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Correlation Expression between P52 and BCL2 among Iraqi Women with Breast Carcinoma

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Abstract:

Breast cancer is the leading cause of death in women and ranks second in cancer-related mortality in worldwide. NF-*κ*B2(P52) is one of the mammalian NF-κB transcription factor family that expressed in breast tumors. BCL2 is an anti-apoptotic protein that also acts as a medical prognostic biomarker for breast carcinoma. This research was aimed to find out the IHC expression of P52 and BCL2 in 67 histological specimens of breast cancer patients and evaluate their correlation with clinicopathological features. Protein IHC expression of BCL2 and P52 was observed in 45 and 46 respectively. There was no correlation between P52 and BCL2 expression with any clinicopathological parameters, while a strong correlation between protein expression of P52 and BCL2.

Keywords: BCL2, Breast cancer, Clinicopathological features, Immunohistochemistry, NF-*κ*B2(P52), Tumor markers.

Introduction:

Breast cancer is the most commonly diagnosed cancer in women and continues to be one of the leading causes of cancer-related death in women around the world[1]. Many researchers have examined the etiological causes of that cancer in order to find a strategy to detect it quickly and manage it effectively [2]. Early diagnosis of breast cancer, both primary and recurring, is critical in clinical practice that enables doctors to make treatment decisions when the tumor burden is low and patients are most likely to react to adjuvant therapy [3].

Tumor biomarkers are proteins produced by tumors or other cells in response to cancer or even some benign masses. Both normal and malignant cells produce the more of these markers, but cancerous cells produced them at much higher levels. A patient's treatment response and the existence of metastasis or relapse are assessed by using markers such as (Ca 27-29, Ca15-3, Ca27.29, P53, Cathepsin D, Cyclin E and Her-2/*neu*) [4]. BCL2 is a member of the anti-apoptotic protein family. It's detected in different tumors, including breast and prostate, also can be seen in colorectal, lung, stomach, and ovarian malignancies [5,6]. In breast malignancies, estrogens trigger BCL2 by a direct consequence of transcriptional activation [7]. BCL2 has recently been discovered to be a useful prognostic marker, mainly in breast cancer with positive expression of hormone receptors (ER and PR)[8,9]. Breast cancer patients with positive BCL2 expression have a better prognosis considering the overall lifespan and relapse-free survival (RFS) [10]. Positive expression of BCL2 is linked with better outcomes of metastatic and early breast cancer patients who are treated with hormone therapy or chemotherapy[11,12]. Several studies have consistently found a link between BCL2 expression and good survival in patients who have a bad prognosis (negative signal of ER, PR and Her2) [13-15]. P52, also known as (NFκB2), is a transcription factor that belongs to the NFκB family. RelA (P65), c-Rel, RelB, NFB1 (P50), and NFκB2 (P52) are members of this family, which are expressed in nearly all cell types and regulate genes with various roles [16].

NFκB was established in 1986 as a nuclear factor which connects to the promoter component of activated B cells' immunoglobulin kappa light-chain (thus, the abbreviation NFκB) [17,18]. NFκB manages roughly 500 genes that are implicated in infection, cell remodeling, preservation, multiplication, oncogenesis and metastasis [19, 20]. NFκB activation causes the expression of target genes that repress programmed death cell, manage cycle of cell, assist of tumor growth and infection, and promote metastatic, as well as resistance of chemo and radio therapy [21]. Previously, researchers have also noted higher P52 activation in breast, lung, prostate, pancreatic, and ovarian malignancies [22–28], in lung cancer cells also showed excessive expression of P52 and has been correlated with a bad prognosis [29]. The current study used immunohistochemistry to investigate the relationship between P52 and BCL2 in Iraqi patients with breast carcinoma, as well as the relationship between the two biomarkers and clinic-pathological variables.

Materials and Methods:

Patients selection

This retrospective study included 67 paraffin block patients with primary breast cancers biopsies diagnosed between August 2020 and July 2021, they were gathered from Dr. Israa Mahdi Al-Sudani Lab. and Iraqi Specialized Lab. in Baghdad city. Hematoxylin and eosin were used to stain a 5-µm section of each submitted paraffin block. All H and E slides were blindly reviewed independently by a consultant pathologist to localized the best area of malignant cells and assess the quality of the reviewed slide for each case for IHC analysis. These slides were also graded according to the Nottingham grading system into grades (I, II, and III). Age, stage and axillary LN were obtained from data files.

Immunohistochemistry

Briefly, a 5µm sections were cut from each biopsy block, mounted on a positive charged slide, deparaffinized in xylene, rehydrated with graded ethanol, and immersed in Tris-buffered saline, then treated with antigen retrieval solution and heated in the microwave for 20 minutes, then allowed to cool at room temperature before being washed in distilled water. For 15 minutes at room temperature, H_2O_2 (3%) was added to sections. Tissue sections were treated with primary antibodies BCL2 (DAKO Monoclonal mouse anti-Human clone 124, code number IS614) and P52 (NFκB2) SANTA CRUZE mouse monoclonal (C-5) and after that add secondary antibody to the slides and incubation at room temperature in a humidified chamber. Positive controls included human lymph node and lung cancer. Each experiment run included negative controls for IHC, which consist of switching the primary antibodies (BCL2 and P52) with normal rabbit or mouse serum.

Assessment of Immunohistochemistry

A semiquantitative approach was used to assess BCL2 and p52 (NFκB2) immunostaining. For BCL2 expression, the intensity of cytoplasmic staining was graded from (0 to 3): (0) no stain, (1) low or weak intensity, (2) intermediate intensity, (3) strong intensity; and the percent of positive cells was categorized on: 0 (none), 1 (1%), 2 (2–10%), 3 (11–30%), 4 (31–60%), 5 (61–70%) (more than 60%) per field. The overall score was calculated by adding the proportion and intensity scores; the tumor was scored ≤ 2 considered negative, while > 2 was a positive expression[30].The assessment of the immunohistochemical expression for P52 was performed according to[31], when staining was observed in more than 10% of cells (cut off value >10%), cases were considered positive. P52 expression was estimated by using the distribution and intensity of cytoplasmic signals. On a grade of 0 to 3, the intensity and the proportion of staining cells were grouped into the following categories: [0: no staining or even less than 10% of staining cells; 1; weak positive in more than 10% or moderate in 10-70 % of tumor cells; 2: moderate in more than 70% or strong in 10-70% of tumor cells; 3: strong positive in more than 70% of tumor cells].

Statistical analysis

The analysis of data was carried out by using of SPSS-27. The data were presented in simple measures of frequency and percentage. The significance of difference of different percentages (semiquantitative data) was tested using Pearson Chi-square test (χ^2-test) with application Fisher Exact test whenever applicable. The statistical significance was considered whenever the P value was equal or less than 0.05.

Results

Clinical and pathological characteristics of the patient

Table 1 illustrates the patient's data. Patients ranged in age from 25 to 77 years old, with a median age of 50.0±11.2. The pathological stages were determined using primary pathology reports (TNM) and AJCC. For 46 patients (68.7%), nodal metastatic status was known, and tumor size was divided into two categories: ≤ 2 cm (5/67) and > 2 cm (62/67).

Table 1. Clinicopathological characteristics of patient

Features		No	%
Age (years)	<40	7	10.4
	40-49	26	38.8
	50-59	18	26.9
	≥ 60	16	23.9
	Mean ±SD	50.0±11.2	(25 -77)
Histology grade (NGS)	I	7	10.4
	II	49	73.1
	III	11	16.4
Pathological stage (TNM)	T1N0	5	7.5
	T2N0	12	17.9
	T2N1	18	26.9
	T2N2	10	14.9
	T3N0	1	1.5
	T3N1	8	11.9
	T3N2	5	7.5
	T4N0	3	4.5
	T4N1	5	7.5
Pathological stage (TNM) AJCC	I	5	7.5
	IIA	12	17.9
	IIB	19	28.4
	IIIA	23	34.3
	IIIB	8	11.9
Tumor size	≤ 2cm	5	7.5
	> 2cm	62	92.5
Lymph nodal status	Positive	46	68.7
	Negative	21	31.3

IHC Expression of BCL2 and P52 (NF-κB2) in Breast Carcinoma

In our study, for both BCL2 and P52 markers, 45, 46 respectively out of 67 were positive expression while negative expression in others for both markers, table. 2 and Fig1. The pattern of BCL2 and P52 immunostaining was cytoplasmic stain of invasive breast carcinoma Fig 2.

Table 2. Frequency score for Bc12 & P52 markers

		No	%
Bcl2	Positive (3-8)	45	67.2
	Negative (0-2)	22	32.8
Bcl2	0	16	23.9
	2	6	9.0
	3	2	3.0
	4	2	3.0
	5	6	9.0
	6	7	10.4
	7	8	11.9
	8	20	29.9
P52	Positive (1-3)	46	68.7
	Negative (0)	21	31.3
P52	No stain	21	31.3
	Weak	6	9.0
	Moderate	9	13.4
	Strong	31	46.3

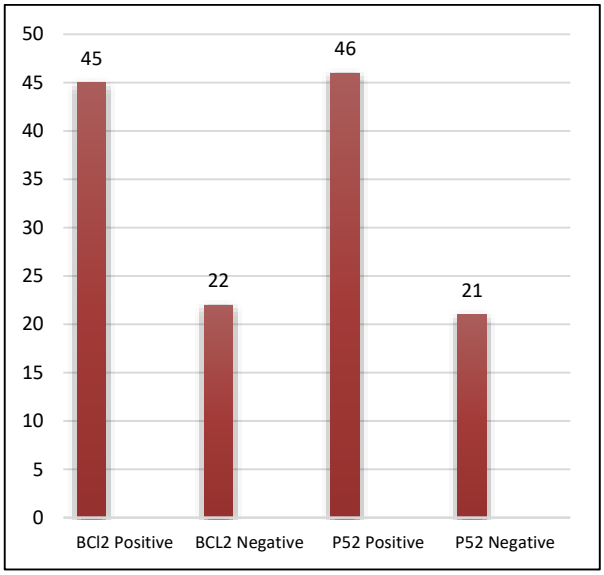

Figure 1. IHC Expression of Bcl2 & P52 markers

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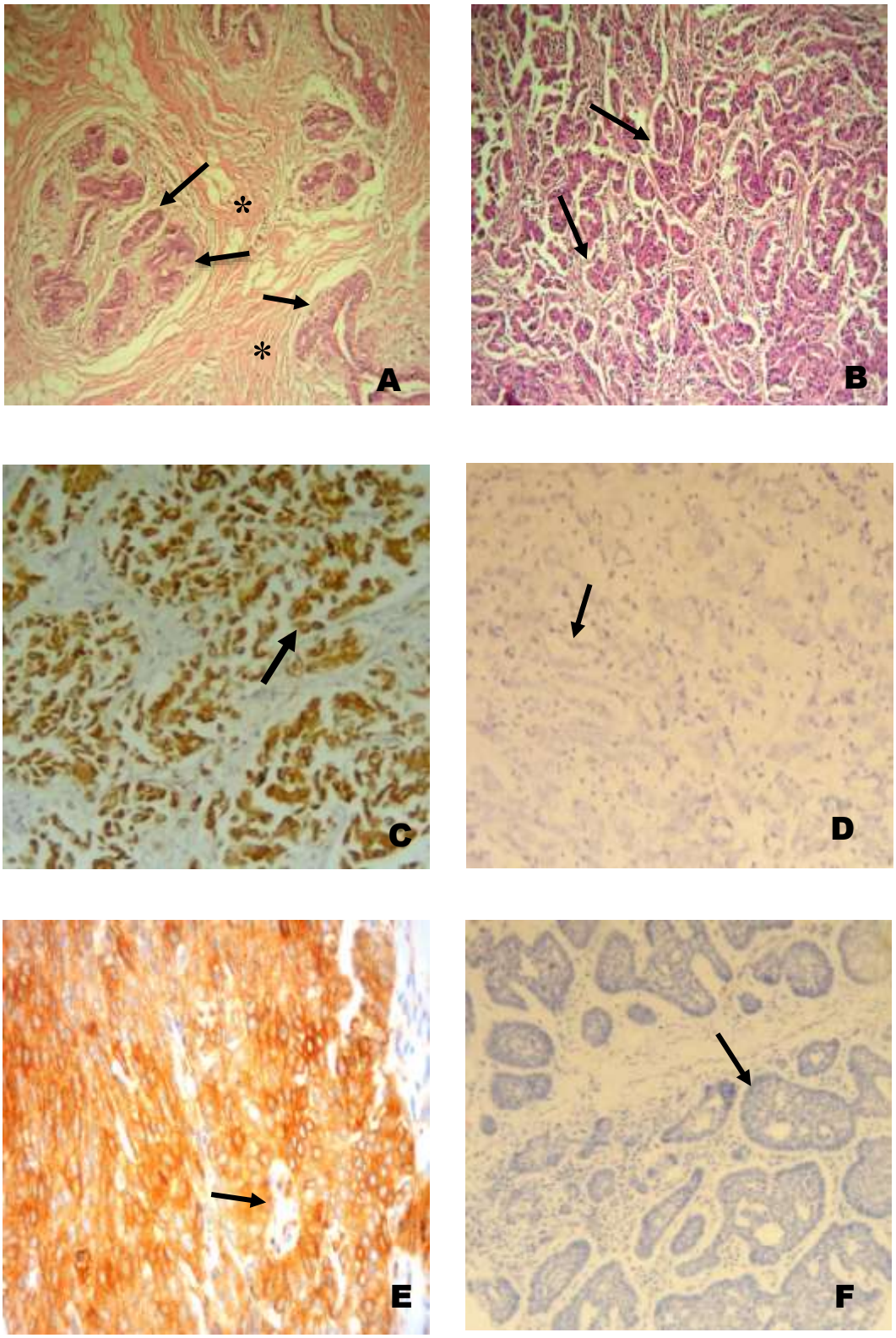

Figure 2. (A) H and E micrograph of histological section of normal epithelial tissue of breast mammary glands (ducts-arrows) surrounded by stromal tissue (*). (B) H and E micrograph of moderately infiltrative ductal breast carcinoma-arrows. (C) Strong diffused cytoplasmic brown expression of BCL2 in moderately differentiated infiltrative ductal breast carcinoma-arrow. (D) Negative control (without primary antibody of BCL2) in infiltrative ductal breast carcinoma-arrow. (E) Strong diffused cytoplasmic golden-brown expression of P52 in poorly differentiated infiltrative ductal breast carcinoma–arrow. (F) Negative control (without primary antibody of P52) in ductal breast carcinoma.

Correlations of BCL2, P52 (NF-κB2) expression and clinicopathological features

Table 3 shows the relationship between BCL2 and P52 (NF-κB2) expression and clinicopathological factors including patients age, histological grade of BC, size of a tumor, and LN metastases. There was no significant association in the present research work between BCL2, P52 expression with clinicopathological features. Also this study was revealed a significant association between the BCL2 expression and P52 (p <0.05) as shown in Table 4.

Table 3. Correlations of BCL2, P52 (NF-κB2) expression and clinicopathological features

Features		Bcl2				value *P*
		Positive (3-8)		(Negative)0-2)		
		No	%	No	%	
Age)years)	<40	5	11.1	2	9.1	0.465
	40-49	15	33.3	11	50.0	
	50-59	12	26.7	6	27.3	
	≥ 60	13	28.9	3	13.6	
	Mean±SD	(29-77) 11.7 ±50.7		(38-70) 10.1±48.5		
Grade	I	4	8.9	3	13.6	0.480
	II	32	71.1	17	77.3	
	III	9	20.0	2	9.1	
Pathological Stage	I	5	11.1	-	-	0.122
	IIA	9	20.0	3	13.6	
	IIB	14	31.1	5	22.7	
	IIIA	11	24.4	12	54.5	
	IIIB	6	13.3	2	9.1	
Tumor size	≤ 2cm	5	11.1	-	-	0.104
	>2cm	40	88.9	22	100.0	
LN status	Positive	28	62.2	18	81.8	0.104
	Negative	17	37.8	4	18.2	
Features		P52				*P* value
		Positive (1-3)		Negative (0)		
		No	%	No	%	
Age (years)	<40	3	6.5	4	19.0	0.255
	40-49	19	41.3	7	33.3	
	50-59	11	23.9	7	33.3	
	≥ 60	13	28.3	3	14.3	
	Mean±SD	(30 -70) 51.1±11.7		(29-60) 47.5±9.7		
Grade	I	5	10.9	2	9.5	0.928
	II	33	71.7	16	76.2	
	III	8	17.4	3	14.3	
Pathological Stage	I	3	6.5	2	9.5	0.143
	IIA	10	21.7	2	9.5	
	IIB	12	26.1	7	33.3	
	IIIA	13	28.3	10	47.6	
	IIIB	8	17.4	-	-	
Tumor size	≤ 2cm	3	6.5	2	9.5	0.664
	>2cm	43	93.5	19	90.5	
LN status	Positive	29	63.0	17	81.0	0.143
	Negative	17	37.0	4	19.0	

Table 4. Association of P52 (NF-κB2) with BCL2 expression in breast carcinoma

Markers		P52				*P value*
		Positive (1-3)		Negative (0)		
		No	%	No	%	
Bcl2	Positive (3-8)	39	84.8	6	28.6	0.0001
	Negative (0-2)	7	15.2	15	71.4	
Bcl2 Score	0	4	8.7	12	57.1	0.001
	2	3	6.5	3	14.3	
	3	2	4.3	-	-	
	4	2	4.3	-	-	
	5	4	8.7	2	9.5	
	6	6	13.0	1	4.8	
	7	7	15.2	1	4.8	
	8	18	39.1	2	9.5	
		Bcl2				
Markers		Positive (3-8)		Negative (0-2)		*P value*
		No	%	No	%	
P52	Positive (1-3)	39	86.7	7	31.8	0.0001
	Negative (0)	6	13.3	15	68.2	
P52 Score	No Stain	6	13.3	15	68.2	0.0001
	Weak	5	11.1	1	4.5	
	Moderate	7	15.6	2	9.1	
	Strong	27	60.0	4	18.2	

Discussion:

In multicellular organisms, apoptosis is an essential step that controls the amount of cells in the body. Singling pathways that control the apoptosis are complicated, and their dysregulation is a critical phase in carcinogenesis, influencing sensitivity of cancer cell to chemotherapy and radiation [32]. Elements of the BCL2 family are important regulators of apoptotic, and their effect in tumor progression has been well established[33]. In cells of mammalian, at least 15 proteins from BCL2 family have been discovered. Bax, Bak, Bad, Bid, and others are categorized as proapoptotic members, while BCL2, BCL-XL, A1/Bfl-1, and others are classed as antiapoptotic [34]. The role of NFκB in the apoptosis process has been a widely discussed in recent years. The transcription of multiple apoptosis-related genes has been found to be controlled by NF-κB [35-38]. NF-κB regulates the expression of two antiapoptotic members (BCL-XL and A1/Bfl-1) [39-45], on the other hand, NF-κB2 suppresses the expression of the proapoptotic Bax protein [46]. The purpose of this research is to find the correlation between BCL2 and P52 in malignant cells of breast carcinoma. This study was aimed to evaluated the immunohistochemically expression of BCL2 and P52 together in Iraqi patients with breast carcinoma. The present study showed no significant association between the positive expression of BCL2 with clinicopathological parameters such as age, grade, stage, tumor size and LN status, our findings agree with Sharmila and Parba [47] were found no significant relation between BCL2 expression and clinicopathological parameters. Another study found that BCL2 was strongly linked to better clinicopathological factors, including small size of tumors, lower histological grade, less lymph node metastasis, and lymphatic invasion [48]. In Czech, study by Čečka *et al*., [30] revealed no significant correlation between BCL2 with tumor size and grade. In addition, a Korean study also found no significant correlation between BCL2 and clinicopathological characteristics [49]. A prior study found no correlation between BCL2 with age, size of tumor, grade, LN status, and direct correlation with (ER and PR) status [50]. BCL2-positive expression was related to a young age (less than 50 years), a low histological grade (low Ki-67 level), and ER+/PR+, HER2- expression [51]. There were no correlations between BCL2 and lymph nodal status, size of tumor, however there were significant correlations with positive expression of ER/PR [52]. BCL2 are significantly correlated with positivity of ER/PR receptors. Positive cases for BCL2 expression showed 100% positivity in relation to positivity for both ER/PR with statistical significance, these findings reflect a high level of responsiveness to hormonal treatment [47]. No significant correlation was seen between P52 and clinicopathological parameters in our study. We evidenced the amount of immunostaining for P52 is extremely restricted in malignant tissues, in comparison to non-tumor neighboring tissue. Previously, researchers hypothesized that NF-kappa B could play a function in development of cancer and proposed that P52 could be involved in the development of breast cancers by isolating other NF-kappa B-related proteins in the cytoplasm [53].

This study also examined if the P52 expression might possibly be linked to BCL2, and reported a significant association between them. Belgium team research was examined the activity of biomarkers (P52 / BCL2) in 7 of breast cancer cell lines-BCCLs. P52 expression has been shown to be higher in cancer tissue than in normal surrounding tissue in 6 out of 7 samples of BCCLs. Five out of these six samples had significant correlation expression between P52 and BCL2, the elevated of BCL2 activity in P52 overexpressing MCF7 A/Z cells suggests that P52 induces BCL2 expression [34]. Our findings confirmed this hypothesis, allowing us to conclude that P52 expression enhanced Bcl2 expression. Finally, clinicopathological variables had no effect on the immunohistochemistry expression of BCL2 and P52 status in our patients; these findings could provide valuable additional information regarding prognosis and provide a suitable target for targeted therapy.

Conclusion:

These results didn't find any relation between immunohistochemically expression of BCL2 and P52 with any one of the clinicopathological criteria (age, grade, stage, LN and tumor size), while significant association between IHC expression of BCL2 and P52, these findings concluded that BCl2 could be target for P52 gene, also this study give us a more information about using these biomarkers as predictive and prognosis markers as well give us a benefit plan for treatment of patients with breast carcinoma**.**

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in Ibn Sina University of Medical and Pharmaceutical Sciences according to the code number (ISU.3.1.22).

Authors' contributions statement:

I. M. Al., Ali Hussein M.A. and Reyadh S.M. designed and conducted the experiment, I. M. Al. and R. S. M. scored and interpreted the immunohistochemically results as well wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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العلاقة التعبيرية بين P52 و BCL2 في النساء العراقيات المصابات بسرطان الثدي

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الخلاصة:

سرطان الثدي هو السبب الرئيسي للوفاة بين النساء ويحتل المرتبة الثانية في الوفيات المرتبطة بالسرطان في جميع أنحاء العالم. NF-κB2 (P52) هي واحدة من عائلة عامل النسخ NF-κB في الثدييات والتي يتم التعبير عنها في أورام الثدي. BCL2 هو بروتين مضاد للخلايا يعمل أيضًا كمؤشر بيولوجي تنبؤي لسرطان الثدي. ان الهدف من هذا البحث هو للكشف عن التعبيرالكيميائي النسيجي المناعي لـ P52 و BCL2 في سرطان الثدي وتقييم ارتباطهما بالصفات السريرية المرضية, تم فحص التعبير لكل من P52 و BCL2 في العينات النسيجية المأخوذة من 67 مريضًا بسرطان الثدي باستخدام طريقة الكيمياء النسيجية المناعية. لوحظ هناك وجود تعبير لكل من BCL2 و P52 في 45 و 46 على التوالي في مرضى سرطان الثدي. ولايوجد ارتباط بين تعبير P52 و BCL2 مع أي من العوامل السريرية ، بينما توجد علاقة قوية في التعبير الكيميائي النسيجي المناعي بين P52 و BCL2.

الكلمات المفتاحية: BCL2 سرطان الثدي , الصفات السريرية المرضية,الكيمياء النسيجية المناعية, NF-κB2(p52) , المعلمات الورمية.