Original Article

Expression of P53 in Different Molecular Subtypes of Invasive Breast Carcinoma

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Abstract

Objective: To evaluate the expression levels of p53 and determine the molecular subtypes of invasive breast carcinoma (IBC) using immunohistochemical methods, and the correlation between p53 expression and these molecular subtypes.

Methodology: This is cross-sectional descriptive was conducted at Department of Pathology, Liaquat University of Medical and Health Sciences, Jamshoro from July 2022 to December 2022. Specimens received in formalin as simple and radical mastectomy specimen, lumpectomy, excisional biopsy, wedge biopsy, were considered and kept in fixation for 24 hours. Standard protocols mentioned in Rosai and Ackerman's Surgical Pathology were followed for grossing. For interpretation of p53 staining, cells with brown-yellow granules in the nucleus positive cells and after counting positive cells in 10 high-power fields (×400) of tumor cells the expression rate of H-score is <5% represented negative while the expression rate of H-score is >5% indicated positive. All the information was collected via study proforma and SPSS version 26 was used for data analysis.

Results: A total of 329 specimens were studied. Mean age of the patients was 45.53+12.10 years. Invasive ductal carcinoma was most common 93.9%. Grade III was most common 65.3%, grade II was 33.4% and grade I was 1.2%. Estrogen receptor was positive in 57.4% of the specimens, progesterone receptor was positive in 50.8% and HER2 positive in 54.1%. According to the frequency of the molecular subtypes of the specimens, HER2 was positive in 24.9%, luminal A was in 37.4% and luminal B was in 20.1%, while Triple negative was in 17.6% of specimen. Frequency of the P53 expressions was positive in 45.6% of the cases. Expressions of p53 according to molecular subtypes of invasive breast carcinoma was statistically significant (p=0.0001).

Conclusion: Aberrant expression of p53 was observed in triple-negative and HER2/neu-overexpressing tumors. A significant correlation was also found between p53 expression and the molecular subtypes of IBC. The elevated level of p53 expression in aggressive breast cancer phenotypes suggests that p53 may serve as a prognostic marker.

Keywords: Breast cancer, p53, HER2, luminal A, luminal B, Triple negative.

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Introduction

Breast cancer is the most common cancer among women and accounts for almost one in four cancer cases in women worldwide,[1] with over 2.1 million new cases diagnosed annually.[2,3] In Pakistan, the prevalence of breast cancer in women is higher than in other parts of Asia and the West, with studies reporting a range of 20% to 50% and an overall prevalence of 31%.[4] Immunohistochemical identification of markers such as estrogen receptor (ER), progesterone receptor (PR), and HER-2/neu has become an important tool for prognostic and therapeutic purposes in recent years.[5] Screening for these markers in breast tumors is now a standard method for determining the appropriate therapy for managing breast cancer patients worldwide.[6]

Breast cancer can be divided into four molecular subtypes according to the levels of ER, PR, and HER2 as measured by immunohistochemistry (IHC). These

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subtypes are Luminal A (ER/PR+, HER2-), Luminal B (ER/PR+, HER2+), HER2-enriched (ER/PR-, HER2+), and triple-negative/basal-like tumors (ER/PR-HER2-).

Worldwide, the ER expression is present in 75% of breast tumors, PR expression in 65%, and HER2/neu expression in 20-25% of breast tumors. Luminal A subtype constitutes the majority (50-60%) of all breast cancers, which has a low proliferation index, a higher expression of ER-related genes as compared to luminal B, and a favorable prognosis with lower relapse rates over a period of 15 years after the diagnosis.[8] Luminal B cancers represent 40% of breast tumors and are associated with a poorer prognosis as compared to luminal A breast cancer. They have a high proliferation index, high histologic grade, and they show higher expression of proliferative genes and require chemotherapy in addition to hormonal therapy for treatment.[8] Amplification of the HER-2/neu gene, which results in overexpression of the receptor, is found in 20%-25% of breast tumors, while triple-negative/basal-like (ER-, PR-, and HER2/neu-) breast tumors account for 15% of breast tumors.[9]

Breast cancer is associated with various genetic mutations, including BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11. TP53 has a tumor-suppressing effect and is a crucial indicator in evaluating the prognosis of breast cancer. The wild-type p53 (wtp53) protein is a critical regulator of cellular homeostasis, often referred to as the guardian of the genome. wtp53 promotes cell cycle arrest and apoptosis, inhibits VEGF-dependent angiogenesis, and counters rapid tumor growth, metastasis, and potential drug resistance. When apoptosis is induced, wtp53 may quickly localize to the mitochondria, resulting in mitochondrial outer membrane permeabilization and the release of pro-apoptotic factors from the intermembrane space. wtp53 also plays a significant role in the DNA damage response, senescence, DNA repair, cell migration, and autophagy. In addition, p53 has the ability to prevent the self-renewal properties of cancer stem cells and hinder metastasis by opposing the epithelial to mesenchymal transition. A mutation in p53 can lead to uncontrolled cell proliferation and infinite growth and proliferation of cancer cells.

Overexpression of TP53 has been linked to a poor prognosis. The p53 gene is located on chromosome 17's short arm and encodes a 375 amino acid nuclear phosphoprotein that prevents the spread of genetically altered cells. Studies have shown that the positive rate of p53 protein is higher in the HER-2 overexpressing and triple-negative subtypes than in the Luminal A and Luminal B subtypes. Despite its well-studied nature in breast cancer, the significance of p53 in predicting clinical outcomes is still remains controversial. This study was designed to correlate the expression of P53 with molecular subtypes of invasive breast carcinoma like Luminal A, Luminal B, Her2 neu enriched and triple negative tumor. Mutation of p53 is linked with tumor aggression, proliferation, resistance to hormonal therapy and reoccurrence. Its identification will help patient to receive modified treatment such as neoadjuvant chemotherapy, which will eventually improve the overall survival and reduce the morbidity and mortality of breast cancers patients.

Methodology

This cross-sectional descriptive study was conducted at Department of Pathology, Liaquat University of Medical and Health Sciences Jamshoro / diagnostic research (DR) laboratory Hyderabad. The duration of study was six months from July 2022 to December 2022. Open-Epi online software was used for sample size calculation**.** The prevalence of breast cancer in Pakistan is 31%. By keeping this value as a reference with 95% confidential interval and keeping 5% of margin of error. The sample size stands to be n=329.

All female patients diagnosed with invasive breast carcinoma irrespective of histological type and histological grade, all wedge biopsies, lumpectomies, wide local excision, simple mastectomies and radical mastectomies (i.e. mastectomy with axillary lymph node dissection) was included. Biopsy specimens with autolytic changes, biopsy specimens with other co-morbidities, patient not willing to participate in the study and trucut biopsies and incisional biopsies were excluded. Specimens received in formalin as simple and radical mastectomy specimen, lumpectomy, excisional biopsy, wedge biopsy, incisional biopsy and trucut biopsy were considered and kept in fixation for 24 hours. Specimens with poorly fixed or fragile cut surfaces were cut in one or more halves and kept again in fresh 10% formalin for another 24 hours in order to achieve proper fixation. Tissue processing procedure was done to achieve uniform consistency of tissue for smooth cutting by clearing, dehydrating, and infiltrating embedding medium. Depending upon size tissue is processed in an automated tissue processor (THERMO SHANDON Citadel 2000) for around 8 to 12 hours, to remove water from the tissue by immersing specimens

in a series of alcohol. Before penetrating it with paraffin wax tissue was cleared from all the traces of alcohol with the help of fresh xylene. Tissue embedding was performed using automatic tissue embedding stations (THERMO SHANDON). After processing, tissues were placed in paraffin blocks using a standard base mold.

Melted wax was poured into the mold, and the tissue was positioned with warm forceps. The mold was placed on a cold spot, gently pressed to level the cut surface, and the cassette was attached with its base dipped in paraffin. The blocks were then cooled on a plate to solidify before removing the mold. A manual Microtome machine (THERMO SHANDON HM340E) was used to obtain 2 to 5µthick paraffin section on a standard glass slide. First, the paraffin block was fixed by using a cassette chuck. Then the knife was cleared and tissue was trimmed to adjust the required thickness. Cutting of the final section was done which was floated on warm water (43º to 46º*C)* and was picked on a glass slide and dried at 60ºC.

The molecular subtypes of breast cancer were determined by analyzing previously prepared immunohistochemistry slides for ER, PR, and HER2/neu, archived from the Diagnostic and Research Laboratory in Hyderabad. HER2 expression was assessed based on cell membrane staining in neoplastic cells and categorized as follows: 0 or 1+ indicated negative staining, 2+ was considered equivocal, and 3+ represented positive staining. The molecular subtypes were defined as follows: Luminal A subtype, identified by ER and/or PR positivity, HER2 negativity, and a low Ki-67 index (<14%); Luminal B subtype, characterized by ER and/or PR positivity, HER2 positivity or negativity, and a high Ki-67 index (>20%); HER2-enriched subtype, defined by positive HER2 and negative ER and PR expressions; and Triple-negative/basal-like subtype, defined by the absence of ER, PR, and HER2 expressions.

For p53 staining, cells with brown-yellow nuclear granules were considered positive, and the expression rate was determined by counting positive cells in 10 high-power fields (×400). An H-score was used to assess expression rates, with <5% indicating negative and >5% indicating positive expression. The H-score was calculated by assigning intensity levels: 0 (negative), 1+ (weak), 2+ (moderate), or 3+ (strong), multiplied by the percentage of tumor cell nuclei stained. The resulting H-score ranged from 0 to 300, with mild (1+), moderate (2+), and strong (3+) expression categories. p53 expression types were further classified as wild type, featuring a mix of negative and mildly to strongly positive cells, or aberrant type, characterized by either complete negativity (0% nuclear staining) or overexpression in positive cells. All the information was entered and analyzed using SPSS version 26**.** Data was analyzed by using Statistical package of social sciences (SPSS) version 26.0.

Results

A total of 329 samples were taken, which met the inclusion criteria. Mean age of the patients was 45.53±12.10 years, minimum age 17 years while maximum 77 years. Out of all study subjects, 319 (97.0%) were married and 10 (3.0%) were unmarried. According to the site, 166 (50.5%) specimens were of left site and 163 (49.5%) specimens were of right site.

From specimens received, excisional biopsy specimens were 80 (24.3%), mastectomy specimens were 183 (55.6%), lumpectomy specimens were 52 (15.8%) and wedge specimens were 14 (04.3%). Estrogen receptor was positive in 189 (57.4%) of the specimens and in 140 (42.6%) it was negative. Progesterone receptor was positive in 167 (50.8%) of the specimens and in 162 (49.2%) it was negative. According HER2 status of the specimens, in 178 (54.1%) it was positive; in 141 (42.9%) it was negative, while in 10 (3.0%) specimens it was equivalent.

According to the frequency of the molecular subtypes of the specimens, HER2 was positive in 82 (24.9%), luminal was in 123 (37.4%) and luminal B was in 66 (20.1%), while Triple negative was in 58 (17.6%) of specimen. (Table I)

Table I: Frequency of the molecular subtypes of the specimens. (n=329)

Molecular subtypes	Frequency	Percent
HER2 Positive	82	24.9
luminal A	123	37.4
luminal B	66	20.1
Triple negative	58	17.6
Total	329	100.0%

In this study expressions of p53 according to molecular subtypes of invasive breast carcinoma was statistically significant (p=0.0001). (Table II)

In this study association of types of expression was statistically significant according to molecular subtypes of invasive breast carcinoma (p=0.0001). Table III

Table II: Expressions of p53 according to molecular subtypes of invasive breast carcinoma. (n=329)

Variables	P53 Negative	P53 positive	Total	p-value
Molecular subtypes of IBC				
HER2 Positive	26	56	82	0.0001
	7.9%	17.0%	24.9%	
luminal A	91	32	123	
	27.7%	9.7%	37.4%	
luminal B	32	34	66	
	9.7%	10.3%	20.1%	
Triple negative	30	28	58	
	9.1%	8.5%	17.6%	
Total	179	150	329	
	54.4%	45.6%	100.0%	

Table III: Molecular subtypes according to types of expression. (n=329)

Variables	Types of expression Aberrant	Wild	Total	p-value
Molecular subtypes of IBC				
HER2 POSTIVE	38	44	82	0.0001
	11.6%	13.4%	24.9%	
luminal A	91	32	123	
	27.7%	9.7%	37.4%	
luminal B	34	32	66	
	10.3%	9.7%	20.1%	
Triple negative	42	16	58	
	12.8%	4.9%	17.6%	
Total	232	97	329	
	70.5%	29.5%	100.0%	

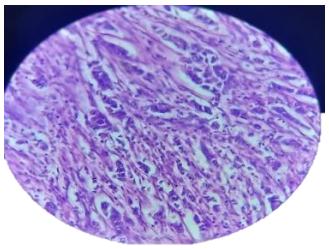

Figure 1. H/E staining High power view of Invasive Ductal carcinoma.

Figure 2. Immunohistochemical staining of strong positive p53

Figure 3. Immunohistochemical staining of moderate positive p53

Figure 4. Immunohistochemical staining of weak positive p53

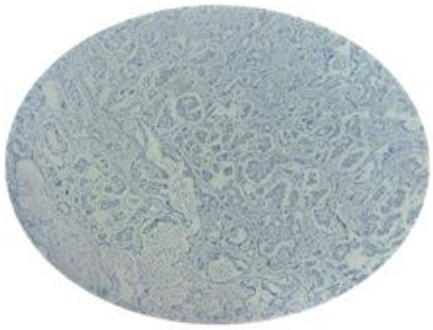

Figure 5. Immunohistochemical staining shows Negative p53. (aberrant type)

Discussion

Breast cancer is commonly detected either through screening procedures or when symptoms prompt a diagnostic examination. Important decisions about treatment are made based on protein expression tests, which do not depend on the physical characteristics of the tumor. These histologic tumor markers are widely used to predict responses to targeted therapy; they are restricted by substantial variations within the tumor, even within a single biopsy specimen. This study has been conducted to determine the expressions of P53 and molecular subtypes of invasive breast carcinoma by Immunohistochemical expression of ER PR and her2 neu, along with correlation of expressions of p53 with molecular subtypes of invasive breast carcinoma.

In this study according to the histological grade of the tumor, grade III was most common 215 (65.3%), grade II was 110 (33.4%) and grade I was 4 (1.2%). In this study according to the histological grade of the tumor, grade III was most common 215 (65.3%), grade II was 110 (33.4%) and grade I was 4 (1.2%). Consistently Younus A et al[10] reported that most of the malignancies, 80%, were Grade-2, with Grade-3 tumours occurring in 18.7%) individuals. Siddiqu et al[11], and Khokher et al[12] also demonstrated the most common tumour grading seen in65% and 55% of these individuals upon manifestation, correspondingly, was grade II. Badar et al[13] at the Shaukat Khanum Memorial Cancer Hospital and Research Center in Lahore, an approximately equivalent proportion of grade-II (41.4%) and grade-III (49.6%) tumors were identified among patients who had invasive ductalcarcinoma. Henna N et al[14] also reported that Indian patients with invasive ductal carcinoma had a relatively comparable distribution of tumor grade, with grade-II tumors accounting for 40.8% and grade-III tumors accounting

for 41.9%. Our findings were also similar to the study by Henna N et al.[15]

In this study estrogen receptor was positive in 189 (57.4%) of the specimens, progesterone receptor was positive in 167 (50.8%) of the specimens and according HER2 status of the specimens, in 178 (54.1%) it was positive. The frequency of the molecular subtypes of the specimens, HER2 was positive in 82 (24.9%), luminal A was in 123 (37.4%) and luminal B was in 66 (20.1%), while Triple negative was in 58 (17.6%) of specimen. In the comparison of this study Henna N et al[15] reported that out of the patient population, 37.2% exhibited a luminal A profile, while 12% demonstrated a luminal B profile. HER2-enriched expression was detected in 20.5% of patients, and 30.1% were categorized as triple negative. Although Millar et al.[16]

Australian research had patients 79.1% Luminal A, 4.6%, Liu X et al. Chinese study group had patients who belong to Luminal A (32.8%), Luminal B (27.9%) 9.9%, Her2-enriched group (13.3%) and Triple negative group comprised of 26.7% of patients.[17] Literature search shows that Luminal A is most prevalent group in Oman, Poland, China, Peru, Tunisia, USA, Riyadh and Jeddah.[18-23] An Iranian study stated that Luminal B was most common (43.73%) in their study group followed by Luminal A (27.97%), HER2 Enriched (20.9%) and triple negative (7.4%)ǁ in descending order.[24]

In this study the frequency of the P53 expressions was positive in 150 (45.6%) of the cases and it was negative in 179 (54.4%) of the specimens and in accordance to its intensity, mildly expressed in 20 (6.1%) specimens, moderately expressed in 36 (10.9%) and strongly expressed in 94 (28.6%) of specimen, while in 179 (54.4%) it was negative. In the comparison to our findings the Dash SS et al[25] reported that the overall, 61.3% of cases were found to be positive for p53. In the study by Raj S et al[26] demonstrated that the expression of p53 was 85%.

Although in the by Kaur S et al[27] also found consisting findings that the P53 positivity was noted in 60 cases comprising of 58.3%. In breast carcinoma, overexpression of p53 is associated with poor prognosis and aggressive tumor behavior. Studies havereported that p53 overexpression is more common in high-grade breast carcinomas, which are associated with a higher risk of recurrence and poor survival outcomes. In addition, p53 overexpression has been associated with resistance to chemotherapy and endocrine therapy in breast cancer.

In this study expressions of p53 were statistically significant according to molecular subtypes and types of expression of –invasive breast carcinomaǁ (p=0.0001). These findings were supported by the study of Dash SS et al.[25] Although p53 expression is more frequent in the triple-negative/basal-like subtype of breast cancer compared to other subtypes. The increased expression of p53 in this subtype may be due to the amplification of the p53 gene or other genetic alterations in the p53 pathway. In contrast, the Luminal A and Luminal B subtypes have a lower frequency of p53 mutations and overexpression because the p53 pathway is normally functional in these subtypes. The association of p53 expression with molecular subtypes of breast cancer can be used to predict tumor behavior and response to therapy.

However, p53 overexpression does not always correlate with the presence of p53 mutations and other factors can also influence p53 expression and function. The use of p53 expression as a prognostic and predictive marker in breast cancer should be interpreted in conjunction with other clinical and pathological factors. While p53 expression is an important marker in breast carcinoma, there are limitations to its use. These limitations include lack of standardization, false positive and negative results, variable association with p53 mutation, limited predictive value, and lack of correlation with other factors. It is important to consider these limitations when interpreting and applying p53 expression as a biomarker in breast cancer.

Conclusion

In our study aberrant expression of p53 were observed in triple negative and HER2neu overexpressed tumors. There is also a significant correlation of the expressions of p53 with molecular subtypes of invasive breast carcinoma. The elevated level of p53 expression in aggressive breast cancer phenotypes suggests that p53 may serve as a prognostic marker. As per the findings, breast malignancy mostly in females may be aggressive type, so p53 immunostaining may be used along with commonly used immunostaining in breast cancer i.e. ER, PR, HER2NEU and Ki67 For better therapeutic and prognosis approach.

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