was performed, comprising 90 tissue samples, with breast carcinoma (60) and non-malignant (30). Total RNA was extracted and converted to complementary DNA (cDNA). The mRNA expression of *TP53*, *BAX*, and *BCL2* was quantified by quantitative real-time PCR, normalized to GAPDH, and calculated using the 2^-ΔΔCt method. Growth patterns were assessed based on tumour grade, tumour size, and lymph-node involvement. **Results:** Carcinoma tissues showed lower *TP53* (0.46 ± 0.18) and *BAX* (0.52 ± 0.21) and higher *BCL2* (2.38 ± 0.74) expression than controls. *TP53* and *BAX* decreased, whereas *BCL2* increased, from Grade I to III tumors. The *BAX*/*BCL2* ratio declined from 1.02 ± 0.18 in controls to 0.11 ± 0.05 in Grade III tumors. Gene expression was also associated with tumor size and lymph node involvement. **Conclusion:** Breast carcinoma showed downregulation of *TP53* and *BAX* and upregulation of *BCL2*, with a progressive decline in the *BAX*/*BCL2* ratio across tumor grades. These findings indicated altered apoptotic regulation associated with clinicopathological features.

Keywords: Apoptosis; bcl-2-Associated X Protein; Breast Neoplasms; Genes, bcl-2; Genes, p53; Real-Time Polymerase Chain Reaction

INTRODUCTION

Breast cancer is one of the leading causes of cancer-related mortality and morbidity worldwide and, based on the most recent estimates of GLOBOCAN, accounts for about 11.8% of new cancer cases and 7.1% of cancer deaths in the world in 2024 [1]. It is a clinically diverse disease, depending on the histological type of the disease, the molecular subtypes, the genomic abnormalities, and the tumor microenvironment [2]. In addition to continued proliferation and chromosomal instability, resistance to programmed cell death facilitates tumor progression, metastasis, and treatment failures [3].

TP53 and the *BCL2* protein family are important regulators of the intrinsic apoptotic pathway [4]. After recognizing damage to the DNA, functional p53 can trigger cell-cycle arrest, DNA repair, senescence, or apoptosis, in part by activating pro-apoptotic mediators, including *BAX* [5]. *TP53* mutations are present in approximately 1/3 of all breast cancers and are more prevalent in high-grade tumors, HER2-enriched tumors, and triple-negative breast cancers, which are aggressive and resistant to therapy [6]. The *BAX* protein increases the permeability of the outer mitochondrial membrane and the release of cytochrome-c, while *BCL2* inhibits the release of pro-apoptotic proteins and also helps to maintain the survival of the cells [7]. Thus, the *BAX*/*BCL2* ratio might be a better indicator of the apoptotic susceptibility than either of the markers separately [8]. *BCL2* expression in some cohorts can be associated with favorable hormone-receptor-positive disease, but its biological and prognostic significance is found to be dependent on the disease subtype and can be interpreted along with *TP53*, *BAX* and clinicopathological variables [9].

In parallel, studies that compare all four genes (*TP53*, *BAX*, *BCL2* and the ratio of *BAX* to *BCL2*) at the tissue level in breast carcinoma, using quantitative methods at the transcript level, are limited. Integrated profiling could help elucidate the link between apoptotic dysregulation, tumour grade, size and lymph-node involvement [10]. The findings may provide molecular insights into apoptotic dysregulation in breast carcinoma and help identify gene-expression patterns associated with clinicopathological characteristics.

The aim of this study was to quantify the expression of the genes *TP53*, *BAX* and *BCL2* in breast carcinoma and healthy breast tissues by RT-qPCR. It was also designed to establish the apoptotic balance by measuring the *BAX*/*BCL2* expression ratio. It also explored correlations of gene-expression profiles and selected clinicopathological features.

METHODOLOGY

The study design and the collection of samples: A molecular case-control study was planned to investigate the expression profile of breast carcinoma tissues involving the genes related to apoptosis. These included 90 tissue samples, including 60 breast cancer samples and 30 healthy breast tissue samples from patients being operated on for breast cancer at authors' affiliated hospital. Sample size was calculated using OpenEpi version 3.0.1 (Emory University, Atlanta, GA, USA; RRID:SCR_021913) for an unmatched case-control study, assuming a two-sided confidence level of 95%, statistical power of 80%, and a case-to-control ratio of 2:1. Based on an expected exposure/proportion of 50% among controls and 75% among cases, the calculated minimum sample size was approximately 87 participants. To account for potential sample loss or inadequate RNA quality, 90 tissue samples were included [11]. Before the molecular diagnosis of breast cancer cases, histopathological routine diagnosis was carried out.

Histopathological Confirmation: Routine histopathologic techniques were used to analyze the tumor samples. Tissues were fixed in 10% neutral buffered formalin, processed in the routine manner, embedded in paraffin, sectioned, and then stained with hematoxylin and eosin. The pathological diagnosis, the type of tumour and the tumour grade were noted based on standard pathological criteria. Data on the clinicopathological parameters, including tumour size, histological grade, lymph node status and receptor profile, were obtained from the pathology record.

Extraction of RNA and Quality Control of RNA: Fresh tissue specimens were immediately frozen in liquid nitrogen/placed in an RNA stabilization solution and stored at −80°C until RNA extraction. Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue sections using the RNeasy FFPE Kit (QIAGEN, Germany) according to the manufacturer's instructions. The RNA concentration and purity were determined by spectrophotometric measurements. Samples of acceptable-quality RNA were selected for further analysis.

cDNA synthesis and quantitative real-time PCR: The extracted RNA was reverse transcribed using a cDNA synthesis kit (Merck) following the manufacturer's instructions. Quantitative real-time PCR was used to measure the gene expression of *TP53*, *BAX*, and *BCL2*. The endogenous reference gene for normalization was GAPDH. Gene-specific primers were used for amplification in the optimized cycling conditions, as presented in **Table I**. The comparative threshold cycle method (2-ΔΔCt) was used to calculate relative levels of gene expression. The expression level of tissues from breast cancer and control tissues was compared.

Table I: Primer sequences, target genes, and amplicon sizes used for quantitative real-time PCR

Gene	Forward primer (5′–3′)	Reverse primer (5′–3′)
BAX	AGCTGCAGAGGATGATTGCC	CCCCAGTTGAAGTTGCCGTC
BCL2	TGTGTGTGGAGAGCGTCAAC	CTACCCAGCCTCCGTTATCC
TP53	GAGCTGAATGAGGCCTTGGA	CTGAGTCAGGCCCTTCTGTCTT

Statistical Analysis: The data were analyzed using SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY, USA). The continuous variable data were presented as mean ± S.D., and the categorical variable data were presented as frequency and percent. Statistical comparisons were used to determine the differences in the expression of each group. A correlation was made between the expression levels of the genes and the different clinicopathological parameters. A p-value < 0.05 was considered statistically significant. The study protocol is in line with the institutional ethical guidelines. Molecular data analysis was performed without any personal identifiers of patients, in order to ensure patient confidentiality.

RESULTS

A total of 90 tissues (60 breast carcinomas and 30 non-malignant breast tissue controls) were tested. The relative gene expression analysis was done by the 2^-ΔΔCt method, using GAPDH as an endogenous control. Analysis demonstrated differential expression of the genes related to apoptosis in the course of malignant tissue versus control tissue. Breast carcinoma samples indicated lower expression levels for tumor suppressor and pro-apoptotic genes, and elevated expression levels for the *BCL2* gene as compared to the control samples. The clinical characteristics of patients with breast cancer used for molecular analysis are shown in **Table II**. Most cases were in women of middle age (40s), and the most common histological type was invasive ductal carcinoma. Tumor grade distribution showed a greater representation of intermediate-grade tumors.

Table II: Clinicopathological Characteristics of Breast Cancer Cases (n=60)

Characteristics	Frequency (n)	Percentage (%)
Age group		
<40 years	18	30.0
40–60 years	32	53.3
>60 years	10	16.7
Histological type		
Invasive ductal carcinoma	49	81.7
Invasive lobular carcinoma	7	11.7
Other types	4	6.6
Histological grade		
Grade I	12	20.0
Grade II	31	51.7
Grade III	17	28.3
Lymph node involvement		
Present	26	43.3
Absent	34	56.7

The extent of the variation in the expression of these genes for apoptosis is indicated in **Table III** when comparing malignant tissue with non-malignant tissue. *TP53* and *BAX* were also seen to be down-regulated, and *BCL2* was up-regulated in breast cancer samples, indicating over-suppression of pro-apoptotic genes and over-activation of survival genes in tumor samples.

Table III: Relative Expression of *TP53*, *BAX*, and *BCL2* Genes in Breast Cancer(N=60) Compared with Controls(N=30)

Gene	Control Tissue (Relative Expression)	Breast Cancer Tissue (Relative Expression)	Expression Pattern
TP53	1.00 ± 0.12	0.46 ± 0.18	Downregulated
BAX	1.00 ± 0.15	0.52 ± 0.21	Downregulated
BCL2	1.00 ± 0.14	2.38 ± 0.74	Upregulated

The expression patterns of the apoptosis-related genes according to tumor grade are shown in **Table IV**. The expression of *TP53* and *BAX* was found to be decreasing with the increasing grade of the tumour, while that of *BCL2* was increasing. These findings indicate an altered apoptotic gene-expression pattern in higher-grade tumors.

Table IV: Comparison of Apoptosis-Related Gene Expression According to Tumor Grade

Gene	Grade I	Grade II	Grade III	Trend
TP53	0.68 ± 0.20	0.49 ± 0.16	0.31 ± 0.14	Decreased expression with higher grade
BAX	0.71 ± 0.25	0.53 ± 0.19	0.35 ± 0.12	Reduced pro-apoptotic activity
BCL2	1.72 ± 0.50	2.31 ± 0.68	3.12 ± 0.91	Increased anti-apoptotic activity

Figure 1 illustrates the relative expression of *TP53*, *BAX*, and *BCL2* according to histological tumor grade. *TP53* expression decreased progressively from Grade I to Grade III tumors, while *BAX* expression showed a similar downward pattern. In contrast, *BCL2* expression increased with increasing tumor grade. The figure therefore demonstrates distinct expression patterns of the three apoptosis-related genes across different histological grades.

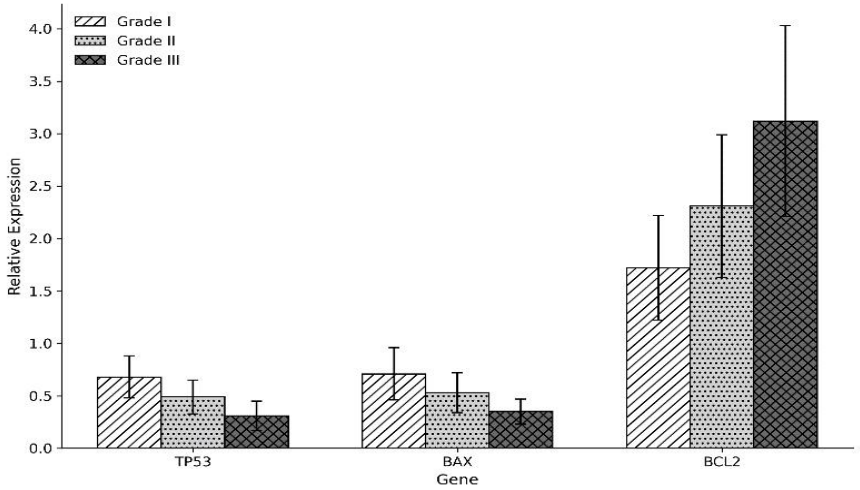

Figure 1. Relative expression of TP53, BAX, and BCL2 according to histological tumor grade.

The associations between gene-expression patterns and clinicopathological features are shown in **Table V**. Associations between the changes in expression of apoptosis-related genes and the size of the tumor, histological grade, and lymph node involvement suggest differential involvement of pro-apoptotic and anti-apoptotic pathways in breast carcinoma progression.

Table V: Distribution of Gene Expression Patterns According to Clinicopathological Features

Variable	*TP53* Expression	*BAX* Expression	*BCL2* Expression
Tumor size >2 cm	Lower expression	Lower expression	Higher expression
High histological grade	Reduced	Reduced	Increased
Lymph-node involvement	Reduced	Reduced	Increased

A balance between pro-apoptotic and anti-apoptotic pathways is emphasized in **Table VI**. The ratio of *BAX*/*BCL2* decreased in the malignant tissues compared with control tissue and became further decreased with an increase in the grade of the cancer. The progressive decline in the *BAX*/BCL2 ratio indicates a relative shift toward anti-apoptotic signaling in higher-grade tumors.

Table VI: *BAX*/*BCL2* Expression Ratio in Breast Cancer Samples(N=60)

Group	*BAX*/*BCL2* Ratio	P- value
Control tissues	1.02 ± 0.18	<0.001
Breast cancer tissues	0.22 ± 0.09	0.001
Grade I tumors	0.41 ± 0.13	<0.001
Grade II tumors	0.24 ± 0.08	<0.001
Grade III tumors	0.11 ± 0.05	<0.001

The relationships between the gene expression levels and pathological parameters are compared, as shown in **Table VII**. *TP53* was inversely associated with aggressive tumor features, *BAX* was inversely associated with aggressive tumor features, and *BCL2* was positively associated with aggressive tumor features, indicating inverse associations of TP53 and BAX expression with aggressive tumor features and a positive association of BCL2 expression with these features.

Table VII: Spearman's Rank Correlation Between Gene Expression and Tumor Characteristics

Parameter	*TP53* (ρ)	*BAX*(ρ)	*BCL2*(ρ)
Tumor grade	-0.61	-0.56	+0.64
Tumor size	-0.42	-0.39	+0.45
Lymph node involvement	-0.51	-0.48	+0.55

Overall, the expression profile demonstrated a consistent shift in the balance between pro-apoptotic and anti-apoptotic signaling with increasing tumor aggressiveness. Reduced *TP53* and *BAX* expression, together with increased *BCL2* expression, was associated with larger tumors, higher histological grade, and lymph-node involvement. The progressive reduction in the *BAX*/BCL2 ratio further supports an apoptosis-resistant molecular pattern in breast carcinoma. These findings provide the basis for interpreting the potential clinical relevance of these apoptosis-related genes.

DISCUSSION

This study shows altered expression of apoptosis-related genes in histologically proven breast carcinomas. The expression levels for *TP53* and *BAX* were found to be 0.46-fold and 0.52-fold, respectively, of the non-malignant tissue, while *BCL2* was 2.38-fold the expression level in non-malignant tissue. In the control, the ratio of *BAX*/*BCL2* was 1.02, while it was 0.22 in carcinomas and was reduced gradually according to the grade of the tumor (from grade I to grade III). This is similar to the mitochondrial apoptosis suppression model, where impaired p53 signaling and *BAX* activity enable anti-apoptotic *BCL2* proteins to maintain mitochondrial integrity [12]. A 2024 long-term follow-up study similarly demonstrated that *TP53* mutations were associated with significantly poorer recurrence-free and overall survival in patients with breast cancer [13]. Studies also found that abnormal p53 immunophenotypes closely predicted *TP53* mutation, and were related to high-grade triple-negative breast carcinomas [14].

Decreased transcript levels may lead to less activation of apoptotic targets like *BAX*, allowing genetically damaged cells to live and gain further oncogenic mutations. This interpretation is consistent with recent clinical evidence showing that a null p53 immunophenotype is associated with poorer disease-free and distant recurrence-free survival in patients with invasive breast cancer [15]. Recent studies also suggest that *TP53* dysfunction contributes to invasion, metabolic adaptation, immune escape, and resistance to systemic therapy [16,17]. However, low *TP53* mRNA is not synonymous with mutation, as there are truncating mutations, copy-number loss, epigenetic repression, and RNA degradation that can lead to low transcripts [18]. The simultaneous downregulation of *TP53* and *BAX*, therefore, facilitates functional pathway suppression and should be confirmed at the protein level and sequenced [19].

The most prominent change in the apoptotic balance was the combination of *BAX* downregulation and *BCL2* upregulation. *BAX* is able to form pores in the mitochondria to allow the release of cytochrome-c, while *BCL2* inhibits *BAX* and other pro-apoptotic proteins [20]. Therefore, the decreasing *BAX*/*BCL2* ratio would be indicative that high-grade tumors might need a more potent stimulus to trigger mitochondrial apoptosis. Experimental research in breast cancer cells also demonstrated that an increased *BAX*/*BCL2* ratio, accompanied by increased caspase-7 and caspase-9 expression, promoted caspase-dependent apoptosis [21]. Sofi et al. found that *BCL2* overexpression is linked to survival pathways and chemoresistance, while Hassan et al. found both favorable and unfavorable associations in hormone receptor-positive and HER2-enriched tumors, respectively [22,23].

The correlations with grade were greater than those with tumour size and nodal involvement, indicating that the apoptotic dysregulation is more likely to be related to biological dedifferentiation. Evaluating *TP53* and *BAX*, *BCL2* and their ratio simultaneously will, therefore, be more informative than evaluating each of them individually. In a 2024 study that included 5,186 patients, Arg72Pro and Pro72Pro genotype were found to be associated with stable disease, but not pathological complete response (pCR) [24]. Combined p53 and *BCL2* immunophenotypes were also associated with prognosis in an age- and subtype-dependent manner in postmenopausal TNBC [25]. Therefore, the *TP53*, *BAX* and *BCL2* panel is still in its exploratory stage, and stage, grade, receptor subtype and lymph-node status are still known prognostic factors [26].

Some of the limitations of this study are the relatively small sample size, the case-control design, the lack of survival and treatment-response data, absence of protein-level validation, absence of *TP53* mutation analysis and the use of bulk-tissue RT-qPCR, with GAPDH as the only endogenous control. To improve future multicenter studies, it is recommended to employ larger cohorts of patients stratified by subtype, paired controls, several validated reference genes, and combined RT-qPCR, immunohistochemistry, digital PCR, and sequencing. Integration of RT-qPCR with protein-level validation, multiple reference genes, *TP53* sequencing, and functional assays of apoptosis would provide stronger evidence regarding the biological significance of these expression patterns. It will be important to find out whether this profile is independently associated with the likelihood of recurrence, therapeutic response, survival, or susceptibility to cell death-inducing drugs in longitudinal and functional analyses.

CONCLUSION

This study demonstrated reduced *TP53* and *BAX* mRNA expression and increased *BCL2* expression in breast carcinoma, with a lower *BAX*/*BCL2* ratio. These patterns were associated with higher tumour grade, size, and lymph-node involvement, suggesting altered apoptotic regulation. However, as only mRNA expression was assessed, the findings remain exploratory and do not establish functional apoptosis resistance or tumour aggressiveness. Larger multicenter studies incorporating mutation, protein, functional, treatment-response, and survival analyses are warranted to determine the clinical and prognostic significance of this gene-expression profile.

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