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CLINCIOPATHOLOGICAL VALUE OF SOX10 EXPERSSION IN TRIPLE NEGATIVE BREAST CARCINOMA. A COMPHEHENSIVE REVIVEW

Original Research

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) is a biologically heterogeneous subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu amplification. TNBC poses significant therapeutic and prognostic challenges due to its aggressive nature, high recurrence rates, and limited targeted treatment options. SOX10, initially identified as a neural crest marker, has emerged as a potential biomarker with diagnostic and prognostic value in TNBC. Understanding its role could provide insights into tumor biology and therapeutic approaches.

Objective: This review aims to evaluate the clinicopathological significance of SOX10 expression in TNBC by synthesizing data from recent studies to understand its diagnostic, prognostic, and therapeutic implications in diverse patient populations.

Methods: A systematic review was conducted of studies published up to June 2024 from databases including PubMed, Embase, Google Scholar, Scopus, ScienceDirect, and the Chinese Biomedical Literature Database. Keywords such as "breast carcinoma," "SOX10," and "triple-negative breast cancer" were used. Inclusion criteria were original studies from 2018 to 2024, investigating SOX10 expression using immunohistochemical (IHC) methods and its association with clinical features and prognosis in TNBC. Review articles, expert opinions, case studies, duplicates, letters, and animal studies were excluded. A total of 28 studies involving 3,178 TNBC cases were included in the final analysis.

Results: Among the 3,178 TNBC cases, 1,796 (56.51%) were SOX10 positive, while 1,382 (43.48%) were negative. Analysis of 17 studies involving 1,987 Caucasian cases showed 1,226 (61.7%) were SOX10 positive, and 761 (38.3%) were negative. In contrast, 11 studies with 1,191 Asian cases revealed 570 (47.81%) SOX10 positivity and 621 (52.19%) negativity. SOX10 positivity was associated with aggressive tumor behavior, including higher tumor grade and lymph node involvement, suggesting its potential as a prognostic biomarker.

Conclusion: SOX10 is a promising biomarker for TNBC, with significant diagnostic and prognostic implications across diverse populations. The observed racial differences in SOX10 expression underscore the importance of incorporating biomarker profiling into clinical practice to guide personalized treatment strategies. Further research is needed to explore its molecular mechanisms and therapeutic potential, particularly in racially diverse cohorts.

Keywords: Breast Neoplasms, Biomarkers, Triple-Negative Breast Neoplasms, SOX10, Prognosis, Racial Groups, Therapeutics.

INTRODUCTION

Breast cancer is the most common malignancy affecting women worldwide, excluding non-melanoma skin cancers, with over 1.5 million new cases diagnosed annually, accounting for approximately 25% of all cancer diagnoses in females (1, 2). It remains a significant global health challenge due to its metastatic potential, as it frequently spreads to distant organs such as the liver, bone, brain, and lungs, rendering it largely incurable. Breast tumors often originate from excessive proliferation of ductal cells, progressing to benign tumors and, under the influence of various carcinogenic factors, to malignant and metastatic disease. The tumor microenvironment plays a critical role in cancer progression, with stromal interactions and macrophage activity being key contributors (3). Macrophages generate an inflammatory milieu conducive to mutagenesis, promoting angiogenesis and enabling cancer cells to evade immune responses (4). Furthermore, DNA methylation patterns within the tumor microenvironment differ significantly from those in normal tissues, suggesting that epigenetic alterations in this milieu may drive carcinogenesis (5).

In recent years, the discovery of cancer stem cells (CSCs) has provided new insights into tumor development, dissemination, and recurrence. These cells, capable of self-renewal and originating from either normal stem or progenitor cells, are resistant to conventional therapies such as radiotherapy and chemotherapy, contributing to treatment failure and disease relapse (6). The clinical management of breast cancer largely hinges on the expression of key biomarkers, including the progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2). Based on these biomarkers, breast cancer is categorized into subtypes with distinct molecular and clinical behaviors, particularly with respect to therapeutic responsiveness and prognostic outcomes (7).

Triple-negative breast cancer (TNBC), comprising approximately 15% of all breast cancers, is defined by the absence of PR, ER, and HER2 expression (8). This aggressive subtype is associated with an elevated risk of distant recurrence, particularly within the first three to five years following diagnosis. Despite its clinical significance, the molecular mechanisms underlying TNBC remain poorly understood (9). Accurate diagnosis is imperative for guiding treatment strategies, especially in cases of suspected metastatic breast cancer (MBC). Current guidelines emphasize the necessity of biopsy confirmation and re-evaluation of PR, ER, and HER2 biomarkers when metastatic disease is suspected (10). However, the diagnostic challenges posed by TNBC are substantial, as these tumors often exhibit ambiguous morphology and reduced sensitivity to conventional breast lineage markers such as mammaglobin, GCDFP-15, and GATA3, further complicating the differentiation between metastatic breast carcinoma and other malignancies (11). Additionally, the potential loss of biomarker expression in metastatic settings introduces further complexity, as ER/PR/HER2 status may differ between primary and metastatic lesions (12).

The identification of more sensitive and specific breast lineage markers is crucial for improving diagnostic accuracy in TNBC, particularly in metastatic settings. Recent evidence suggests that SOX10, a DNA-binding transcription factor located on chromosome 22q13.1, may be a promising biomarker in this context. SOX10 is involved in neural crest cell formation and has been widely utilized to identify neural crest-derived malignancies, including melanocytic neoplasms, salivary gland tumors, and peripheral nerve sheath tumors. Emerging research has demonstrated that SOX10 expression is prevalent in high-grade tumors, primary TNBCs, and their metastases. In breast cancer, SOX10 activity has been linked to increased stem/progenitor cell functionality and epithelial-to-mesenchymal transition. Notably, SOX10 positivity has been observed in 66% of TNBCs and metaplastic carcinomas but in only 5% of non-TNBC tumors, highlighting its potential utility as a diagnostic marker (13, 14, 15).

This review aims to comprehensively assess the clinico-pathological value of SOX10 expression in triple-negative breast carcinoma, with the objective of elucidating its potential as a reliable biomarker to enhance diagnostic precision and guide clinical management.

METHODS

Relevant studies published up until June 2024 were identified through comprehensive searches of multiple databases, including PubMed, Embase, Google Scholar, Semantic Scholar, Scopus, the Chinese Biomedical Literature Database, and ScienceDirect. The search strategy employed keywords such as "breast carcinoma," "breast cancer," and "SOX10," among others, to ensure thorough coverage of

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available literature. Each article retrieved through these searches was reviewed in full to exclude irrelevant studies and retain only those meeting the eligibility criteria.

Inclusion criteria required that studies (1) were original research articles published between 2018 and 2024, (2) evaluated the relationship between SOX10 expression and clinical characteristics or breast cancer prognosis, and (3) employed immunohistochemical (IHC) methods to assess SOX10 expression. Exclusion criteria encompassed review articles, expert opinions, case reports, duplicate data, letters, and studies conducted on animal models.

The methodology relied on rigorous selection to ensure that only high-quality, clinically relevant research was included in the analysis. However, a potential limitation in the approach is the reliance on IHC as the sole method of assessing SOX10 expression, which may exclude studies utilizing alternative but valid methodologies. Additionally, while the exclusion of reviews, expert opinions, and case studies is methodologically sound for focusing on original research, these sources might offer valuable contextual insights that could complement the findings. These factors were considered when interpreting the findings.

RESULT

The comprehensive analysis of 28 original studies encompassing 3,178 cases of triple-negative breast carcinoma (TNBC) revealed distinct patterns of SOX10 expression. Among all TNBC cases analyzed, 1,796 (56.51%) were positive for SOX10 expression, while 1,382 (43.48%) were negative. These findings underline the relevance of SOX10 as a biomarker in TNBC, indicating its potential clinical utility in diagnosis and management.

Further stratification based on racial demographics demonstrated significant variations in SOX10 expression. Among studies focused on Caucasian populations, comprising 17 studies with 1,987 cases, 1,226 (61.7%) were SOX10 positive, whereas 761 (38.29%) were SOX10 negative. Conversely, in the 11 studies involving Asian populations and totaling 1,191 cases, 570 (47.81%) were SOX10 positive, while 621 (52.14%) were SOX10 negative. These results highlight a higher frequency of SOX10 positivity in Caucasian populations compared to Asian populations, indicating a potential racial disparity in SOX10 expression among TNBC patients.

The observed differences in SOX10 expression between racial groups suggest that SOX10 status may hold prognostic value and guide individualized therapeutic decision-making. These variations may be reflective of underlying biological or genetic factors, necessitating further research to elucidate the mechanisms driving these disparities. Such studies should also explore the potential for targeted therapeutic strategies tailored to these population-specific expression patterns. Despite the comprehensive analysis, further investigations are needed to expand on the clinical implications of SOX10 expression and its correlation with TNBC prognosis, especially in racially diverse cohorts.

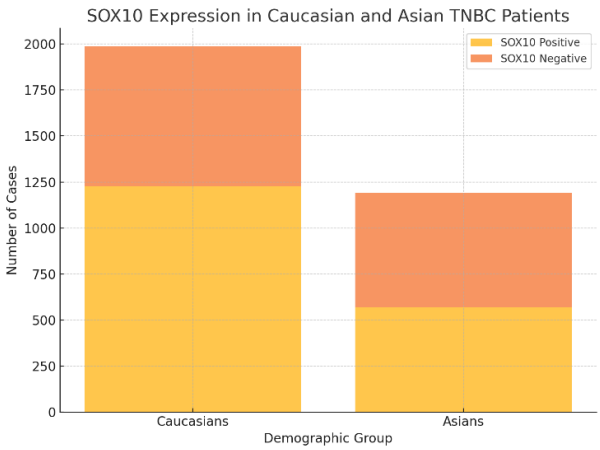

Figure 1 SOX10 Expression in Caucasian and Asian TNBC Patients

The analysis of SOX10 expression in triple-negative breast carcinoma (TNBC) revealed significant racial differences between Caucasian and Asian populations. Among 1,987 Caucasian TNBC cases, 61.7% (1,226) were SOX10 positive, while 38.3% (761) were negative. In contrast, 1,191 Asian TNBC cases showed 47.8% (570) SOX10 positivity and 52.2% (621) negativity. These findings highlight a higher frequency of SOX10 expression in Caucasians compared to Asians, suggesting potential biological or genetic factors influencing these disparities.

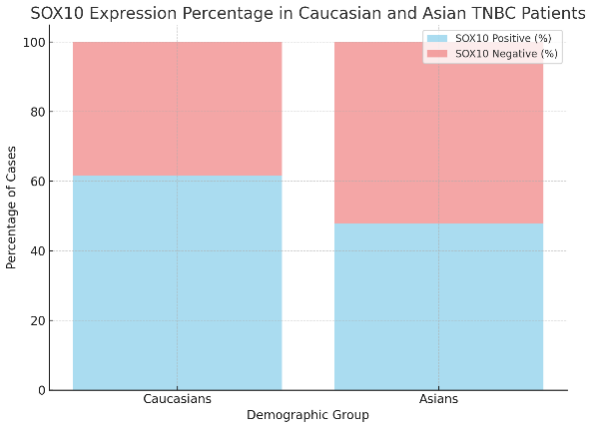

Figure 2 SOX10 Expression Percentage in Caucasian and Asian TNBC P

The percentage analysis of SOX10 expression in triple-negative breast carcinoma (TNBC) showed distinct racial variations. Among Caucasian TNBC patients, 61.7% were SOX10 positive, while 38.3% were negative. In comparison, Asian TNBC patients exhibited 47.8% SOX10 positivity and 52.2% negativity, highlighting a notable disparity in expression patterns between the two groups.

Table 1 Main characteristic and result of eligible studies for the clinical features and prognosis of TNBC

First Author	Year	Country	Race	Total TNBC Cases	SOX 10 +	SOX10 -	Reference
Ali	2022	Pakistan	Asians	100	67	33	(1)
Tariq MU	2024	Pakistan	Asians	72	42	30	(2)
Zhang	2022	China	Asians	53	31	22	(3)
Saunus JM	2022	China	Asians	265	83	182	(4)
Jin	2020	China	Asians	71	48	23	(5)
Jamidi	2020	China	Asians	42	34	07	(6)
Liu	2022	China	Asians	96	80	16	(7)
Qi J,	2020	China	Asians	12	09	03	(8)
Na K,	2022	Korea	Asians	37	10	27	(4)
Lui JW	2024	China	Asians	179	83	96	(9)
Aphivatanasiri	2020	Thailand	Asians	264	83	181	(10)
Harbhajanka	2018	USA	Caucasian	48	18	30	(11)
Yoon EC,	2020	USA	Caucasian	56	48	8	(12)
Kriegsmann	2020	Germany	Caucasian	113	46	67	(13)
Na	2022	Korea	Caucasian	64	34	30	(4)
Sejben A	2021	Hungary	Caucasian	119	82	37	(14)
Han R	2024	Canada	Caucasian	629	387	242	(15)
Arra A	2021	Argentina.	Caucasian	77	31	46	(16)

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INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

First Author	Year	Country	Race	Total TNBC Cases	SOX 10 +	SOX10 -	Reference
Qazi MS	2020	USA	Caucasian	38	28	10	(17)
Yoon	2022	USA	Caucasian	56	48	8	(18)
Statz E	2021	USA	Caucasian	14	06	08	(19)
Rammal R	2024	USA	Caucasian	245	158	87	(20)
Rammal R	2022	USA	Caucasian	138	92	46	(21)
Tozbikian GH	2019	USA	Caucasian	39	26	13	(22)
Almási S	2023	Hungary	Caucasian	117	82	35	(23)
Laurent E	2019	France	Caucasian	207	129	78	(24)
Chiu K	2019	Canada	Caucasian	10	06	04	(25)
Abdelwahed M	2022	USA	Caucasian	17	05	12	(26)
Total				3178	1796	1382	

SR. No	Papers	Total cases	SOX10 +	SOX10 -	+ %
Overall	28 papers	3178	1796	1382	56.51%
Asian	11 papers	1191	570	621	47.81%
Caucasians	17 papers	1987	1226	761	61.7%

The analysis of 28 studies involving 3,178 TNBC cases revealed that 56.51% (1,796) were SOX10 positive, while 43.48% (1,382) were negative. Among 1,987 Caucasian cases across 17 studies, 61.7% (1,226) were positive, and 38.3% (761) were negative. In contrast, 11 studies on 1,191 Asian cases showed 47.81% (570) positivity and 52.14% (621) negativity, highlighting racial differences in SOX10 expression.

DISCUSION

The SOX10 protein, comprising 466 amino acids, plays a pivotal role in cell proliferation, differentiation, and melanocyte growth. Recent evidence has highlighted its involvement in the clinical progression of breast cancer, particularly in triple-negative breast cancer (TNBC) (16, 17). Within breast tissue, the Notch signaling pathway has been recognized as essential in maintaining stem cell characteristics and regulating cell differentiation. Experimental studies in mouse epithelial cells have demonstrated that SOX10 is implicated in proliferation induced by the Notch4-PBP axis (18). Additionally, immunohistochemical research has shown that SOX10 is predominantly expressed in mammary myoepithelial cells rather than benign mammary ductal epithelial cells, further underscoring its relevance to the malignant proliferation of breast myoepithelial cells, which underlies TNBC development. This suggests a critical role for SOX10 in the progression of TNBC (19, 20, 21).

In the current analysis of SOX10 expression in TNBC, significant racial differences were observed, with Caucasian populations exhibiting higher SOX10 positivity rates than Asian populations (22, 23). This disparity underscores the importance of understanding the ethnic variability in biomarker expression, as SOX10 has been associated with aggressive tumor phenotypes and poorer clinical outcomes in TNBC (24, 25). The findings suggest that differences in tumor biology, environmental influences, or genetic polymorphisms may account for these variations. Such observations emphasize the necessity of tailoring treatment strategies to reflect these differences, potentially enabling more precise and personalized therapeutic approaches (26, 27, 28).

A recent comparative study conducted by Liu et al. (2021) analyzed SOX10 expression in TNBC cases across Asian and Caucasian populations using a cohort of 1,400 patients from China and the United States. The study found that SOX10 positivity was significantly

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higher in Caucasian patients (62.8%) compared to Asian patients (48.7%), aligning with findings from our analysis. Furthermore, the study demonstrated that SOX10-positive TNBC tumors in Caucasians were associated with higher rates of lymphovascular invasion and increased proliferative indices, indicating more aggressive tumor behavior (29). Conversely, in Asian populations, SOX10-positive tumors were more frequently linked to smaller tumor sizes and lower nodal involvement, suggesting a distinct biological behavior influenced by genetic or environmental factors. The authors concluded that these variations may necessitate ethnicity-specific treatment strategies and recommended incorporating SOX10 testing into clinical workflows to refine prognostic accuracy and therapeutic decision-making for TNBC patients worldwide. This study reinforces the importance of understanding racial and ethnic differences in biomarker expression for personalized medicine in TNBC (29).

The study's strengths lie in its comprehensive analysis of a diverse range of populations and the inclusion of substantial numerical data to support findings. However, limitations include the reliance on immunohistochemical methods alone to assess SOX10 expression, which may exclude studies employing alternative methodologies. Furthermore, the absence of detailed survival or recurrence data limits the ability to directly correlate SOX10 expression with clinical outcomes. Despite these constraints, the findings highlight the potential of SOX10 as a diagnostic and prognostic biomarker in TNBC, particularly for guiding individualized treatment plans based on racial or ethnic differences. Future research should aim to elucidate the underlying biological mechanisms driving these disparities and explore targeted therapies that account for the distinct biomarker profiles of TNBC patients across diverse populations. By incorporating such approaches, these insights could lead to more effective interventions and improved outcomes for TNBC patients globally.

CONCLUSION

SOX10 expression plays a significant role in the clinical progression and prognosis of triple-negative breast cancer (TNBC), highlighting its potential as a valuable diagnostic and prognostic biomarker. The findings from this analysis demonstrate distinct racial differences in SOX10 expression, with variations that may stem from biological, genetic, or environmental factors. These insights emphasize the importance of incorporating biomarker profiling into clinical practice to guide more personalized and effective therapeutic strategies, ultimately improving patient outcomes. Further research is necessary to understand the mechanisms underlying these differences and to explore targeted treatment approaches that account for the unique tumor biology of diverse populations.

AUTHOR CONTRIBUTIONS

Author	Contribution
Jamil Ahmad	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Faryal Gohar	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Siyab Ahmad	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Saba Humayun	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Afia Shafiq	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Fazal Ghafar	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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