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A Comparative Clinical Study in Patients with Breast Cancer with and Without P53 Expression

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Abstract

Background: The most common genetic change in human neoplasia is P53. Furthermore, the most common visceral cancer among Iranian women is breast cancer. Several studies have reported that breast cancer associated with mutations in P53 tends to be more aggressive and presents different prognoses and clinical outcomes.

Objectives: The aim of current study was to evaluate and compare the prognostic factors and clinical outcomes related to TP53 expression in Iranian women with breast cancer.

Methods: In a longitudinal study conducted from 2003 to 2017, data were extracted from the Cancer Research Center's database for 801 breast cancer patients. These patients were categorized into two groups: Those with mutated P53, comprising 300 individuals, and those wild type P53 expression, totaling 501 individuals. The clinical outcomes and prognostic factors for these two groups were subsequently assessed and compared.

Results: Among the total samples, patients with mutated P53 accounted for 37.5%, while those with wild P53 made up 62.5%. The mean ages for these groups were 44.2 years (SD = 9.4) for the mutated P53 group and 47.7 years (SD = 10.9) for the wild P53 group, with a statistically significant difference (OR: 2.01, 95% CI: 1.47 - 2.74, P < 0.0001). Patients exhibiting mutated P53 factors showed a higher prevalence of advanced disease stages (OR: 1.44, 95% CI: 1.07 - 1.95, P = 0.0162), lymph node involvement (OR: 1.55, 95% CI: 1.14 - 2.12, P = 0.0047), positive lymphovascular invasion (OR: 1.40, 95% CI: 1.03 - 1.90, P = 0.0296), premenopausal status (OR: 1.36, 95% CI: 1.02 - 1.82, P = 0.0339), negative Estrogen receptor status (OR: 1.35, 95% CI: 1.01 - 1.81, P = 0.0374), and positive HER2 status (OR: 1.37, 95% CI: 1.00 - 1.87, P = 0.0494) compared to those with wild P53. In terms of survival rates, the five-year disease-free survival was 81% in the mutated P53 group and 86.4% in the wild P53 group (HR: 1.49, 95% CI: 1.01 - 2.19, P = 0.0413), while the five-year overall survival rates were 70% and 76.8%, respectively (HR: 1.42, 95% CI: 1.03 - 1.96, P = 0.0323).

Conclusions: It appears that patients without P53 expression have better clinical outcomes and more favourable prognostic factors compared to patients with P53 expression.

Keywords: P53 Expression, Breast Cancer, Clinical Outcomes

1. Background

Breast cancer is the most common visceral cancer and the second leading cause of cancer death among women in Iran and worldwide (1). Annually, 13,400 new cases of breast cancer are reported in Iran, with an incidence rate of 32 per 100,000 women (1). The average age of onset for this disease is 49 ± 12 years, approximately a decade earlier than the onset age for

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women in developed countries (1). Thus, breast cancer is a significant health and medical issue in the country (1).

Breast cancer is a heterogeneous disease, with its prognosis and clinical outcomes dependent on various factors such as age, time of diagnosis, menopausal status, family history of breast cancer, type of primary tumor pathology in the breast, tumor size, axillary lymph node involvement, disease stage, lymphovascular invasion, P53 factor status, tumor differentiation grade, KI-67 percentage in the primary tumor, and the status of estrogen receptors, progesterone receptors, and HER2 oncogenes (1). Mutation of the P53 gene is a common phenomenon occurring in multiple human tumors, including breast cancer (2). This tumor suppressor gene mutation leads to cell cycle arrest at the G1 phase, cell death, DNA repair, apoptosis, and cell senescence (2, 3). The mutation results in the accumulation of non-functional P53 protein in the cell nucleus, which can be detected by immunohistochemical (IHC) methods (2, 3). The P53 gene mutation has been shown to be an important factor for poor prognosis in breast cancer patients, leading to more aggressive tumors, increased distant metastasis, and reduced patient survival (2, 3).

Currently, aside from a limited study conducted in western Iran on Kurdish patients that examined the relationship between P53 gene expression and clinical and pathological characteristics without evaluating clinical outcomes, there are no other studies on this topic in the country (4, 5).

2. Objectives

The aim of the current study was to evaluate P53 gene expression in Iranian women with breast cancer and its correlation with the clinical and pathological characteristics of these patients, as well as the clinical outcomes (disease recurrence and survival) derived from it. This study used data from the Cancer Research Center at Shahid Beheshti University of Medical Sciences and compared these factors with other studies.

3. Methods

In this longitudinal study, all 3010 patients with breast cancer registered in the data center of the Cancer Research Centre at Shahid Beheshti University of Medical Sciences, which is the largest and most comprehensive referral centre for breast cancer patients in Iran, were included.

Between December 2017 and September 2002, only 801 patients with complete medical records and a diagnosis of primary or metastatic breast cancer were included in the study, while 2209 patients who lacked complete information and did not meet all inclusion criteria were excluded.

The inclusion criteria included breast cancer patients with acceptable follow-up after diagnosis and having all 17 of the following variables: P53 factor status, age at diagnosis, menopausal status, family history of breast cancer, type of primary tumor pathology in the breast, tumor size, axillary lymph node involvement, disease stage, lymphovascular invasion, tumor differentiation grade, KI-67 percentage in the primary tumor, status of estrogen receptors, progesterone receptors, HER2 oncogene, local recurrence of the primary tumor, distant recurrence, and time of death due to breast cancer.

The P53 factor status was measured and evaluated using the immunohistochemistry (IHC) method and categorized as either mutated P53 (indicating the presence of mutations) or wild P53 (indicating the absence of mutations).

The exclusion criteria were patients with breast cancer who did not have acceptable follow-up after the end of treatment or did not have all 17 variables mentioned above (missing even one of the 17 variables resulted in exclusion from the study).

All 801 patients who met the inclusion criteria were divided into two groups: The mutated P53 group (group A) with 300 patients and wild P53 group (group B) with 501 patients. Clinical outcomes and prognostic factors were then assessed and compared between the two groups.

After the end of treatment, all 801 patients were followed according to the global standard protocol for breast cancer patients, undergoing a complete examination every three to six months for five years, and then annually. All patients underwent annual mammography or ultrasound or both. If a patient exhibited symptoms suspicious for recurrence during the examinations, they underwent biopsy or imaging or both to confirm the recurrence.

By December 2017, all 801 breast cancer patients had been completely followed up, with a median follow-up time of 71 months. The interval between the initial diagnosis of breast cancer and local or distant recurrence (if any) was considered as the disease-free survival period, and the interval between the initial diagnosis of breast cancer and death (if any) was considered as overall survival.

This study was conducted using retrospective patient data, with no interventions involved. The Ethics Committee of the Cancer Research Center at Shahid Beheshti University of Medical Sciences approved this studyapp (ethics code: SBMU.IR.MSP.REC.1396.358). The

study adhered to the principles of integrity and confidentiality, ensuring that all patient data were anonymized and securely handled.

Data analysis and comparison of the 17 variables between the two groups (group A, 300 patients; group B, 501 patients) were performed using descriptive statistics. Statistical tests, including the chi-square test for categorical variables and the *t*-test for continuous variables, were conducted using SPSS software (version 22.0). For clinical and pathological outcomes, odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the strength of associations. For survival outcomes, hazard ratios (HR) with 95% CI were derived using Cox proportional hazards regression analysis. A P-value of < 0.05 was considered statistically significant.

4. Results

In this study, 801 patients W breast cancer with complete information were analyzed. The mean age of the patients at diagnosis was 46.4 ± 10.3 years, and all 801 patients were women. Among them, 300 (37.5%) patients were Mutated P53, and 501 (62.5%) patients were Wild P53. The demographic characteristics, clinical features, and pathology of all patients are summarized in Table 1.

Patients with a mutated P53 factor (group A) had a mean age of 44.2 years (SD = 9.4), which was younger than those with a wild P53 factor (group B) with a mean age of 47.7 years (SD = 10.9) (OR: 2.01, 95% CI: 1.47 - 2.74, P < 0.0001). Additionally, group A had a higher proportion of premenopausal patients compared to group B (OR: 1.36, 95% CI: 1.02 - 1.82, P = 0.0339). There was no statistically significant difference between the two groups regarding family history of breast cancer (OR: 1.33, 95% CI: 0.93- 1.92, P = 0.1165), type of primary tumor pathology (OR: 0.98, 95% CI: 0.60 - 1.60, P = 0.9581), tumor differentiation grade (OR: 1.28, 95% CI: 0.92 - 1.78, P = 0.1373), KI-67 percentage greater than 20% (OR: 0.89, 95% CI: 0.63 - 1.26, P = 0.6419), and primary tumor size (OR: 0.89, 95% CI: 0.58 - 1.35, P = 0.5868).

Group A had a higher incidence of axillary lymph node involvement (OR: 1.55, 95% CI: 1.14 - 2.12, P = 0.0047) and greater lymphovascular invasion of the primary tumor (OR: 1.40, 95% CI: 1.03 - 1.90, P = 0.0296) compared to group B. Additionally, the disease was more frequently in advanced stages (stage III and stage IV) in group A (OR: 1.44, 95% CI: 1.07 - 1.95, P = 0.0162). Group A also had a higher rate of negative estrogen receptors compared to group B (OR: 1.35, 95% CI: 1.01 - 1.81, P = 0.0374), but there was no significant difference in progesterone receptor status between the two groups (OR: 0.90, 95% CI: 0.67 - 1.20, P = 0.4795). HER2 positivity was observed in 32% of patients in group A, which was statistically higher than the 25.5% in group B (OR: 1.37, 95% CI: 1.00 - 1.87, P = 0.0494).

The analytical comparison of demographic characteristics, clinical features, and pathology of the two groups is summarized in Table 2.

In terms of local recurrence-free survival over five years, 96.7% of the Mutated P53 patients (group A) were free from local recurrence, compared to 96.4% of the Wild P53 patients (group B), showing no statistically significant difference (HR: 0.92, 95% CI: 0.42 - 2.03, P = 0.8466).

Regarding distant recurrence-free survival over five years, 252 (84%) of the Mutated P53 patients were free from distant recurrence, compared to 450 (89.8%) of the Wild P53 patients, with group A showing a statistically significant lower rate (HR: 1.68, 95% CI: 1.10 - 2.56, P = 0.0162).

Eighty one percent of group A patients had disease-free survival over five years, which was lower than the 86.4% of group B patients (HR: 1.49, 95% CI: 1.01 - 2.19, P = 0.0413). The five-year overall survival rate for group A was 70%, which was lower than the 76.8% overall survival rate for Group B (HR: 1.42, 95% CI: 1.03 - 1.96, P = 0.0323). Therefore, patients with a mutated P53 factor had lower five-year recurrence-free survival and overall five-year survival compared to patients with a wild P53 factor. The comparison of local recurrence-free survival, distant recurrence-free survival, disease-free survival, and overall five-year survival between the two groups is summarized in Table 3.

5. Discussion

The present study demonstrated that the five-year recurrence-free period and overall five-year survival in breast cancer patients without the P53 factor were better than in those with the P53 factor. This study, conducted using the data center of the Cancer Research Center at Shahid Beheshti University of Medical Sciences, compared clinical and pathological characteristics, local and distant recurrences, five-year recurrence-free periods, and overall five-year survival between 801 breast cancer patients with and without the P53 factor. This is considered to be the largest and most comprehensive study of its kind in Iran.

The current study showed that patients with a mutated P53 factor were younger and more frequently premenopausal compared to those with a negative P53 factor. These findings contrast with a 2014 study by Qing et al., which found no significant statistical relationship

Table 1. Demographic, Clinical, and Pathological Characteristics of Eight Hundred and One Breast Cancer Patients Based on the Data Center of the Cancer Research Center at Shahid Beheshti University of Medical Sciences

Variables	No. (%)
Gender	
Female	801 (100)
Male	0 (0)
Mean age at diagnosis (y)	46.4 ± 10.3
P53 factor	
Positive	300 (37.5)
Negative	501 (62.5)
Menopausal status	
Premenopausal	346 (43.2)
Postmenopausal	455 (56.8)
Family history of breast cancer	
Positive	146 (18.2)
Negative	655 (81.8)
Type of primary tumor pathology	
Invasive ductal carcinoma	732 (91.4)
Invasive lobular carcinoma	58 (7.3)
Other	10 (1.3)
Tumour size (cm)	
≤ 2	234 (29.2)
2 - 5	456 (56.9)
≥ 5	111 (13.9)
Tumor differentiation grade	
Low	164 (20.5)
Moderate	444 (55.4)
High	193 (24.1)
Lymphovascular invasion	
Positive	520 (64.9)
Negative	281 (35.1)
Involvement of lymph nodes	
Positive	522 (65.2)
Negative	270 (34.8)
Stage of the disease	
Stage I	146 (18.3)
Stage II	392 (48.9)
Stage III	226 (28.2)
Stage IV	37 (4.6)
KI67 percentage	
≤ 20	441 (55.1)
> 20	360 (44.9)
Estrogen receptor status	
Positive	449 (56.1)
Negative	352 (43.9)
Progesterone receptor status	
Positive	433 (54.1)
Negative	368 (45.9)
HER2 oncogene status	
Positive	224 (28)
Negative	577 (72)
All patients	801 (100)

between the P53 factor and patients' age or menopausal status (6, 7).

The study indicated no statistically significant differences in tumor differentiation, KI-67 percentage above 20%, and primary breast tumor size between the two groups, similar to studies by Jasar et al. in 2015 (8) and el-A Helal et al. in 2000 (9), but contrary to Osanai et al. in 2005 (10), which reported that P53 positive patients had larger primary tumors, lower differentiation grades, and higher KI-67 percentages compared to P53 negative patients.

In a clinical trial by Arun et al. in 2003 (11), it was found that breast cancer patients with a mutated P53 factor had more axillary lymph node involvement,

Table 2. Comparative and Analytical Relationship of P53 Factor with Demographic Characteristics, Clinical Features, and Pathology in Eight Hundred and One Breast Cancer Patients Based on the Data Center of Cancer Research Center, Shahid Beheshti University of Medical Sciences [a]

Variables and Category One vs. Category Two	Group A, Positive P53	Group B, Negative P53	Odds Ratio (95% CI)	P-Value
Mean age at diagnosis (y)	44.2 ± 9.4	47.7 ± 10.9	2.01 - 4.99	< 0.0001
Menopausal status			1.36 (1.02 - 1.82)	0.0339
Premenopausal	144 (48)	202 (40.3)		
Postmenopausal	156 (52)	299 (59.7)		
Family history of breast cancer			1.33 (0.93 - 1.92)	0.1165
Positive	63 (21)	83 (16.6)		
Negative	237 (79)	418 (83.4)		
Type of primary tumor pathology			0.98 (0.60 - 1.60)	0.9581
Invasive ductal carcinoma	271 (90.3)	452 (90.2)		
Other	29 (9.7)	49 (9.8)		
Tumor size			0.89 (0.58 - 1.35)	0.5868
T1, T2	261 (87)	429 (85.6)		
T3, T4	39 (13)	72 (14.4)		
Tumor differentiation grade			1.28 (0.92 - 1.78)	0.1373
High and moderate	219 (73)	389 (77.6)		
Low	81 (27)	112 (22.4)		
Lymphovascular invasion			1.40 (1.03 - 1.90)	0.0296
Positive	209 (69.7)	311 (62.1)		
Negative	91 (30.3)	190 (37.9)		
Involvement of lymph nodes			1.55 (1.14 - 2.12)	0.0047
Positive	214 (71.3)	308 (61.5)		
Negative	86 (28.7)	193 (38.5)		
Stage of the disease			1.44 (1.07 - 1.95)	0.0162
Stage I and II	186 (62)	352 (70.2)		
Stage III and IV	114 (38)	149 (29.8)		
KI67 percentage				
≤ 20	162 (54)	279 (55.7)		
> 20	138 (46)			
Estrogen receptor status			1.35 (1.01 - 1.81)	0.0374
Positive	154 (51.3)	295 (58.9)		
Negative	146 (48.7)	206 (41.1)		
Progesterone receptor status			0.90 (0.67 - 1.20)	0.4795
Positive	167 (55.7)	266 (53.1)		
Negative	133 (44.3)	235 (46.9)		
HER2 oncogene status			1.37 (1.00 - 1.87)	0.0494
Positive	96 (32)	128 (25.5)		
Negative	204 (68.1)	373 (74.5)		
All patients	801	100		

[a] Values are expressed as mean ± SD or No. (%).

greater lymphovascular invasion, and more advanced disease stages (stage III and IV) compared to those with a negative P53 factor (11). They concluded that a mutated P53 factor is a poor prognostic indicator, which aligns with the current study's findings (11).

Regarding hormonal receptor status, the current study revealed that breast cancer patients with a mutated P53 factor had more negative estrogen receptors compared to P53 negative patients, which is consistent with a 2003 study by Vernet-Tomas et al. (12) However, we did not observe a significant difference in progesterone receptor status between the two groups (P = 0.4795). Separate studies by Sirvent et al. in 1995 (4) and Wang et al. in 2015 (13) indicated that HER2 positivity was higher in P53 positive patients, consistent with the current study's results (13).

Table 3. Comparison of Disease-Free Survival Over Five Years, Distant Metastasis-Free Survival Over Five Years, Disease-Free Survival Over Five Years, and Overall Survival Over Five Years Among Eight Hundred and One Breast Cancer Patients Based on Positive and Wild P53 Factor

Groups	Patient Number	No. (%)	HR 95% CI	P-Value
Period free of local recurrence over five years			0.92 (0.42 - 2.03)	0.8466
Group A, mutated P53 factor	300	290 (96.7)		
Group B, wild P53 factor	501	483 (96.4)		
Period free of distant recurrence Over five years			1.68 (1.10 - 2.56)	0.0162
Group A, mutated P53 factor	300	252 (84)		
Group B, wild P53 factor	501	450 (89.8)		
Period free of disease Over five years			1.49 (1.01 - 2.19)	0.0413
Group A, mutated P53 factor	300	243 (81)		
Group B, wild P53 factor	501	450 (89.8)		
Overall five-year survival			1.42 (1.03 - 1.96)	0.0323
Group A, mutated P53 factor	300	210 (70)		
Group B, wild P53 factor	501	385 (76.8)		

Abbreviations: HR, hazard ratios; CI, confidence interval.

In this study, 96.7% of P53 positive patients were free from local recurrence over five years, compared to 96.4% of P53 negative patients, showing no statistically significant difference (P = 0.8466), similar to a study by Voduc et al. in 2015 (14). However, the same study by Voduc et al. also showed that the five-year distant recurrence-free period was lower in P53 positive patients (82%) compared to P53 negative patients (87.6%) (P = 0.001), consistent with the current study (14). Additionally, Voduc et al.'s study reported a lower five-year disease-free period in P53 positive patients, but did not examine overall five-year survival, which is a crucial prognostic factor in patients with cancer (14).

For the first time, the current study showed that the overall five-year survival rate for P53 positive patients is 70%, lower than the 76.8% rate for P53 negative patients (P = 0.0323).

5.1. Conclusions

In conclusion, the results of this study suggest that patients with breast cancer with a mutated P53 factor have higher lymph node involvement, higher distant recurrence rates, lower overall five-year survival, and worse clinical prognosis compared to those with a negative P53 factor. It is recommended that future studies include longer follow-up periods to compare ten-year and even twenty-year overall survival for more precise and definitive results.

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Footnotes

Authors' Contribution: Study concept and design: A. R.; Acquisition of data: A. Y. K.; Analysis and interpretation of data: M. K. Kh., A. Sh. Y. K.; Drafting of the manuscript: M. K. Kh.; Critical revision of the manuscript for important intellectual content: A. R.; Statistical analysis: A. Y. K.

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Data Availability: The dataset presented in the study is available on request from the corresponding author

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