"EXPRESSION OF ANDROGEN RECEPTOR IN INFILTRATING DUCTAL CARCINOMA OF BREAST AND ITS ASSOCIATION WITH PROGNOSTIC FACTORS"

BY

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DISSERTATION SUBMITTED TO

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
CAP	College of American Pathologists
DAB	3,3'-Diaminobenzidine
DCIS	Ductal Carcinoma In Situ
EDTA	Ethylenediaminetetraacetic Acid
ER	Estrogen Receptor
H&E	Hematoxylin and Eosin
HER2	Human Epidermal Growth Factor Receptor 2
HRP	Horseradish Peroxidase
IDC	Infiltrating Ductal Carcinoma
IHC	Immunohistochemistry
IARC	International Agency for Research on Cancer
Ki67	Proliferation Marker Protein Ki-67
LVI	Lymphovascular Invasion
MBR	Modified Bloom-Richardson (Grading)
NOS	Not Otherwise Specified
PR	Progesterone Receptor
SOP	Standard Operating Procedure

Abbreviation	Full Form
SPSS	Statistical Package for the Social Sciences
TILs	Tumor-Infiltrating Lymphocytes
TNBC	Triple-Negative Breast Cancer
TNM	Tumor, Node, Metastasis (Staging System)
WHO	World Health Organization
χ^2	Chi Square
Df	Degrees of Freedom
P	Probability Value

ABSTRACT

BACKGROUND

Androgen receptor (AR) expression in breast cancer has emerged as a potential prognostic marker and therapeutic target. This study aimed to evaluate AR expression in infiltrating ductal carcinoma and its association with established prognostic factors.

METHODS

A laboratory-based cross-sectional study was conducted on 96 infiltrating ductal carcinoma specimens. AR expression was evaluated by immunohistochemistry and analyzed using three methods: Allred score, H-score, and nuclear positivity. Associations with clinicopathological parameters were assessed using chi-square tests and Fischer's exact test.

RESULTS

AR expression was observed in 68.75% of samples by Allred score and 69.79% by nuclear positivity criteria. Significant associations were found between AR expression and both ER status (p=0.000) and PR status (p=0.003). AR expression varied significantly across molecular subtypes (p=0.001), with highest prevalence in Luminal B (92.6%) and lowest in HER2+ (33.3%). No significant associations were observed between AR and HER2 status, Ki67 expression, lymphovascular invasion or tumor-infiltrating lymphocytes.

CONCLUSION

AR is expressed in a significant proportion of breast cancers, with notable variation across molecular subtypes. The strong association with hormone receptor status suggests potential interplay between steroid hormone signaling pathways. These findings support the relevance of AR as both a prognostic marker and potential therapeutic target, particularly in specific molecular subtypes of breast cancer.

KEYWORDS

Androgen receptor; Breast cancer; Infiltrating ductal carcinoma; Molecular subtypes; Hormone receptors

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INTRODUCTION

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer related deaths among women worldwide.[1] Infiltrating ductal carcinoma (IDC) accounting for 70-80% of all invasive breast cancers, exhibits significant heterogeneity in clinical presentation, morphology, molecular characteristics, and response to therapy.[2] The current prognostic and therapeutic decision-making paradigm for breast cancer relies heavily on the assessment of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2neu) and Ki-67 proliferation index. However, these conventional markers fail to fully address the biological complexity and clinical diversity of breast cancer, more so in triple-negative breast cancers (TNBC) due to lack of expression of ER, PR, and HER2.[3]

In recent years, androgen receptor (AR) has emerged as a potential biomarker and therapeutic target in breast cancer. AR is expressed in approximately 70-90% of primary breast cancers and has been detected across all molecular subtypes, including TNBC.[4] The biological role of AR in breast carcinogenesis appears complex and may differ depending on the hormonal context and molecular subtype. While AR signalling has been associated with anti-proliferative effects in ER-positive breast cancers, potentially through opposition of estrogen-driven proliferation, its role in ER-negative contexts may promote tumor growth and progression.[3]

Despite growing evidence suggesting the prognostic significance of AR in breast cancer, its association with established histopathological and immunohistochemical prognostic factors remains incompletely understood. Furthermore, the predictive value of AR expression for treatment response and its potential utility as a therapeutic target require further investigation, particularly across different molecular subtypes.[5] This study aims to evaluate AR expression in IDC and investigate its association with histopathological factors including grade, mitotic activity, tubule formation, tumor-infiltrating lymphocytes, lymphovascular invasion, lymph node metastasis, as well as immunohistochemical markers (ER, PR, HER2, Ki-67) and molecular subtypes, to better understand its role in breast cancer biology and clinical outcomes.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

Aim: To study the expression of androgen receptor in Infiltrating Ductal Carcinoma of Breast.

Objective:

1. To determine the expression of Androgen receptor in Infiltrating Ductal Carcinoma (not otherwise specified)
2. To study the association of Androgen Receptor with histopathological factors including grade, mitotic activity, tubule formation, tumor-infiltrating lymphocytes, lymphovascular invasion, lymph node metastasis and extra nodal spread.
3. To study the association of Androgen Receptor with immunohistochemical (IHC) prognostic factors like ER, PR, Her 2 neu, Ki67 and molecular subtype.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ANATOMY OF BREAST

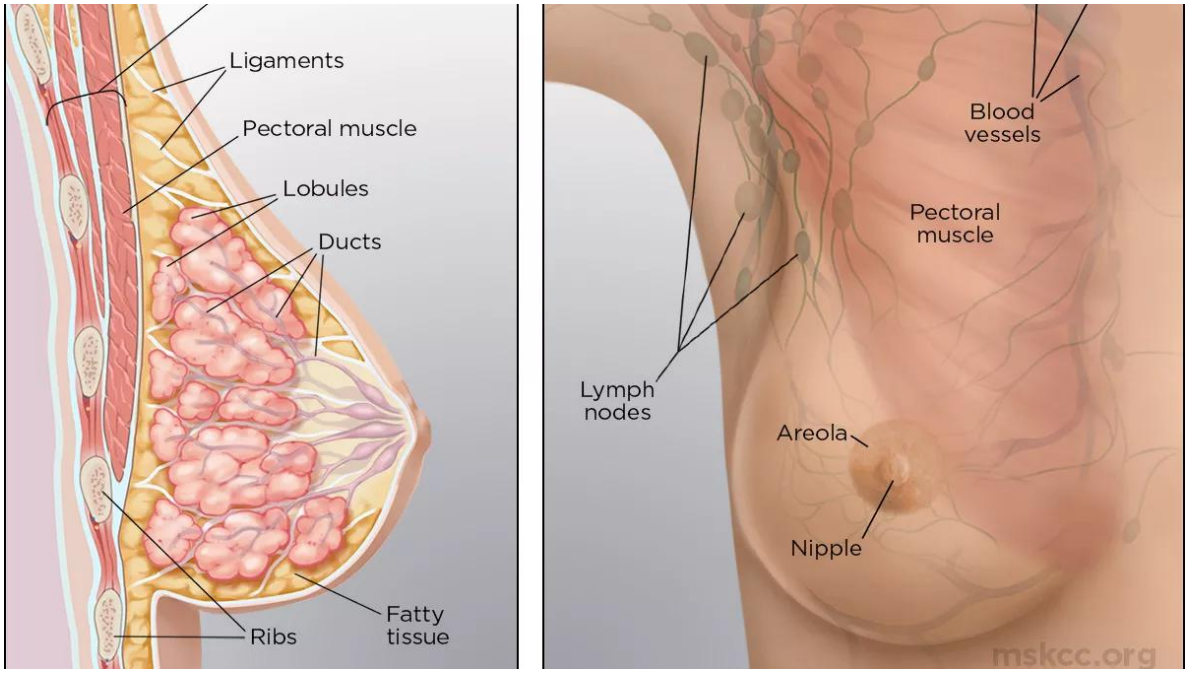

FIGURE 1: GROSS ANATOMY OF BREAST

Gross Anatomy and Structural Components

The mammary gland forms the secondary sexual characteristics of females and breast milk is the only source for nutrition for neonates. Mammary glands are superficial organ located on the anterior thoracic wall, extending from the second to sixth ribs vertically and from the sternal edge to the midaxillary line horizontally. Structurally, the breast consists of three primary components: glandular tissue, fibrous stroma and adipose tissue. The glandular tissue, responsible for milk production is organized into 15–20 lobes, each draining via lactiferous duct that converges at the nipple. These lobes are embedded within a matrix of fibrous connective tissue known as the suspensory ligaments of Cooper which anchor the breast to the chest wall and provide structural support.[6] Adipose tissue distributed variably between and within lobes contributes to the breast's volume and contour.

The nipple-areolar complex (NAC) is a central feature located at the fourth intercostal space in most individuals. The areola contains sebaceous glands (Montgomery glands) that lubricate the skin during lactation. Beneath the breast lies the pectoralis major muscle separated from the

glandular tissue by a layer of retromammary fat and deep fascia. This anatomical arrangement influences surgical approaches such as mastectomy and imaging techniques like mammography.[7]

Blood Supply, Lymphatic Drainage and Innervation

The breast receives a rich blood supply from multiple sources ensuring its metabolic demands are met. The internal mammary artery, arising from the subclavian artery, supplies the medial breast via perforating branches accounting for approximately 60% of its arterial input. Laterally, the lateral thoracic artery and branches of the thoracoacromial artery contribute, while intercostal arteries supply the posterior aspect.[8]

Venous drainage mirrors the arterial supply with superficial veins forming an anastomotic circle around the nipple and deeper veins draining into the axillary, internal mammary and intercostal veins.

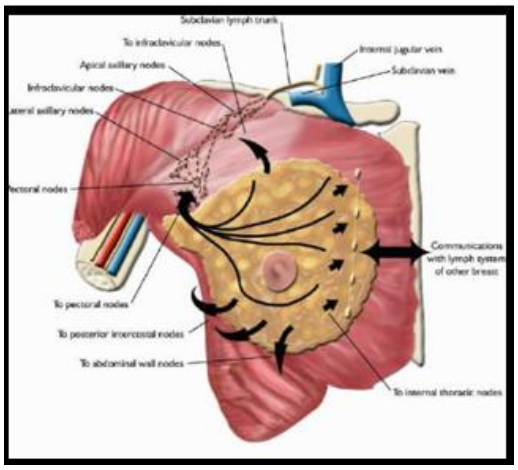

FIGURE 2: LYMPHATIC DRIANAGE OF BREAST

Lymphatic drainage is a critical aspect of breast anatomy due to its relevance in cancer metastasis. Approximately 75% of lymph drains to the axillary lymph nodes, divided into levels I–III based on their relation to the pectoralis minor muscle. The internal mammary nodes located along the parasternal region drain the medial breast and receive about 20% of lymphatic flow. Minor pathways include the intercostal and supraclavicular nodes.[9]

Recent studies using sentinel lymph node mapping have refined our understanding of these patterns highlighting variability in drainage routes that impact staging and treatment of breast carcinoma.[10]

Innervation of the breast is primarily sensory derived from the anterior and lateral cutaneous branches of the second to sixth intercostal nerves. The nipple and areola are particularly sensitive due to a dense network of nerve endings, with the fourth intercostal nerve playing a dominant role. Sympathetic innervation, via the autonomic nervous system regulates vascular tone and sweat gland activity but has no direct motor function in the breast.[11] This sensory innervation explains post-surgical neuropathic pain following breast procedures.

HISTOLOGY OF THE BREAST

Microscopic Structure of Breast Tissue

Histologically, the breast is a modified apocrine sweat gland with a dual-layered epithelial structure embedded in a stromal matrix. The glandular unit termed the terminal duct lobular unit (TDLU) is the functional and histological cornerstone of the breast. The TDLU consists of 1) The terminal ductules whose epithelium differentiates and 2) Intralobular collecting ducts.[12] Surrounding the TDLU is a loose intralobular stroma, rich in fibroblasts and capillaries which contrasts with the denser interlobular stroma that separates lobes. Adipose tissue intersperses these elements, varying in proportion with age and hormonal status.

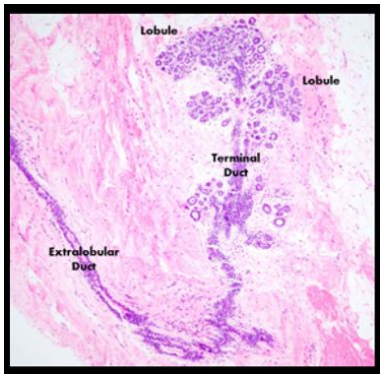

FIGURE 3: HISTOLOGY OF NORMAL BREAST

The breast undergoes dynamic histological changes across the lifespan. In premenopausal women, lobules are well-developed, with active epithelial proliferation during the menstrual cycle. Post-menopause involution occurs characterized by lobular atrophy, stromal fibrosis and increased adiposity.[13] These changes influence the histological presentation of breast diseases and their detection on imaging.

Cellular Components (Ducts, Lobules, Stroma)

The ductal system begins at the lactiferous sinuses beneath the nipple, extends into major ducts and branches into terminal ducts within the TDLU. These ducts are lined by a bilayered epithelium: an inner luminal layer of columnar or cuboidal cells and an outer myoepithelial layer with contractile properties. Myoepithelial cells identified by markers like p63 and smooth muscle actin play a role in milk ejection and act as a barrier against neoplastic invasion.[14] In IDC, disruption of this myoepithelial layer is a hallmark of invasive disease.

Lobules, the milk-producing units, consist of acini lined by luminal epithelial cells capable of apocrine secretion. During pregnancy and lactation, these cells hypertrophy and the lobules expand significantly. In non-lactating states, lobules are smaller and less prominent particularly in postmenopausal women. The epithelial cells express hormone receptors - estrogen receptor (ER), progesterone receptor (PR) and notably AR—linking histology to molecular pathology in breast cancer.[15]

Stromal changes such as desmoplasia are common in IDC and influence tumor behaviour and prognosis.[16] Adipocytes within the stroma secrete adipokines which may modulate local inflammation and cancer progression.[17]

The anatomy and histology of the breast provide a critical framework for understanding its physiological functions and pathological states such as IDC. The gross anatomy - encompassing glandular lobes, adipose tissue and the Nipple areolar complex along with its vascular and lymphatic networks dictates the clinical presentation and metastatic potential of breast cancer. Histologically, the TDLU and its cellular components (ducts, lobules, and stroma) are the epicentres of neoplastic transformation, with hormone receptor expression, including AR, bridging structure to molecular pathology.

COMMON INFLAMMATORY CONDITIONS

Acute Mastitis

Acute mastitis is the most prevalent inflammatory breast condition predominantly affecting lactating women. It occurs in approximately 2–10% of breastfeeding mothers typically within the first six weeks postpartum due to milk stasis or bacterial entry through cracked nipples.[18] Staphylococcus aureus is the primary causative organism often leading to localized erythema, pain, and fever. In severe cases, abscess formation complicates up to 5–11% of episodes, requiring drainage.[19]

The pathophysiology of acute mastitis involves bacterial invasion, typically through breaches in the nipple-areolar complex during lactation. Milk stasis creates a nutrient-rich environment, promoting S. aureus proliferation. This triggers an innate immune response with neutrophil infiltration and cytokine release (e.g., IL-6, TNF-α) causing tissue edema and pain. [25] Abscess formation occurs when pus accumulates within a walled-off cavity reflecting failed resolution of the inflammatory cascade.

Histologically, Mixed dense inflammatory infiltrate, predominantly neutrophils with tissue necrosis may be present. Granulation tissue and chronic inflammation is noted on resolution.

Chronic Mastitis and Duct Ectasia

Chronic mastitis including periductal mastitis and mammary duct ectasia affects non-lactating women often in their 30s to 50s. Duct ectasia results from ductal dilation and inspissation of secretions leading to periductal inflammation and fibrosis. Clinically it presents with nipple discharge (often bloody or greenish), retraction or a palpable mass mimicking carcinoma.[20] Smokers are at higher risk with studies suggesting a link to nicotine-induced ductal damage.[21]

Duct ectasia arises from obstruction and dilation of major ducts leading to stagnation of lipid-rich secretions. Leakage of these contents into surrounding tissue incites a chronic

inflammatory response, with macrophage and lymphocyte infiltration. Over time, periductal fibrosis and plasma cell infiltration develop contributing to nipple retraction.[27] The role of smoking is notable as it induces oxidative stress and epithelial injury amplifying inflammation.[21] This chronicity distinguishes it from acute mastitis and aligns it with benign proliferative disorders.

Grossly, Firm fibrotic breast tissue with prominent dilated and thick-walled ducts filled with a tan-white secretions. Histologically, Dilation of ducts with foamy histiocytes within the luminal secretions. Periductal inflammation with lymphocytes, plasma cells and neutrophils along with periductal fibrosis can also be noted.

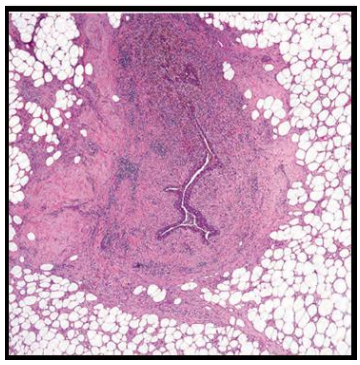

FIGURE 4: DUCT ECTASIA. Chronic inflammation and fibrosis around ectatic duct.[26]

Granulomatous Mastitis

Granulomatous mastitis (GM) is a rare chronic inflammatory condition characterized by non-caseating granulomas. It can be idiopathic or secondary to infections or foreign body reactions. Predominantly affects women of reproductive age, presenting as a painful, firm mass with skin changes, often mistaken for malignancy.[22] Its incidence is rising particularly in Middle Eastern and Asian populations with a prevalence of 1.8–3 cases per 1000 breast biopsies.[23]

In idiopathic granulomatous mastitis, the exact trigger remains unclear, though an autoimmune etiology is hypothesized. Histologically, non-caseating granulomas form around lobules,

accompanied by multinucleated giant cells and lymphocytic infiltrates.[28] Some studies suggest a link to prior pregnancy or hyperprolactinemia possibly due to immune sensitization to ductal secretions.[29]Secondary granulomatous mastitis causes are tuberculosis involves caseating granulomas driven by Mycobacterium tuberculosis while sarcoidosis features systemic granulomatous inflammation.

Fat Necrosis

Fat necrosis though not a primary inflammatory disease often presents with inflammation secondary to trauma, surgery or radiation therapy. It manifests as a palpable lump with overlying skin changes such as dimpling or bruising, and is histologically marked by fat degeneration, macrophage infiltration and fibrosis.[24] Its clinical significance lies in its mimicry of IDC necessitating imaging and biopsy for differentiation.

Fat necrosis begins with adipocyte injury often from mechanical trauma or ischemia post-surgery. Damaged fat cells release lipids triggering a foreign-body reaction with macrophage recruitment. This evolves into an inflammatory phase with foamy histiocytes followed by fibrosis or calcification.[30] The process mimics malignancy due to its stromal reaction but it lacks epithelial atypia distinguishing it histologically from IDC.

Clinical Relevance of Inflammatory Breast Conditions

Diagnostic Challenges

Inflammatory breast conditions frequently mimic malignancy complicating diagnosis. Acute mastitis may present with erythema and warmth resembling inflammatory breast cancer (IBC), a rare but aggressive carcinoma. IBC however, features dermal lymphatic invasion and rapid progression which is absent in mastitis.[31] Granulomatous mastitis and fat necrosis often form palpable masses which results in necessity of mammography and core biopsy to rule out IDC.

Duct ectasia's nipple discharge and retraction further overlap with carcinoma underscoring the need for multimodal evaluation.[32]

Impact on Breast Cancer Management

Inflammatory diseases can coexist with or mask breast cancer affecting staging and treatment. For instance, chronic inflammation in duct ectasia may increase local tissue reactivity, potentially influencing hormone receptor expression including AR in nearby carcinoma cells.[33] Abscesses or fistulae from mastitis may delay cancer detection, while granulomatous mastitis steroid responsive nature contrasts with cancer's resistance guiding therapeutic decisions. Fat necrosis common post-radiation can obscure recurrence surveillance requiring advanced imaging like MRI.[24]

Prognosis and Complications

Most inflammatory conditions resolve with appropriate management - antibiotics for acute mastitis. Recurrent mastitis or GM can lead to scarring and cosmetic deformity impacting quality of life.[34] Rarely, chronic inflammation may predispose to malignancy via sustained epithelial proliferation, though evidence remains inconclusive.[35] In the context of IDC, distinguishing these entities ensures accurate prognostic assessment and avoids overtreatment.

BENIGN LESIONS OF THE BREAST

Benign lesions of the breast constitute a heterogeneous group of conditions that while non-malignant yet frequently present diagnostic and management challenges due to their prevalence and potential to mimic carcinoma such as infiltrating ductal carcinoma (IDC). These lesions ranging from fibroadenomas to cysts account for the majority of breast-related complaints particularly in premenopausal women.

Types of Benign Breast Lesions

Fibroadenoma

Fibroadenomas are the most common benign breast tumors, comprising approximately 50% of all breast biopsies in women under 30 years of age.[32] These well-circumscribed, mobile masses arise from the terminal duct lobular unit (TDLU). They are hormonally responsive, often enlarging during pregnancy or the menstrual cycle and regressing post-menopause. Complex fibroadenomas characterized by cysts, sclerosing adenosis or calcifications represent about 15–20% of cases and carry a slightly elevated risk of future malignancy compared to simple fibroadenomas. Grossly, well circumscribed, firm mass with bosselated surface and lobulations. Cut surface shows slit-like spaces.

Histologically, fibroadenomas exhibit a characteristic biphasic pattern: ductal epithelial elements surrounded by a fibrous stroma. The epithelium forms slit-like or branching ducts, often compressed by the stroma in a pericanalicular pattern or rounded in an intracanalicular pattern. The stroma is typically hypocellular with collagen deposition though complex fibroadenomas show additional features like cysts (>3 mm), sclerosing adenosis or microcalcifications.[33]

Breast Cysts: Fibrocystic Changes

Breast cysts are fluid-filled sacs within the breast most prevalent in women aged 35–50 with an incidence peaking just before menopause. They originate from dilated ducts or lobules often linked to fibrocystic change- benign proliferative condition affecting up to 50% of women. Simple cysts are lined by a flattened or cuboidal epithelium often with apocrine metaplasia. The cyst fluid varies from clear to turbid. Complicated cysts may show epithelial hyperplasia or mild atypia, though these remain benign unless associated with ADH.[34] The surrounding stroma often exhibits fibrosis or lymphocytic infiltration hallmarks of fibrocystic change.

Intraductal Papilloma

Intraductal papillomas are benign epithelial tumors arising within the ductal system typically presenting with spontaneous nipple discharge which may be bloody. They are classified as central or peripheral with the latter associated with a higher risk of atypia. These lesions occur most often in women aged 40–60yrs. Multiple papillomas though still benign are linked to proliferative breast disease and warrant closer monitoring. Intraductal papillomas are characterized by fibrovascular cores lined by a dual layer of epithelial and myoepithelial cells projecting into the duct lumen. The epithelium may exhibit usual ductal hyperplasia (UDH) while myoepithelial cells confirm benignity by their presence.[35]Peripheral papillomas may show sclerosis or epithelial crowding increasing the likelihood of atypia or ductal carcinoma in situ (DCIS) in adjacent tissue. Unlike IDC, papillomas lack stromal invasion and maintain an intact myoepithelial layer.

Phyllodes Tumor (Benign Variant)

Phyllodes tumors are rare fibroepithelial neoplasms with a biphasic composition of epithelial and stromal elements. The benign variant accounting for 60–70% of cases feature mild stromal cellularity and minimal atypia distinguishing it from borderline or malignant forms. These tumors typically present as painless, rapidly growing masses in women aged 40–50. While

benign phyllodes tumors have a low recurrence rate after excision their potential for local recurrence or progression to malignancy underscores their clinical importance. Benign phyllodes tumors feature a leaf-like architecture, with epithelial-lined clefts surrounded by a mildly cellular stroma. The stroma contains spindle-shaped fibroblasts with minimal mitotic activity (<5 mitoses/10hpf) and no significant atypia. [36]The epithelial component resembles normal ducts or lobules often with mild hyperplasia. This contrasts with malignant phyllodes tumors which exhibit stromal overgrowth and pleomorphism and IDC which lacks the biphasic pattern.

Epithelial Hyperplasia of the Breast

Epithelial hyperplasia refers to the proliferation of epithelial cells within the breast ducts and lobules. It is a common benign finding but can serve as a precursor necessitating careful histopathological evaluation.[26]

Histological Classification

1. Usual Ductal Hyperplasia (UDH): Characterized by an increase in the number of epithelial cell layers within the ducts. The architecture remains organized without significant atypia. Typically lacks necrosis or calcification.[26]

2.Atypical Ductal Hyperplasia (ADH): Exhibits architectural and cytological features resembling low-grade DCIS but is limited in extent. Defined by partial involvement of ducts and/or a size ≤2 mm. Shows uniform, monotonous cells with mild-to-moderate atypia. The differentiation between ADH and low-grade DCIS can be challenging due to overlapping features. Consensus criteria often define ADH as lesions ≤2 mm or involving ≤2 duct spaces.[26]

Ductal Carcinoma In Situ (DCIS)

DCIS, a non-invasive precursor to invasive carcinoma, is confined within the ductal system without stromal invasion. It is subclassified by nuclear grade (low, intermediate, high) and architectural pattern (e.g., comedo, cribriform, micropapillary).[46] Comedo DCIS, with central necrosis and high-grade nuclei carries a higher risk of progression to invasive disease. The

WHO recognizes DCIS as a heterogeneous entity with management ranging from excision to mastectomy based on extent and risk factors.

Histopathological Assessment

Diagnosis begins with histological evaluation of tumor architecture and cellular features, typically from core biopsy or surgical specimens. The presence of invasive nests or cords without specialized patterns confirms the diagnosis with grading based on the Nottingham system (tubule formation, nuclear pleomorphism, mitotic count).[47] Special subtypes rely on defining features: tubular carcinoma demands >90% tubule formation, while mucinous carcinoma requires >50% mucin production.[44] DCIS diagnosis hinges on confinement within ducts, assessed via myoepithelial markers (eg: p63, calponin) to confirm an intact basement membrane.

Clinical Significance of Benign Breast Lesions

Diagnostic Implications

Benign breast lesions frequently mimic malignancy necessitating a triple assessment—clinical examination, imaging, and biopsy. Fibroadenomas with their rubbery consistency are often distinguishable on ultrasound as oval hypoechoic masses with smooth borders but large or complex variants may require biopsy to exclude phyllodes tumors or carcinoma.[37] Cysts are reliably diagnosed via ultrasound with aspiration reserved for symptomatic cases, complicated cysts with solid components require further investigation to rule out intracystic carcinoma. Papillomas presenting with bloody discharge raise suspicion for malignancy particularly if imaging shows an intraductal mass.

Risk of Malignancy

Most benign lesions carry no significant cancer risk but certain subtypes elevate future breast cancer risk. Complex fibroadenomas are associated with a 1.5–2-fold relative risk due to proliferative features.[33] Cysts alone are benign but their association with fibrocystic change and epithelial hyperplasia may signal risk increase if atypia is present.[34] Multiple peripheral papillomas elevate risk when linked to ADH or DCIS.[35] Benign phyllodes tumors rarely transform into malignancy though recurrence or borderline progression occurs in 10–15% of cases.[36]

WHO CLASSIFICATION OF BREAST TUMORS - 2019 [39]

The World Health Organization (WHO) classification of breast carcinoma provides a standardized, globally accepted framework for categorizing breast malignancies based on histopathological features, facilitating accurate diagnosis, treatment planning, and research. Updated periodically, with the most recent edition published in 2019 (5th edition), this system reflects advances in molecular pathology and clinical insights, refining our understanding of breast cancer diversity beyond broad entities like infiltrating ductal carcinoma (IDC). By delineating key categories and diagnostic criteria, the WHO classification bridges morphology with prognosis and therapeutic response, including the role of markers like the androgen receptor (AR).[39]

WHO CLASSIFICATION OF BREAST TUMORS:

Table 1: WHO Classification of Breast tumors 2019

EPITHELIAL TUMORS	
INVASIVE BREAST CARCINOMA	Infiltrating ductal carcinoma – NOS
	Oncocytic carcinoma
	Lipid rich carcinoma
	Glycogen rich carcinoma
	Sebaceous carcinoma
	Lobular carcinoma – NOS
	Cribriform carcinoma – NOS
	Tubular carcinoma

	Mucinous adenocarcinoma
	Mucinous cystadenocarcinoma-NOS
	Metaplastic carcinoma – NOS
	Invasive micropapillary carcinoma of breast
Rare and salivary gland like tumors	Secretory carcinoma
	Acinar cell carcinoma
	Adenoid cystic carcinoma
	Mucoepidermoid carcinoma
	Polymorphous adenocarcinoma
Neuroendocrine neoplasm	Neuroendocrine tumor, NOS
	Neuroendocrine tumor grade 1
	Neuroendocrine tumor grade 2
	Neuroendocrine carcinoma, NOS
	Neuroendocrine carcinoma, Small cell
	Neuroendocrine carcinoma, Large cell
Epithelial myoepithelial Tumors	Pleomorphic adenoma
	Adenomyoepithelioma with carcinoma
	Epithelial myoepithelial carcinoma
Ductal carcinoma in situ	Ductal carcinoma, non-infiltrating, NOS
Adenosis and benign sclerosing lesions	Sclerosing adenoma
	Apocrine adenoma
	Microglandular adenoma
	Radial scar/ complex sclerosing lesion
Papillary neoplasms	Intraductal papilloma
	DCIS, Papillary
	Encapsulated papillary carcinoma
	Encapsulated papillary carcinoma, with invasion
	Solid papillary carcinoma in situ
	Solid papillary carcinoma with invasion
Adenomas	Tubular adenoma
	Lactating adenoma
	Duct adenoma
MESENCHYMAL TUMORS	
Vascular tumors	Haemangioma, NOS
	Angiomatosis
	Atypical vascular lesions
	Angiosarcoma
	Postradiation angiosarcoma
Fibroblastic and myofibroblastic tumors	Nodular fasciitis
	Myofibroblastoma
	Desmoid like fibromatosis
	Inflammatory myofibroblastic tumor
Peripheral nerve sheath tumors	Schwanomma
	Neurofibroma
	Granular cell tumor, NOS
	Granular cell tumor, Malignant
Smooth muscle tumors	Leiomyoma, NOS
	Leiomyosarcoma,NOS
Adipocytic tumors	Lipoma
	Angiolipoma
	Liposarcoma
Fibroepithelial tumors	Fibroadenoma

	Phyllodes tumor
	Hamartoma
TUMORS OF NIPPLE	Nipple adenoma
	Syringoma
	Paget disease of nipple
MALIGNANT LYMPHOMA	Diffuse large B cell lymphoma
	Burkitts's lymphoma
	Follicular lymphoma
	Breast implant associated anaplastic large cell lymphoma
METASTATIC TUMORS	
TUMORS OF THE MALE BREAST	Gynecomastia
	Carcinoma

Key Categories of Breast Carcinoma

Invasive Carcinoma of No Special Type (NST)

Invasive carcinoma NST formerly IDC-NOS, is the most common breast cancer subtype accounting for 70–80% of invasive cases.[41] Histologically, it ranges from well-differentiated (grade 1) to poorly differentiated (grade 3) with stromal invasion beyond the basement membrane distinguishing it from DCIS. Its prognosis varies widely based on grade, receptor status and molecular profile.[42]

Invasive Lobular Carcinoma (ILC)

Invasive lobular carcinoma (ILC) comprises 5–15% of breast cancers and originates from the lobular epithelium. It is characterized by a single-file ("Indian file") pattern of discohesive cells often with signet-ring morphology due to intracytoplasmic mucin.[43] ILC frequently lacks E-cadherin expression a molecular hallmark detectable by IHC which contributes to its infiltrative growth and propensity for multifocality.

Special Subtypes

Special subtypes though less common, exhibit unique histological features with prognostic implications. Tubular carcinoma forms well-differentiated tubules with minimal atypia with an

excellent prognosis.[44] Mucinous carcinoma features tumor cells floating in extracellular mucin pools often ER-positive and slow-growing. Medullary carcinoma (<1%) displays syncytial growth, lymphoid infiltration and pushing borders paradoxically associated with favorable outcomes despite high grade.[45] Other rare entities, like metaplastic carcinoma (spindle cell or squamous differentiation) and adenoid cystic carcinoma highlight the diversity of breast malignancies.

Clinical and Research Implications

Diagnostic Precision and Treatment

The WHO system enhances diagnostic accuracy by providing clear criteria, reducing interobserver variability. For example, distinguishing NST from tubular carcinoma alters management-lumpectomy suffices for the latter, while NST may require adjuvant therapy based on stage and receptors.[50] DCIS classification guides risk stratification, with high-grade cases prompting radiation or endocrine therapy post-excision. This precision supports personalized treatment particularly in AR-positive carcinomas where targeted therapies are emerging.

ETIOLOGY AND RISK FACTORS OF BREAST CARCINOMA

Breast carcinoma including infiltrating ductal carcinoma (IDC), arises from a complex interplay of genetic predispositions and environmental influences, making its etiology multifaceted and its risk factors diverse. While the disease's histopathological and molecular features are well-documented understanding its causative elements is critical for prevention, early detection and personalized management. Genetic factors such as BRCA1 and BRCA2 mutations along with environmental and lifestyle factors amplify risk across populations.

Genetic Factors in Breast Carcinoma

BRCA1 and BRCA2 Mutations

Mutations in the BRCA1 and BRCA2 genes are the most well-established genetic risk factors for breast carcinoma, accounting for 5–10% of all cases and up to 20–25% of hereditary cases.[48] These tumor suppressor genes located on chromosomes 17q21 and 13q12 respectively encode proteins critical for DNA double-strand break repair via homologous recombination. Pathogenic variants disrupt this process leading to genomic instability and oncogenesis. Women with BRCA1 mutations face a lifetime breast cancer risk of 60–70% often presenting with triple-negative tumors while BRCA2 mutations confer a 50–60% risk typically linked to ER-positive disease.[49] The prevalence of these mutations varies by ethnicity with higher rates in Ashkenazi Jewish populations compared to the general population.[50]

Other High and Moderate Penetrance Genes

Beyond BRCA1/2, mutations in other high-penetrance genes like TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome) and CDH1 (hereditary diffuse gastric cancer syndrome) significantly elevate breast cancer risk though they are rare collectively accounting for <1% of cases.[51] TP53 mutations confer a 50–60% lifetime risk often with early-onset disease while

PTEN mutations increase risk 2–4-fold alongside benign breast lesions. Moderate-penetrance genes such as CHEK2, ATM and PALB2 contribute to 10–20% of familial cases. For instance, PALB2 mutations carry a 35–50% lifetime risk particularly when combined with family history.[52] These genes impair DNA repair or cell cycle checkpoints, synergizing with environmental triggers.

Polygenic Risk Scores

Low-penetrance genetic variants identified through genome-wide association studies (GWAS), collectively influence sporadic breast cancer risk. Over 300 single nucleotide polymorphisms (SNPs) have been linked to susceptibility each conferring a modest risk.[53] Polygenic risk scores (PRS) aggregating these variants enhance risk stratification in the general population. A high PRS can elevate risk 2–3-fold particularly in women with dense breasts or hormonal exposures, though clinical utility remains under investigation.[54]

Environmental and Lifestyle Risk Factors

Hormonal Exposures

Prolonged exposure to endogenous or exogenous estrogens is a major environmental risk factor driving epithelial proliferation in the breast. Early menarche (<12 years) and late menopause (>55 years) increase risk by 20–30% due to extended ovulatory cycles.[55] Nulliparity or late first full-term pregnancy (>35 years) elevates risk 1.5–2-fold compared to early childbirth as pregnancy-induced differentiation of breast tissue confers a protective effect.[56] Exogenous hormones such as combined oral contraceptives and postmenopausal hormone replacement therapy (HRT) increase risk.[57]

Reproductive and Lifestyle Factors

Breastfeeding reduces breast cancer risk by 4% per year of lactation likely due to reduced ovulatory cycles and terminal differentiation of lobular epithelium.[58] Obesity, particularly postmenopausal increases risk 1.5–2-fold via increased peripheral aromatization of androgens to estrogens in adipose tissue a mechanism less pronounced in premenopausal women where obesity may be protective.[59] Alcohol consumption is a consistent risk factor with each 10 g/day raising risk by 7–10% possibly through acetaldehyde-induced DNA damage and elevated estrogen levels.[60] Physical inactivity independently increases risk by 10–20% with exercise reducing circulating hormones and inflammation.

Environmental Carcinogens

Ionizing radiation especially during breast development is a potent risk factor. Survivors of Hodgkin lymphoma treated with chest radiotherapy face a 3–7-fold increased risk with latency of 10–20 years.[48] Occupational or environmental exposure to endocrine-disrupting chemicals such as bisphenol A (BPA) and phthalates is implicated in preclinical studies for mimicking estrogen though human evidence remains inconclusive due to measurement challenges.[55]

Night shift work, disrupting circadian rhythms and melatonin production increases risk by 10–20% in long-term workers with stronger associations in premenopausal women.[56]

Gene-Environment Interactions

Genetic predisposition amplifies environmental risks. BRCA1/2 mutation carriers exposed to radiation or hormonal factors exhibit earlier disease onset with studies suggesting a synergistic effect.[50] CHEK2 mutations enhance susceptibility to estrogen-driven carcinogenesis, doubling risk in HRT users compared to non-users.[52]

Epigenetic Modifications

Environmental factors influence breast cancer etiology via epigenetic changes such as DNA methylation and histone modification. Obesity and alcohol upregulate aromatase expression through promoter hypomethylation increasing local estrogen production.[59]

Clinical and Preventive Implications

Risk Assessment and Screening

Identifying genetic and environmental risk factors informs personalized screening. BRCA1/2 carriers benefit from annual MRI and mammography starting at age 25–30 while moderate-risk gene carriers may begin at 40.[51] Women with strong lifestyle risks (e.g.: HRT use, obesity) counselling and earlier screening.

Prevention Strategies

Genetic counselling and prophylactic measures (e.g.: mastectomy and salpingo-oophorectomy) reduce risk by 90% in BRCA1/2 carriers.[48] Lifestyle modifications-weight loss, alcohol reduction and exercise-lower risk by 20–30% in the general population.[60] Chemoprevention with selective estrogen receptor modulators (e.g.: tamoxifen) halves risk in high-risk women though uptake remains low due to side effects.[57]

INFILTRATING DUCTAL CARCINOMA (IDC)

Infiltrating ductal carcinoma (IDC) also termed invasive carcinoma of no special type (NST) in the WHO classification represents the most prevalent form of breast cancer characterized by its ability to invade beyond the ductal epithelium into surrounding stroma.

Definition

IDC is defined as an invasive breast carcinoma originating from the ductal epithelium that lacks the specific histological features of special subtypes. It is characterized by malignant epithelial cells breaching the basement membrane infiltrating the breast stroma and potentially metastasizing to regional lymph nodes or distant sites.[58]

Epidemiology

IDC accounts for 70–80% of all invasive breast cancers making it the leading subtype globally.[59] Its incidence varies by region with age-standardized rates highest in North America and Western Europe (80–100 per 100,000 women) and lower in Africa and Asia (20–40 per 100,000),though rates are rising in developing nations due to lifestyle shifts.[60] The median age at diagnosis is approximately 60 years with a bimodal distribution showing peaks in premenopausal and postmenopausal women. Racial disparities are notable: African American women present with more aggressive IDC and at younger ages compared to Caucasian women.[61]

Histopathological Features

Tumor Architecture

Histologically, IDC exhibits a heterogeneous growth pattern ranging from well-formed tubular or glandular structures to solid sheets of cells. The hallmark is stromal invasion with irregular nests or cords of malignant cells disrupting the normal breast architecture.[62] The degree of

tubule formation varies influencing grading: well-differentiated tumors show >75% tubular structures while poorly differentiated ones display <10%.

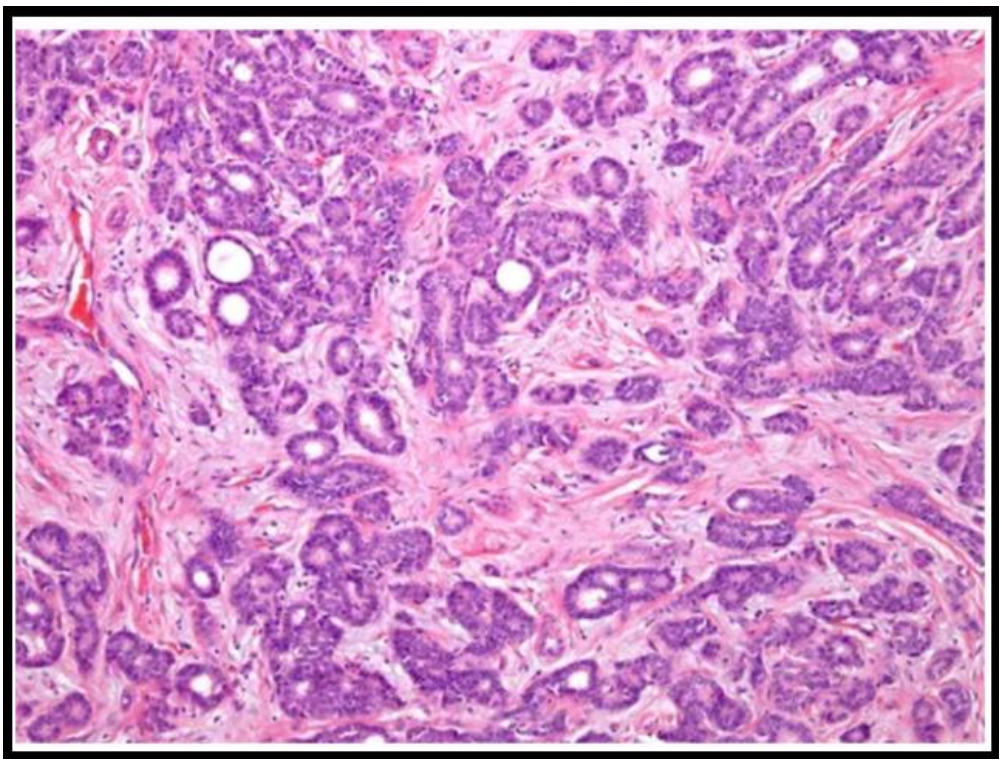

FIGURE 5: MICROSCOPY 4X:INFILTRATING DUCTAL CARCINOMA - Tumor cells arranged predominantly in tubules

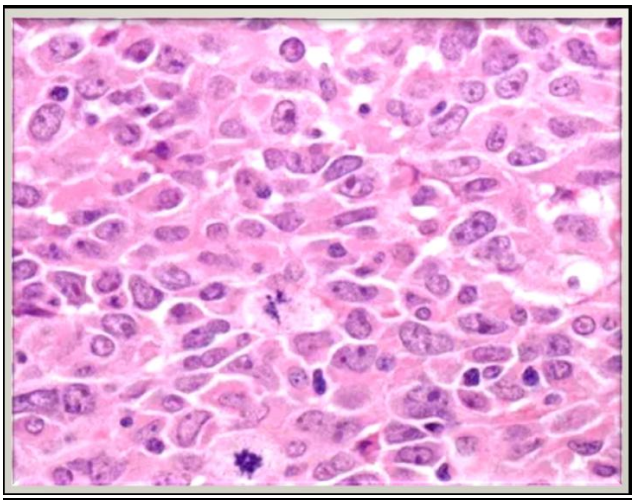

FIGURE 6: MICROSCOPY 40X: INFILRATING DUCTAL CARCINOMA – High grade nuclei with mitotic figure.

Cellular Characteristics

IDC cells typically show nuclear pleomorphism with enlarged, irregular nuclei and prominent nucleoli. Mitotic figures are frequent in high-grade tumors reflecting rapid proliferation. The presence of necrosis or microcalcifications detectable on mammography is variable but more common in aggressive subtypes.[63] Immunohistochemistry reveals a spectrum of receptor expression: 60–70% of IDC cases are ER-positive, 50–60% PR-positive, and 15–20% HER2-positive with 10–15% triple-negative.[64] AR expression though less routinely assessed occurs in 60–80% of cases often coexisting with ER positivity.

Microenvironment

The tumor microenvironment in IDC includes infiltrating lymphocytes, fibroblasts and adipocytes which modulate progression. Tumor-infiltrating lymphocytes (TILs) are prominent in triple-negative and HER2-positive IDC correlating with immune response and prognosis.[65] Lymphovascular invasion identified histologically signals metastatic potential and is present in 20–30% of cases at diagnosis.

Diagnostic Approach

Diagnosis relies on the triple assessment: clinical examination, imaging and biopsy. Mammography reveals IDC as a spiculated mass or asymmetric density, often with microcalcifications, while ultrasound shows a hypoechoic, irregular lesion with posterior shadowing.[66] Core needle biopsy guided by imaging provides histological confirmation with IHC for ER, PR, HER2 and Ki-67 informing subtype and grade. Fine-needle aspiration cytology may assess lymph nodes.[68]

Grading and Prognostic Implications

Histological Grading

IDC is graded using the Nottingham Histological Grade (NHG) a modification of the Scarff-Bloom-Richardson system based on three parameters: tubule formation, nuclear pleomorphism, and mitotic count.[62]

Nottingham–Bloom–Richardson (NBR) histologic grading system

I. Tubule formation as an expression of glandular differentiation

- Score 1: tubular formation of more than 75% of the tumor
- Score 2: tubular formation 10 to 75% of the tumor
- Score 3: tubular formation of less than 10% of the tumor

II. Nuclear pleomorphism

- Score 1: nuclei with minimal or mild variation in size and shape
- Score 2: nuclei with moderate variation in size and shape
- Score 3: nuclei with marked variation in size and shape

III. Mitotic counts

- Score 1: 0-9 /10HPF
- Score 2: 10-19/ 10HPF
- Score 3: >20 /10HPF

Grade 1 – Well differentiated: 3-5 points.

Grade 2 – Moderately differentiated: 6-7 points.

Grade 3 – Poorly differentiated: 8-9 points.

Prognostic Implications

Grade strongly predicts outcome: 10-year survival exceeds 90% for grade 1 IDC but drops to 50–60% for grade 3.[65] Receptor status refines prognosis: ER/PR-positive tumors respond to endocrine therapy improving survival while HER2-positive cases benefit from targeted agents like trastuzumab. Triple-negative IDC often grade 3 carries a poorer prognosis with 5-year survival of 60–70% due to limited therapeutic options.[69] Lymph node status is an important prognostic factor, node-negative patients have a 5-year survival of 85–90% whereas 60–70% with nodal involvement. AR expression prevalent in luminal subtypes may confer a favorable prognosis though its role in triple-negative IDC remains under investigation.[70]

Tumor size (>2 cm), lymphovascular invasion and high Ki-67 (>20%) worsen prognosis while TIL-rich tumors may predict better response to immunotherapy particularly in aggressive subtypes.[65]

OTHER MALIGNANT BREAST LESIONS

Infiltrating Lobular Carcinoma (ILC)

Infiltrating lobular carcinoma (ILC) is the second most common invasive breast cancer, comprising 5–15% of cases.[68] Originating from the lobular epithelium, ILC often presents as a subtle, ill-defined mass or diffuse thickening rather than a discrete lump reflecting its infiltrative growth pattern. It has a higher propensity for bilaterality (10–20%) and multifocality compared to IDC with metastases favoring unusual sites like the gastrointestinal tract, peritoneum and ovaries.[69] ILC is typically hormone receptor-positive (ER/PR >90%) with HER2 overexpression rare (<5%) influencing its therapeutic approach. ILC's hallmark is its discohesive single-file growth pattern often described as "Indian file" due to loss of E-cadherin, a cell adhesion protein detectable by immunohistochemistry.[68] Histologically small, uniform cells with minimal tubule formation and frequent signet-ring cells containing intracytoplasmic mucin.

Medullary Carcinoma

Medullary carcinoma is a rare subtype, accounting for less than 1% of breast cancers, often occurring in younger women.[70] Despite its high-grade histology, it carries a paradoxically favorable prognosis. It is strongly associated with triple-negative status and BRCA1 mutations aligning it with basal-like molecular profiles. It has syncytial growth pattern of large,

pleomorphic cells with indistinct borders with dense lymphocytic infiltrate and pushing margins.[70] IHC typically shows negativity for ER, PR and HER2 with high Ki-67 (>50%) .

Mucinous Carcinoma

Mucinous carcinoma, representing 2–5% of invasive breast cancers is characterized by abundant extracellular mucin production. It typically affects older women and presents as a slow-growing, palpable mass with a gelatinous consistency.[71] Pure mucinous carcinoma where >90% of the tumor is mucin is less aggressive than mixed forms with ductal elements. It is usually ER-positive and HER2-negative contributing to its favorable prognosis compared to IDC. It has extracellular mucin pools, within which clusters of tumor cells "float" comprising >50% of the tumor volume in pure forms with low to intermediate nuclear grade, minimal mitotic activity.[71] Its ER positivity (80–90%) and low HER2 expression align it with luminal subtypes.

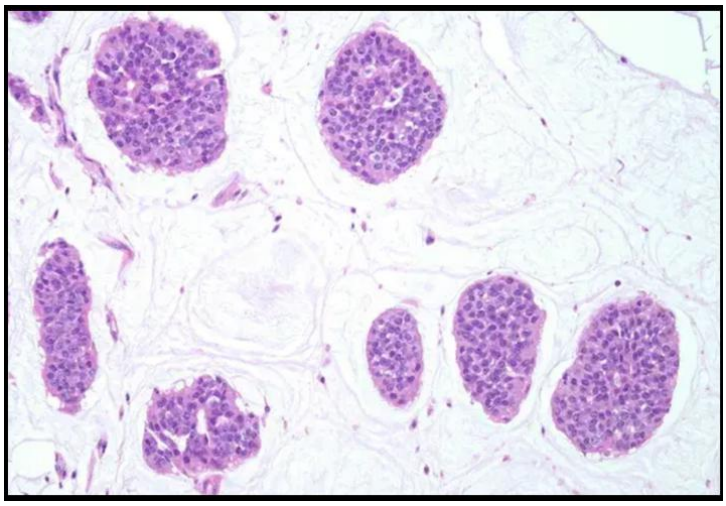

FIGURE 7: 10X: MICROSCOPIC IMAGE OF MUCINOUS CARCINOMA OF BREAST

MOLECULAR CLASSIFICATION OF BREAST CARCINOMA

The molecular classification derived from gene expression profiling identifies four primary subtypes with distinct biological and clinical profiles.[73] Luminal A comprising 40–50% of cases is characterized by high estrogen receptor (ER) and progesterone receptor (PR) expression, low proliferation (Ki-67 <14%) and a favourable prognosis. Luminal B (20–30%) also expresses ER/PR but exhibits higher Ki-67 (>14%) or HER2 positivity indicating greater aggressiveness. HER2-enriched tumors (10–15%) lack ER/PR expression but overexpress HER2 driving rapid growth and requiring targeted therapy. Triple-negative breast cancer (10–20%) is absence of ER, PR and HER2 often aligning with basal-like features and poor outcomes.[74]

Molecular Markers and Their Significance

Key markers define these subtypes and guide management. ER and PR assessed by immunohistochemistry (IHC) predict endocrine therapy response in luminal subtypes, with Luminal A showing superior sensitivity due to lower proliferation.[73] HER2 overexpression, confirmed by IHC or fluorescence in situ hybridization (FISH), identifies candidates for trastuzumab in HER2-enriched and some Luminal B cases improving survival.[75] Ki-67 distinguishes Luminal A from B. TNBC lacks these targets but often expresses basal markers linking it to BRCA1 mutations and chemotherapy sensitivity.[74] AR expressed in 60–80% of breast cancers is emerging as a modulator particularly in Luminal A and TNBC with potential prognostic and therapeutic implications.[76]

Table 2: Molecular Classification of Breast Carcinoma

Subtype	Prevalence	Key Molecular Markers	Characteristics	Therapeutic Implications	Prognosis
Luminal A	40–50%	ER+, PR+, HER2-, Ki-67 <14%	High hormone receptor expression, low proliferation	Endocrine therapy	Favorable
Luminal B	20–30%	ER+, PR+/-, HER2+/-, Ki-67 >14%	Hormone receptor-positive, higher proliferation or HER2+	Endocrine therapy ± chemotherapy ± HER2-targeted therapy	Intermediate
HER2-enriched	10–15%	ER-, PR-, HER2+	HER2 overexpression, rapid growth	HER2-targeted therapy (e.g., trastuzumab) + chemotherapy	Intermediate to poor
Triple-negative	10–20%	ER-, PR-, HER2-, often basal markers (CK5/6, EGFR)	Lacks standard receptors, aggressive	Chemotherapy, emerging immunotherapy	Poor

TNM STAGING OF BREAST CARCINOMA

The TNM system maintained by the American Joint Committee on Cancer (AJCC) stages breast cancer based on primary tumor size (T), regional lymph node involvement (N) and distant metastasis (M). The 8th edition (2017) integrates prognostic factors like grade and receptor status, refining traditional anatomic staging.[77]

TNM Staging

TNM staging directs surgical and adjuvant decisions. Early-stage (I–II) tumors favour breast-conserving surgery, while Stage III (locally advanced) may require neoadjuvant therapy to downstage disease.[77] Stage IV mandates systemic approaches with palliative therapy.

Table 3: TNM Staging of Breast Carcinoma

Component	Category	Description
Tumor (T)	T0	No evidence of primary tumor
	T1	Tumor ≤2 cm (T1a: ≤0.5 cm, T1b: 0.5–1 cm, T1c: 1–2 cm)
	T2	Tumor 2–5 cm
	T3	Tumor >5 cm
	T4	Tumor with direct extension to skin/chest wall (e.g.: ulceration, satellites)
Node (N)	N0	No regional lymph node involvement
	N1	Metastasis to movable ipsilateral axillary nodes
	N2	Metastasis to fixed/matted axillary nodes or internal mammary nodes
	N3	Metastasis to supraclavicular, infraclavicular or multiple nodal regions
Metastasis (M)	M0	No distant metastasis
	M1	Distant metastasis (e.g.: lung, liver, bone)

ANDROGEN RECEPTOR IN BREAST CARCINOMA

The androgen receptor (AR) has emerged as a pivotal player in breast carcinoma including infiltrating ductal carcinoma (IDC) extending beyond its traditional role in prostate cancer. Expressed in 60–80% of breast tumors AR's influence spans tumor biology, prognosis and potential therapeutic targeting. Understanding AR's structure, signalling mechanisms and detection methods is critical for understand its role in breast cancer dynamics especially its interplay with other pathways like the estrogen receptor (ER).

STRUCTURE OF THE ANDROGEN RECEPTOR (AR)

The AR, a member of the nuclear receptor superfamily is a 110-kDa protein encoded by the AR gene on chromosome Xq11-12.[78] It comprises four functional domains: the N-terminal domain (NTD), DNA-binding domain (DBD), hinge region and ligand-binding domain (LBD). The NTD, highly variable and unstructured contains activation function 1 (AF-1), driving transcriptional activity independent of ligand binding. The DBD with two zinc fingers, binds androgen response elements (AREs) in DNA while the hinge region facilitates nuclear localization. The LBD, at the C-terminus, binds androgens (eg: testosterone, dihydrotestosterone) and houses activation function 2 (AF-2), which recruits coactivators upon ligand binding.[79] Alternative splice variants such as AR-V7 lack the LBD rendering them constitutively active and relevant in resistant tumors.[80]

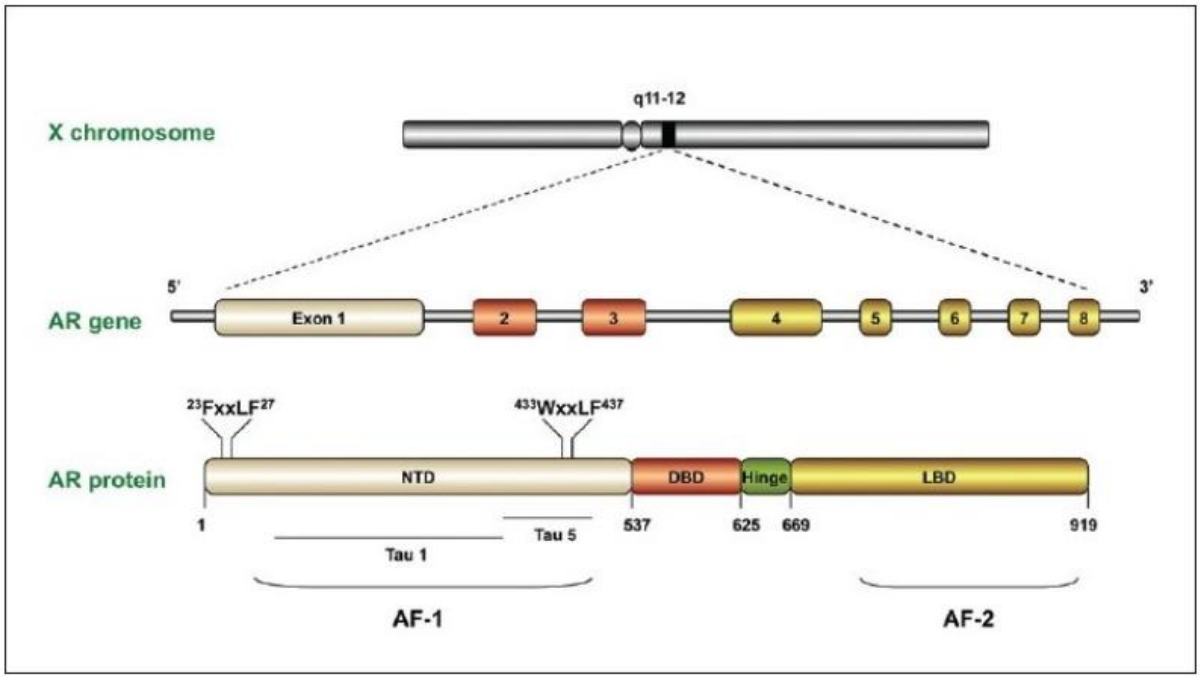

FIGURE 8: Schematic representation of the androgen receptor gene and protein, with indications of its specific motifs and domains[38]

AR regulates gene expression by translocating to the nucleus upon androgen binding, dimerizing and interacting with AREs to modulate transcription of genes involved in cell proliferation, apoptosis, and differentiation.[78] In non-malignant breast tissue, AR maintains epithelial homeostasis, counteracting estrogen-driven proliferation. Its ligand-dependent and -independent activities mediated by AF-1 and AF-2 allow flexibility in cellular responses while post-translational modifications fine-tune its function.[81]

MECHANISM OF AR IN BREAST CARCINOMA

In ER-positive tumors (e.g.: Luminal A/B) AR often acts as a tumor suppressor, inhibiting ER-driven proliferation by competing for coactivators or binding sites.[82] Conversely, in ER-negative tumors like TNBC, AR can drive oncogenesis, activating genes like PI3K and MYC that promote cell survival and growth.[83] This dichotomy reflects AR's context-specific effects, modulated by ligand availability and co-regulator expression. In IDC, AR positivity is reported in 60–80% of cases, with higher rates in well-differentiated tumors.[84]

AR's impact on tumor growth varies: in ER-positive IDC, high AR expression correlates with smaller tumors, lower grade and reduced metastasis suggesting an inhibitory role.[84] In TNBC, AR-positive tumor exhibit slower proliferation but greater invasiveness driven by epithelial-to-mesenchymal transition (EMT) genes like ZEB1.[87] AR also modulates chemotherapy response with AR-positive TNBC showing resistance to anthracyclines but sensitivity to AR inhibitors like enzalutamide in clinical trials.[88]

METHODS OF IDENTIFYING AR EXPRESSION

Polymerase Chain Reaction (PCR) for AR mRNA

Quantitative real-time PCR (qRT-PCR) detects AR mRNA levels in breast tumor samples, offering high sensitivity and specificity. Fresh-frozen or formalin-fixed paraffin-embedded (FFPE) tissues are processed to extract RNA reverse-transcribed and amplified using AR-specific primers.[89] This method quantifies total AR expression including splice variants and correlates with protein levels in 70–80% of cases. Its advantages include detecting low-abundance transcripts and assessing AR isoforms, though it requires specialized equipment and cannot localize expression within tumor architecture.[90]

Immunohistochemistry (IHC) for AR Protein

IHC is the gold standard for assessing AR protein expression in clinical practice using monoclonal antibodies on FFPE sections. Nuclear staining indicates active AR scored as percentage of positive cells and intensity.[91] IHC is widely available, cost-effective and preserves tissue context revealing heterogeneity. Limitations include antibody variability and inability to distinguish functional isoforms, though it remains the primary method for AR assessment in breast cancer.[92]

IHC SCORING OF AR

Scoring Systems for AR Expression

Two main systems quantify AR by IHC: the Allred score and H-score. The Allred score combines proportion (0–5 scale: 0% to >66% positive cells) and intensity (0–3: none to strong), yielding a 0–8 total, with >2 considered positive.[93] The H-score multiplies percentage of positive cells (0–100) by intensity (1–3), ranging from 0–300, with cutoffs (e.g., >10) varying by study.[94] Both systems assess nuclear AR, reflecting active signalling and are adapted from ER/PR scoring due to their nuclear receptor similarity.

Interpretation

SCORING FOR ANDROGEN RECEPTORS:

1. **Allred Scoring System**

Table 4: Allred scoring system

Component	Score	Description
Proportion Score (PS)	0	No cells are positive
	1	<1% of cells are positive
	2	1–10% of cells are positive
	3	11–33% of cells are positive
	4	34–66% of cells are positive
	5	67–100% of cells are positive
Intensity Score (IS)	0	No staining
	1	Weak staining
	2	Moderate staining

Component	Score	Description
	3	Strong staining
Total Score (TS)	0–8	PS + IS; a score ≥3 is considered positive

2. **H score:** Ten fields were chosen at random at 40X magnification and the staining intensity in the malignant cell nuclei was scored as 0, 1, 2, or 3 corresponding to the presence of no stain, weak, moderate, and strong brown staining, respectively.[40]

- Score of 0 to 300 from multiplying proportion as percentage (0 - 100) and intensity (0 - 3) of ER positive tumor cells
- H-Score = % of tumor cells with weak staining x 1 + % of tumor cells with moderate staining x 2 + % of tumor cells with strong staining x 3
- Interpretation:

  0–50: Negative

  51- 100: low expression

  101–200: Moderate expression

  201–300: High expression

3. Immuno-histochemical scoring of AR expression was evaluated according to the percentage of tumor cells showing nuclear positivity.

Percentage of AR positive tumor cells	Scoring for AR	Inference
<10%	0	Negative
>10%	1+	Positive

RECENT ADVANCES AND CONTROVERSIES IN AR RESEARCH

Emerging Studies on AR in Breast Cancer

Recent investigations have expanded our understanding of AR's role across breast cancer subtypes. In TNBC single-cell RNA sequencing has identified AR-positive subsets with distinct transcriptomic profiles suggesting a luminal androgen receptor (LAR) phenotype responsive to AR inhibition.[93] Studies in ER-positive tumors have used CRISPR-based models to demonstrate AR's suppression of epithelial-to-mesenchymal transition (EMT), reinforcing its protective role in luminal subtypes.[94] Advances in proteomics have also revealed AR's interaction with novel co-regulators (e.g., GATA3) in IDC potentially modulating chemotherapy sensitivity.[95] These findings highlight AR's subtype-specific functions driving interest in its clinical utility.

Conflicting Findings on AR as a Prognostic Marker

AR's prognostic value remains contentious. In ER-positive IDC, high AR expression is consistently linked to improved disease-free survival, attributed to its antagonism of ER signalling.[96] However, in TNBC results diverge, some cohorts show AR positivity correlating with lower recurrence rates and better overall survival while others report increased metastasis and resistance to standard therapies.[97] A 2022 meta-analysis of 19 studies found AR's prognostic impact varies by detection method and cutoff with IHC positivity (>10%) predicting better outcomes in luminal tumors but worse in TNBC.[98]

Current Debates in the Field

Researchers debate whether AR acts primarily as an oncogene in TNBC versus a tumor suppressor in ER-positive disease with preclinical data suggesting context dependent co-factor

recruitment as a determinant.[94] Another contentious issue is the optimal AR expression threshold for prognostication, with proposals ranging from 1% to 75% positivity lacking consensus.[99]

THERAPEUTIC APPROACHES TARGETING AR

Key Drugs Targeting AR

AR-targeted therapies, repurposed from prostate cancer, are gaining traction in breast cancer. Enzalutamide, a second-generation AR antagonist, blocks ligand binding and nuclear translocation, showing promise in AR-positive TNBC.[100] Bicalutamide, a first-generation nonsteroidal anti-androgen, inhibits AR by competitive binding, with efficacy explored in ER-positive and TNBC settings. Abiraterone, a CYP17A1 inhibitor, reduces androgen synthesis, offering an alternative approach in AR-driven tumors.[101] These agents target AR's ligand-dependent activity, with ongoing research into inhibitors of ligand-independent variants.

Clinical Trials and Outcomes

Clinical trials have yielded mixed but encouraging results. The phase II TBCRC032 trial (NCT01889238) tested enzalutamide in AR-positive TNBC (IHC >10%) reporting a clinical benefit rate of 25% at 16 weeks with progression-free survival (PFS) of 2.9 months particularly in LAR subtypes.[100] A phase II study of bicalutamide in AR-positive, ER/PR-negative metastatic breast cancer (NCT00468715) showed a CBR of 19% and median PFS of 12 weeks, suggesting modest activity.[102] Combining enzalutamide with exemestane in ER-positive advanced disease (NCT02007512) improved PFS (4.6 vs. 3.7 months) versus exemestane alone hinting at synergy in luminal tumors. Abiraterone plus prednisone in AR-positive TNBC (NCT01842321) achieved a CBR of 20%, though responses were limited by AR heterogeneity. Challenges include variable AR expression, resistance via AR variants and small sample sizes, necessitating larger phase III trials to confirm efficacy.[101]

MATERIALS AND METHODS

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Study Design

A laboratory-based cross-sectional study was conducted to evaluate the expression of androgen receptor in infiltrating ductal carcinoma of breast and its association with prognostic factors.

Source of Data

The study utilized both prospective and retrospective data. Prospective cases included all mastectomy specimens received in the Department of Pathology from April 2023 to October 2024. Retrospective cases comprised blocks, slides, and patient demographic details retrieved from the archives of the Department of Pathology from April 2019 to March 2023 after anonymizing the samples.

Study Duration

The study was conducted over a period of 18 months from April 2023 to October 2024.

Inclusion and Exclusion Criteria

The study included all cases of Infiltrating Ductal Carcinoma (Not otherwise specified).

The following cases were excluded from the study:

- Male breast carcinoma
- Samples received after post-chemotherapy and post-radiotherapy
- Trucut Biopsy specimens

Sample Size Calculation

The sample size was calculated using the formula:

Sample size = $Z1-\alpha2 \times p \times (1-p) / d2$

Where:

- $Z1-\alpha2$ = Standard normal variant
- p = Expected proportion in population based on previous studies
- d = Absolute error of 10%

Based on the study by Vellaisamy G et al.[67], who observed nuclear staining of 10%, and considering an absolute error of 10% with 95% confidence interval, the estimated sample size for the cross-sectional study was determined to be 96 cases.

Method of Collection

Prospective Cases

All mastectomy specimens received in the Department of Pathology were grossed as per standard protocol. Appropriate sections were taken, processed, embedded, and cut according to the Standard Operating Procedures (SOPs). Data regarding the clinical details (Age, Gender, and Stage of disease) were collected.

Retrospective Cases

Patient demographic details, information regarding tumor size, and number of lymph nodes were collected from the files. Blocks and slides were retrieved from the archives of the department and recut.

Histopathological Examination

For both prospective and retrospective cases, all the Hematoxylin and Eosin (H&E) stained slides were reviewed for histological type, grade, mitotic activity, tubule formation, tumor-infiltrating lymphocytes, lymphovascular invasion, lymph node metastasis, and extranodal spread. Following thorough examination, appropriate sections were chosen for immunohistochemical analysis.

Immunohistochemistry Protocol

Materials

The immunohistochemistry was performed using Primary Antibody from M/s Biocare Medicals, USA, Secondary detection kit MACH 1 from Biocare Medicals, USA, Decloaking Chamber from Biocare Medicals for Antigen Retrieval, and Wash Buffer (in-house preparation, pH 7.4).

Specimen Preparation

Formalin-fixed paraffin-embedded tissue blocks were sectioned at 3-4 µm thickness and mounted on positively charged slides. The slides were kept in a hot air oven at 60°C overnight.

Deparaffinization and Rehydration

The sections were deparaffinized and rehydrated following a sequential process. The slides were placed in Xylene for two 10-minute washes, followed by decreasing concentrations of ethanol (100% for two 3-minute washes, then 95% and 70% for 3 minutes each), and finally in distilled water for 5 minutes. The slides were kept in distilled water, ensuring they did not dry at any point during the subsequent steps.

Antigen Retrieval

Antigen retrieval was performed using EDTA Solution with pH 8.0:

- The slides were placed in the antigen retrieval solution container
- The container was placed in the Decloaking chamber
- The program was set for 110°C for 30 minutes
- After antigen retrieval, the slides were cooled in distilled water
- The slides were then kept in buffer solution for 5 minutes

Immunohistochemical Staining

Immunohistochemical staining was performed using the Autostainer Intelipath from Biocare according to the following procedure:

1. Peroxide Block – 5 minutes, followed by buffer rinse
2. Sniper Protein Block – 10 minutes, followed by buffer rinse
3. Primary Antibody – 60 minutes, followed by buffer rinse
4. MACH 1 Mouse Probe – 15 minutes, followed by buffer rinse
5. MACH 1 HRP Polymer – 30 minutes, followed by buffer rinse
6. Betazoid DAB Chromogen – 5 minutes, followed by buffer rinse
7. CAT Hematoxylin Counterstain – 1 minute, followed by distilled water rinse

DAB Recipe: 1 ml Buffer and 1 drop chromogen CAT Hematoxylin Recipe: 5 drops distilled water and 1 drop Hematoxylin

Controls

Positive and negative controls were run simultaneously for each batch of immunohistochemical staining. Prostate tissue was used as a positive control for androgen receptor.

Interpretation of Immunohistochemistry

- Grading of ER/PR immunohistochemistry was done according to the Allred Scoring System
- Grading of Her2 immunohistochemistry was done according to the ASCO/CAP Scoring System
- Grading of Ki67 immunohistochemistry was done according to molecular classification
- For AR immunohistochemistry,

    1. Tumors with >10% nuclear staining of neoplastic cells were considered positive (Group II), while those with ≤10% were considered negative (Group I).
    2. Allred scoring system
    3. H-Scoring system

Data Collection

A detailed proforma was used to collect patient data including:

- Demographic information (age, gender)
- Clinical details (chief complaints, history of present illness, past history, family history, menstrual history)
- Clinical diagnosis with TNM staging
- Type of surgery
- Tumor location and side (right/left)
- Gross features (specimen size, skin status, tumor measurements, axillary dissection, lymph node count, nipple/areola involvement, skin involvement, skeletal muscle invasion)
- Microscopic features (tubule formation, mitosis, grade, tumor-infiltrating lymphocytes, lymphovascular invasion, pathologic staging)
- Histological and molecular type
- Modified Bloom-Richardson Grading
- TNM staging

- Immunohistochemical scoring for ER, PR, Her2 neu, Ki67, and Androgen Receptor

Statistical Analysis

Data were entered into Microsoft Excel spreadsheets and analyzed using SPSS version 22 software. Qualitative data variables were expressed by frequency or percentages, while quantitative data variables were represented by mean and standard deviation. Chi-square test was used as a test of significance for categorical variables and independent t-test was used to identify the mean difference between groups. A p-value <0.05 was considered statistically significant.

RESULTS

RESULTS

A total of 96 samples were studied. The median age of participants was 53 years (range:28-82 years).

Table 5. Distribution of patients based on the TNM staging

Cancer staging	No.samples	Percentage
IA	5	5.21%
IIA	37	38.54%
IIB	22	22.92%
IIIA	12	12.50%
IIIB	9	9.38%
IIIC	10	10.42%
IV	1	1.04%
Grand Total	**96**	**100.00%**

In the studied samples, Stage IIA was the most common accounting for 37 samples (38.54%), followed by Stage IIB with 22 samples (22.92%), Stage IIIA had 12 samples (12.50%), Stage IIIC had 10 samples (10.42%), Stage IIIB had 9 samples (9.38%), and Stage IA had 5 samples (5.21%). Stage IV was the least common, with only 1 sample (1.04%). This distribution indicates that most cases (61.46%) were diagnosed at Stage II suggesting relatively early detection in the majority of cases.

Table 6. Distribution of patients based on the Tumor Grading

Grade	No.samples	Percentage
1	51	53.13%
2	29	30.21%
3	16	16.67%
Grand Total	**96**	**100.00%**

Regarding tumor grade, Grade 1 (well-differentiated) was most common with 51 samples (53.13%), followed by Grade 2 (moderately differentiated) with 29 samples (30.21%) and Grade 3 (poorly differentiated) with 16 samples (16.67%). The predominance of Grade 1 tumors suggests that over half of the cases had a potentially better prognosis based on differentiation status.

Table 7. Lymphovascular invasion

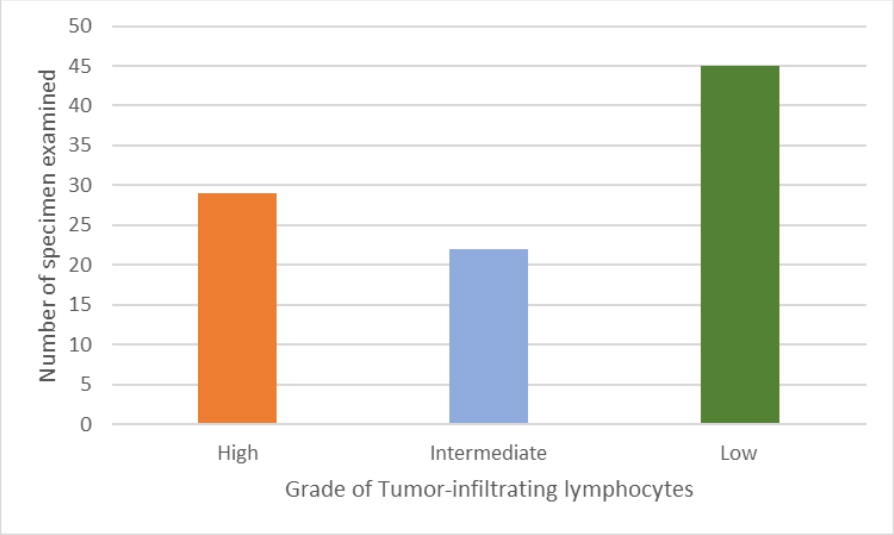
Lymphovascular invasion	No.samples	Percentage
Absent	38	39.58%
Present	58	60.42%
Grand Total	**96**	**100.00%**

Lymphovascular invasion was present in 58 samples (60.42%) and absent in 38 samples (39.58%). This indicates that a majority of tumors had already infiltrated blood or lymphatic vessels which is typically associated with a higher risk of metastasis.

Table 8. Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes	No.samples	Percentage
High	29	30.21%
Intermediate	22	22.92%
Low	45	46.88%
Grand Total	**96**	**100.00%**

Graph 1: Distribution of patients based on Tumor infiltrating lymphocytes



The distribution of tumor-infiltrating lymphocytes showed that 45 samples (46.88%) had low TILs, 22 samples (22.92%) had intermediate TILs and 29 samples (30.21%) had high TILs.

This suggests that nearly half of the cases had minimal immune response within the tumor microenvironment.

Table 9. Distribution of patients based on the ER status

Estrogen Receptor	No.samples	Percentage
Negative	41	42.71%
Positive	55	57.29%
Grand Total	**96**	**100.00%**

Graph 2: Distribution of patients based on the ER status

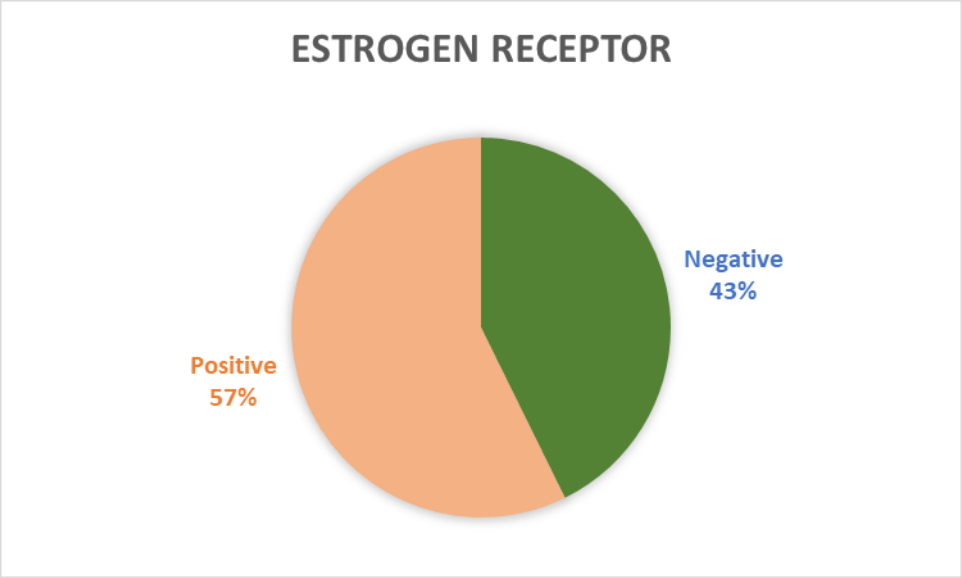
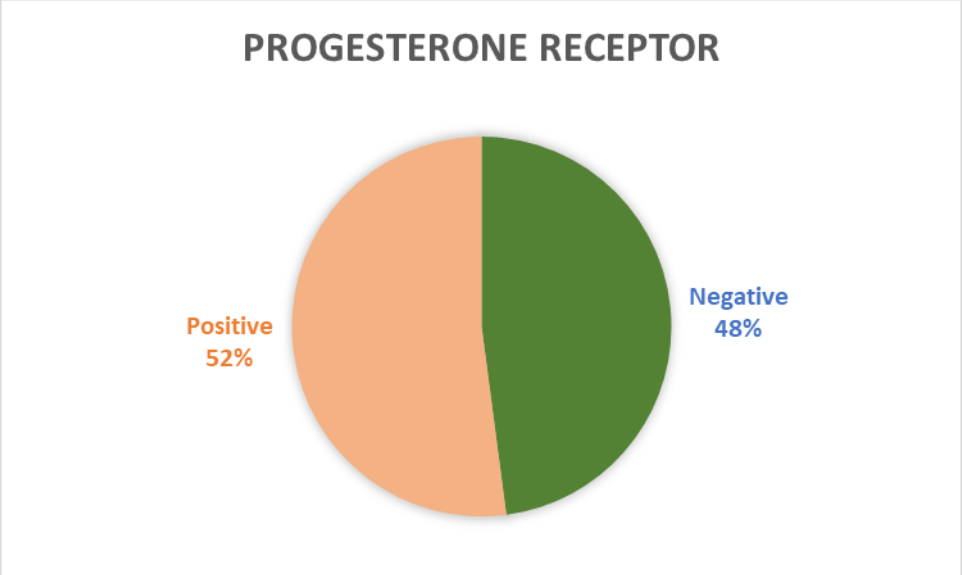


Table 10. Distribution of patients based on the PR status

Progesterone Receptor	No.samples	Percentage
Negative	46	47.92%
Positive	50	52.08%
Grand Total	**96**	**100.00%**

Graph 3: Distribution of patients based on the PR status

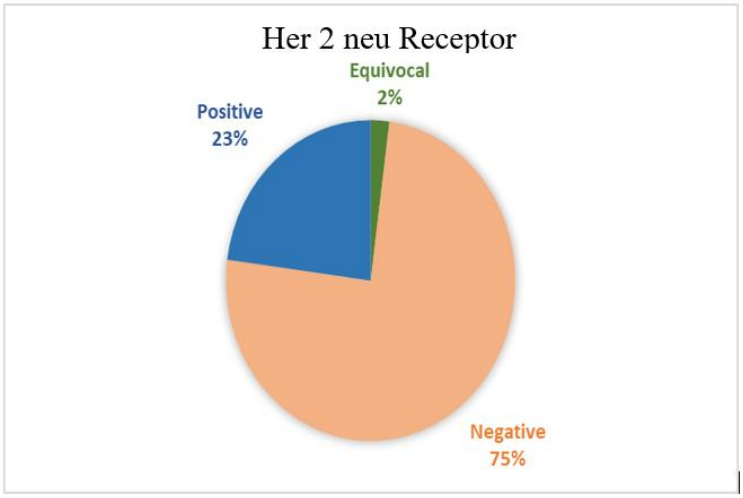


For Estrogen Receptor (ER), 55 samples (57.29%) were positive and 41 samples (42.71%) were negative. For Progesterone Receptor (PR), 50 samples (52.08%) were positive and 46 samples (47.92%) were negative. This distribution suggests that slightly more than half of the cases were hormone receptor-positive which implies potential responsiveness to hormone therapy.

Table 11. Distribution of patients based on the Her 2 neu status

HER2-neuReceptor	No.samples	Percentage
Equivocal	2	2.08%
Negative	72	75.00%
Positive	22	22.92%
Grand Total	**96**	**100.00%**

Graph 4: Distribution of patients based on the Her 2 neu status



The HER2-neu receptor was negative in 72 samples (75.00%), positive in 22 samples (22.92%), and equivocal in 2 samples (2.08%). The predominance of HER2-negative cases indicates that the majority of tumors would not respond to HER2-targeted therapies.

Table 12: Distribution of patients based on the Ki67 status

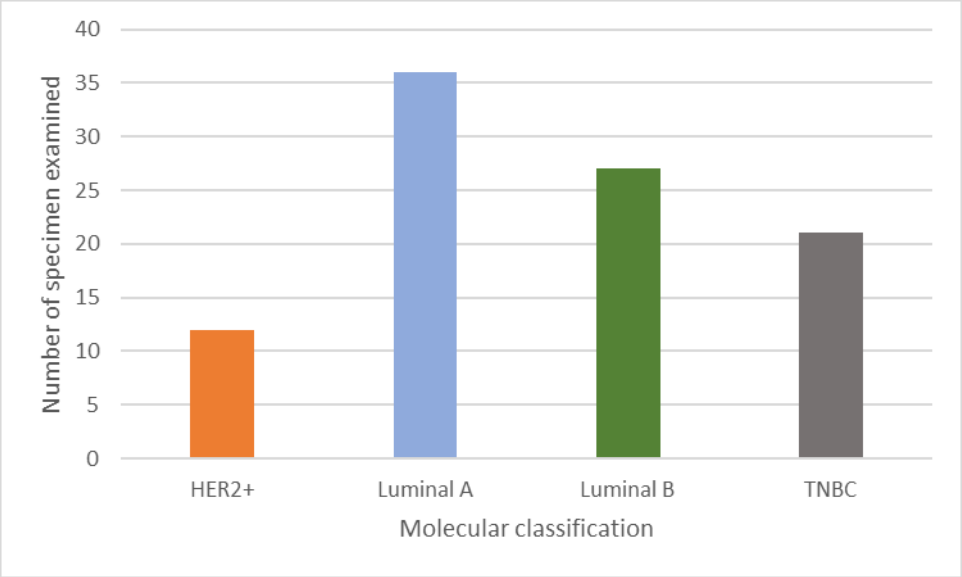
Ki67 expression	No.samples	Percentage
<14%	46	47.92%
>14%	50	52.08%
Grand Total	**96**	**100.00%**

Ki67 expression, a marker of cellular proliferation was >14% in 50 samples (52.08%) and <14% in 46 samples (47.92%). This relatively even distribution indicates that approximately half of the tumors had a high proliferation rate, which is typically associated with more aggressive disease.

Table 13: Distribution of patients based on the molecular typing

Molecular classification	No.samples	Percentage
HER2+	12	12.50%
Luminal A	36	37.50%
Luminal B	27	28.13%
TNBC	21	21.88%
Grand Total	**96**	**100.00%**

Graph 5: Distribution of patients based on the molecular typing



Regarding molecular classification, Luminal A was most common with 36 samples (37.50%), followed by Luminal B with 27 samples (28.13%), Triple Negative Breast Cancer (TNBC) with 21 samples (21.88%) and HER2+ with 12 samples (12.50%). This distribution aligns with typical breast cancer molecular subtype frequencies with hormone receptor-positive types (Luminal A and B) comprising the majority (65.63%) of cases.

Table 14: AR scoring by Allred scoring system

Allred score	No.samples	Percentage
Negative	30	31.25%
Positive	66	68.75%
Grand Total	**96**	**100.00%**

Table 15: AR scoring by H – Scoring system

Allred score	H-score	No.samples	Percentage
Negative	Negative	30	31.3%
Positive	Weak	22	22.9%
	Moderate	27	28.1%
	Strong	17	17.7%
Grand Total		96	100%

Graph 6 : AR scoring by H – Scoring system

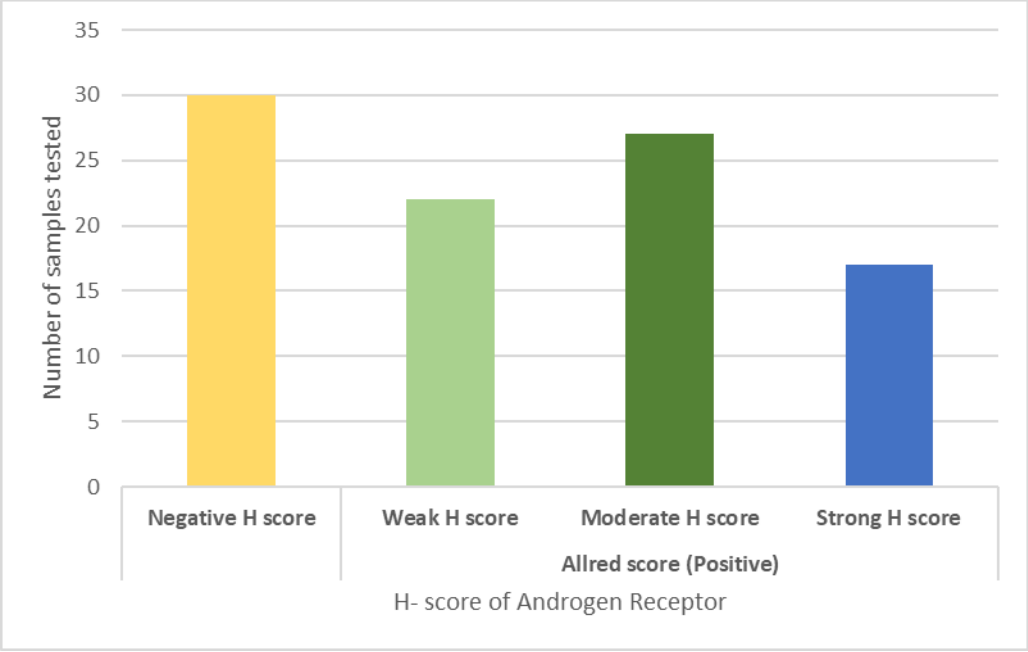


Table 16: AR scoring by 10% Nuclear positivity

Nuclear positivity	No.samples	Percentage
>10%	67	69.79%
Negative	29	30.21%
Grand Total	**96**	**100.00%**

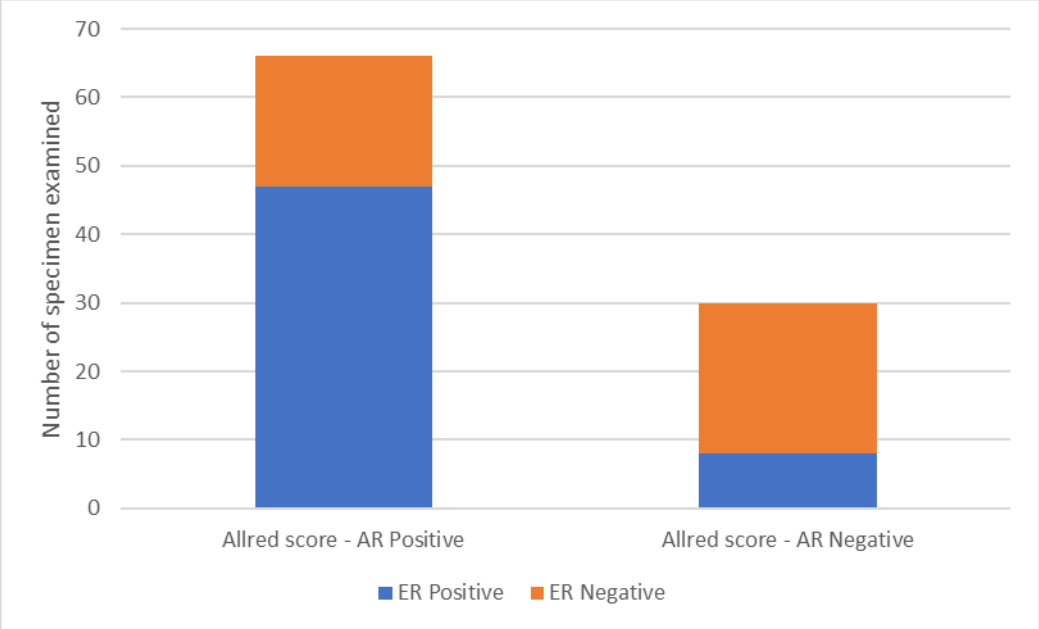
The Allred score for Androgen Receptor was positive in 66 samples (68.75%) and negative in 30 samples (31.25%). This indicates that more than two-thirds of the samples expressed the androgen receptor at clinically significant levels. Breaking down the H-score distribution: 30 samples (31.3%) were negative, 22 samples (22.9%) showed weak positivity, 27 samples (28.1%) showed moderate positivity and 17 samples (17.7%) showed strong positivity. This detailed stratification demonstrates varying degrees of AR expression intensity among the positive samples. Nuclear positivity for AR was >10% in 67 samples (69.79%) and negative in 29 samples (30.21%). This closely mirrors the Allred score findings, confirming that approximately 70% of the samples had significant AR expression.

Table 17: Association between different parameters and Allred Score – AR

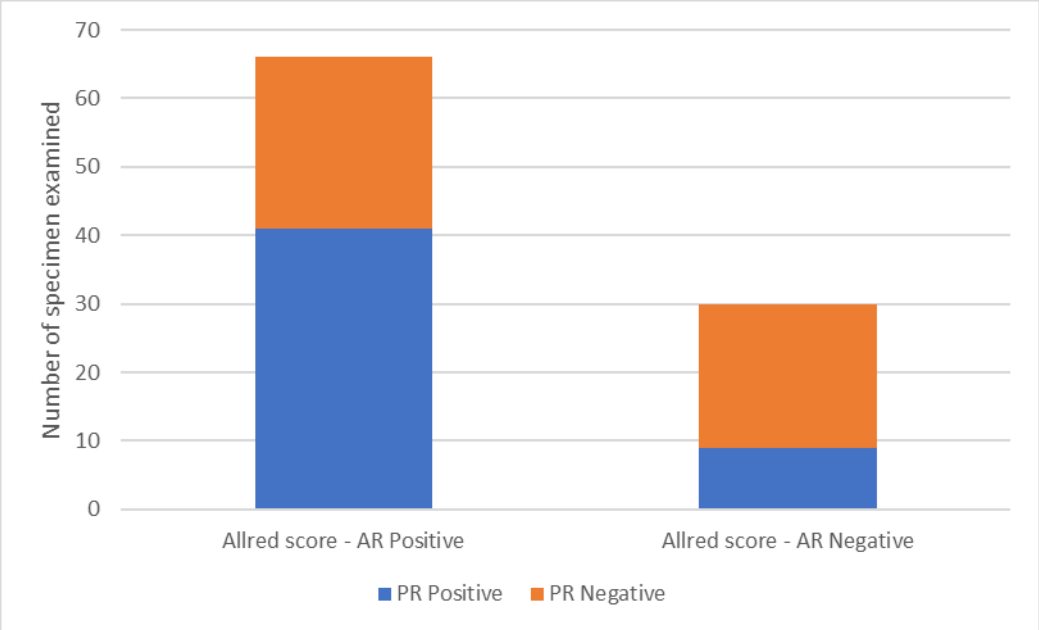
	Allred score - AR			Chi Square (df, p value)
LVI	**Positive**	**Negative**	**Total**	
Present	38	20	58	χ^2 =0.713, df= 1, p = >0.05
Absent	28	10	38	
TILS	**Positive**	**Negative**	**Total**	
High	19	10	29	χ^2 =0.261, df= 2, p = >0.05
Intermediate	15	7	22	
Low	32	13	45	
ER	**Positive**	**Negative**	**Total**	
Positive	47	8	55	χ^2 =16.726, df= 1, p = <0.05*
Negative	19	22	41	
PR	**Positive**	**Negative**	**Total**	
Positive	41	9	50	χ^2 =8.527, df= 1, p = <0.05*
Negative	25	21	46	
Her2 Neu	**Positive**	**Negative**	**Total**	
Positive	15	7	22	Fischer's Exact p value = 0.9033
Negative	50	22	72	
Equivocal	1	1	2	
Ki67	**Positive**	**Negative**	**Total**	
<14%	35	11	46	χ^2 =2.213, df= 1, p = >0.05
>14%	31	19	50	
Molecular classification	**Positive**	**Negative**	**Total**	
HER2+	4	8	12	χ^2 =25.671, df= 3, p = <0.05*
Luminal A	29	7	36	
Luminal B	25	2	27	

TNBC	8	13	21	

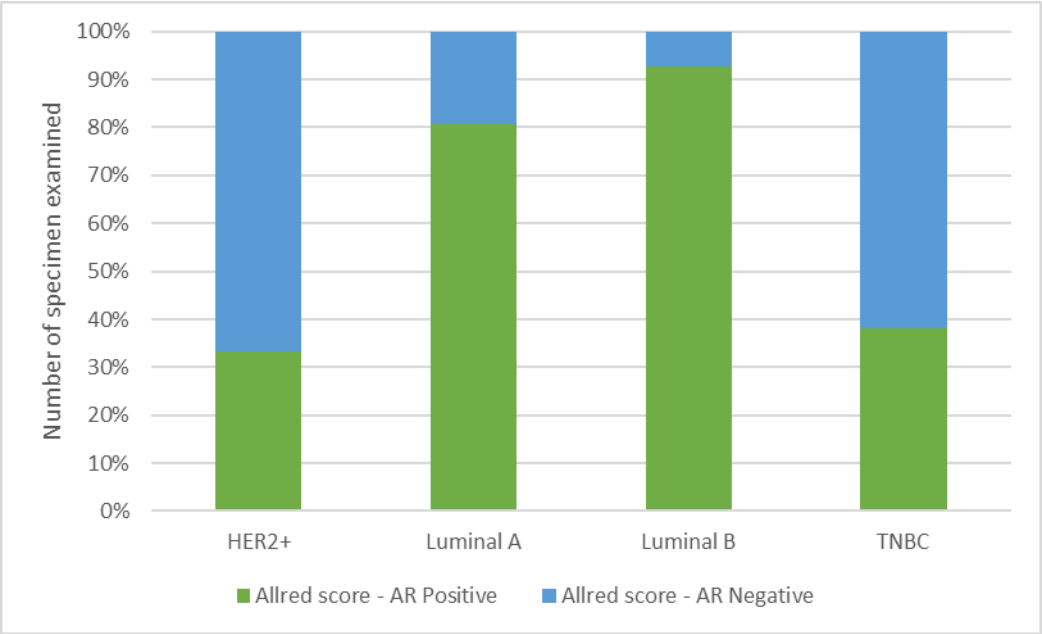
Graph 7: Number of cases in association with Allred score AR and ER status



Graph 8: Number of cases in association with Allred score AR and PR status



Graph 9: Number of cases in association with Allred score AR status and molecular types



Among samples with present lymphovascular invasion (LVI) 38 were Allred-positive and 20 were Allred-negative. Among samples with absent LVI, 28 were Allred-positive and 10 were Allred-negative. Statistical analysis showed no significant association ($\chi^2 = 0.713$, df = 1, p = 0.398). For tumor-infiltrating lymphocytes (TILs), among high TILs samples, 19 were Allred-positive and 10 were Allred-negative. For intermediate TILs, 15 were Allred-positive and 7 were Allred-negative. For low TILs, 32 were Allred-positive and 13 were Allred-negative. No significant association was found ($\chi^2 = 0.261$, df = 2, p = 0.878).

For estrogen receptor (ER) status, among ER-positive samples, 47 were Allred-positive and 8 were Allred-negative. Among ER-negative samples, 19 were Allred-positive and 22 were Allred-negative. A statistically significant association was observed ($\chi^2 = 16.726$, df = 1, p = 0.000*). Regarding progesterone receptor (PR) status, among PR-positive samples, 41 were Allred-positive and 9 were Allred-negative. Among PR-negative samples, 25 were Allred-positive and 21 were Allred-negative. This association was statistically significant ($\chi^2 = 8.527$, df = 1, p = 0.003*).

For HER2-neu receptor status, among HER2-positive samples, 15 were Allred-positive and 7 were Allred-negative. Among HER2-negative samples, 50 were Allred-positive and 22 were Allred-negative. Among equivocal samples, 1 was Allred-positive and 1 was Allred-negative. No significant association was found (Fischer's Exact p = 0.9033). Regarding Ki67 expression, among samples with Ki67 <14%, 35 were Allred-positive and 11 were Allred-negative. Among samples with Ki67 >14%, 31 were Allred-positive and 19 were Allred-negative. No significant association was observed ($\chi^2 = 2.213$, df = 1, p = 0.137).

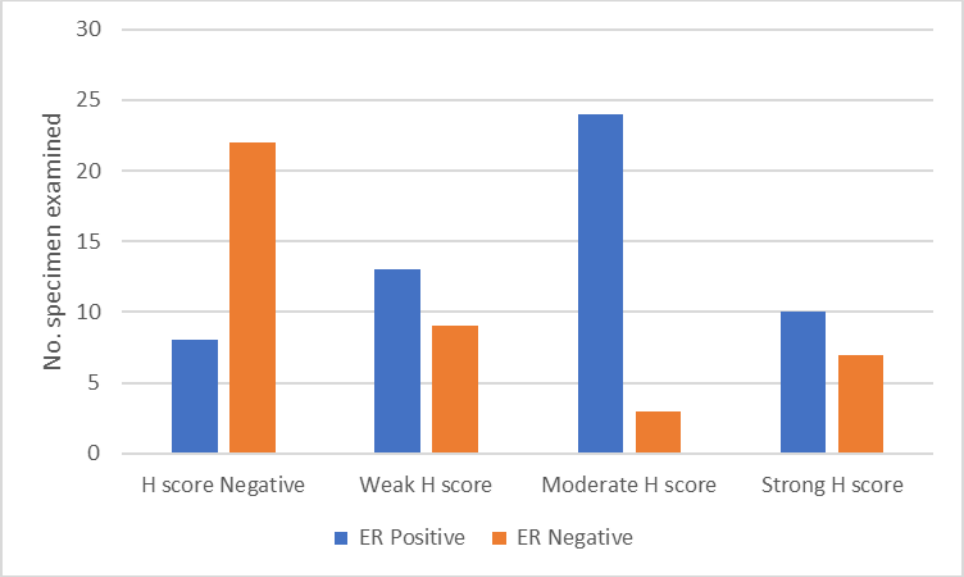
For molecular classification, among HER2+ samples 4 were Allred-positive and 8 were Allred-negative. For Luminal A, 29 were Allred-positive and 7 were Allred-negative. For Luminal B, 25 were Allred-positive and 2 were Allred-negative. For TNBC, 8 were Allred-positive and 13 were Allred-negative. A strong statistically significant association was found ($\chi^2 = 25.671$, df = 3, p = 0.001*).

Table 18: Association between different parameters and H - Score - AR

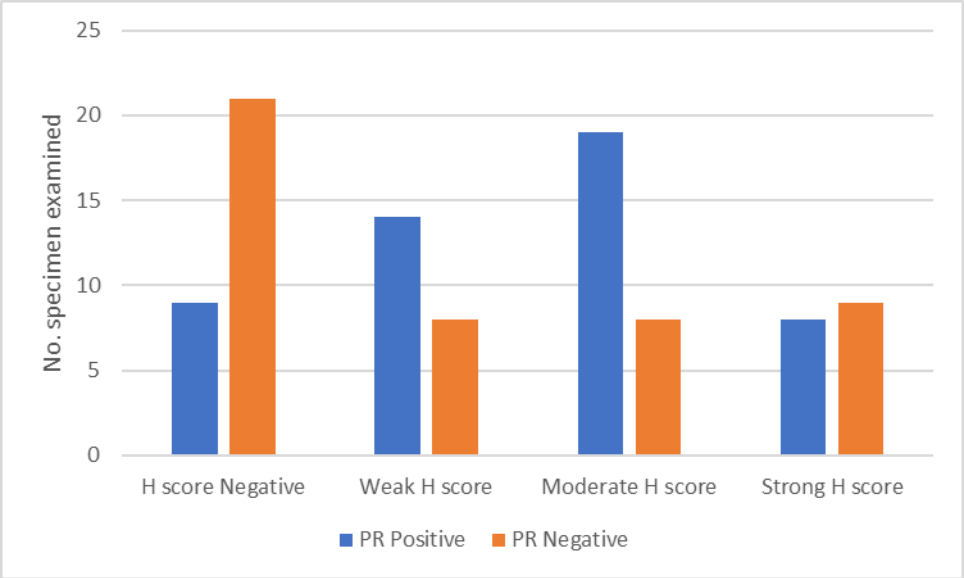
	H Score – AR					Chi Square (df, p value)
LVI	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
Present	20	13	15	10	58	χ^2 =0.791, df= 3, p = >0.05
Absent	10	9	12	7	38	
TILS	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
High	10	7	7	5	29	Fischer's Exact p value = 0.895
Intermediate	7	5	8	2	22	
Low	13	10	12	10	45	
ER	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
Positive	8	13	24	10	55	χ^2 =22.562, df= 3, p = <0.05*
Negative	22	9	3	7	41	
PR	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
Positive	9	14	19	8	50	χ^2 =10.829, df= 3, p = <0.05*
Negative	21	8	8	9	46	
Her2 Neu	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
Positive	7	4	4	7	22	Fischer's Exact p value = 0.406
Negative	22	18	22	10	72	
Equivocal	1	0	1	0	2	
Ki67	**Negative**	**Weak**	**Moderate**	**Strong**	**Total**	
<14%	11	14	15	6	46	χ^2 =5.416, df= 3, p = >0.05
>14%	19	8	12	11	50	

Molecular classification	Negative	Weak	Moderate	Strong	Total	
HER2+	8	1	1	2	12	Fischer's Exact p value = <0.05*
Luminal A	7	13	14	2	36	
Luminal B	2	2	11	12	27	
TNBC	13	6	1	1	21	

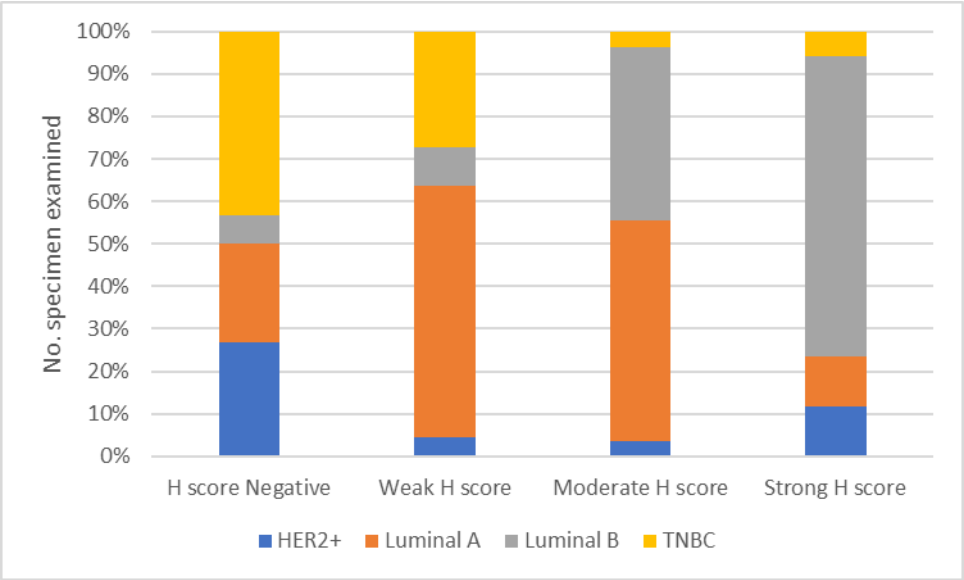
Graph 10: Number of cases in association with ER Status with H-Score of AR



Graph 11: Number of cases in association with PR Status with H-Score of AR



Graph 12: Number of cases in association with molecular classification with H-Score of AR



Lymphovascular invasion (LVI) was analyzed across four H-score categories (negative, weak, moderate, strong). Among samples with present LVI: 20 were negative, 13 were weak, 15 were moderate, and 10 were strong. Among samples with absent LVI: 10 were negative, 9 were weak, 12 were moderate, and 7 were strong. No significant association was found ($\chi^2 = 0.791$, df = 3, p = 0.852). For tumor-infiltrating lymphocytes (TILs), high TILs samples showed: 10 negative, 7 weak, 7 moderate, and 5 strong. Intermediate TILs showed: 7 negative, 5 weak, 8 moderate, and 2 strong. Low TILs showed: 13 negative, 10 weak, 12 moderate, and 10 strong. No significant association was observed (Fischer's Exact p = 0.895).

For estrogen receptor (ER) status, ER-positive samples showed: 8 negative, 13 weak, 24 moderate, and 10 strong. ER-negative samples showed: 22 negative, 9 weak, 3 moderate, and 7 strong. A strong statistically significant association was found ($\chi^2 = 22.562$, df = 3, p = 0.000*). Regarding progesterone receptor (PR) status, PR-positive samples showed: 9 negative, 14 weak, 19 moderate, and 8 strong. PR-negative samples showed: 21 negative, 8

weak, 8 moderate, and 9 strong. This association was statistically significant ($\chi^2 = 10.829$, df = 3, p = 0.012*).

For HER2-neu receptor status, HER2-positive samples showed: 7 negative, 4 weak, 4 moderate, and 7 strong. HER2-negative samples showed: 22 negative, 18 weak, 22 moderate, and 10 strong. Equivocal samples showed: 1 negative, 0 weak, 1 moderate, and 0 strong. No significant association was observed (Fischer's Exact p = 0.406). Regarding Ki67 expression, samples with Ki67 <14% showed: 11 negative, 14 weak, 15 moderate, and 6 strong. Samples with Ki67 >14% showed: 19 negative, 8 weak, 12 moderate, and 11 strong. No significant association was found ($\chi^2 = 5.416$, df = 3, p = 0.144).

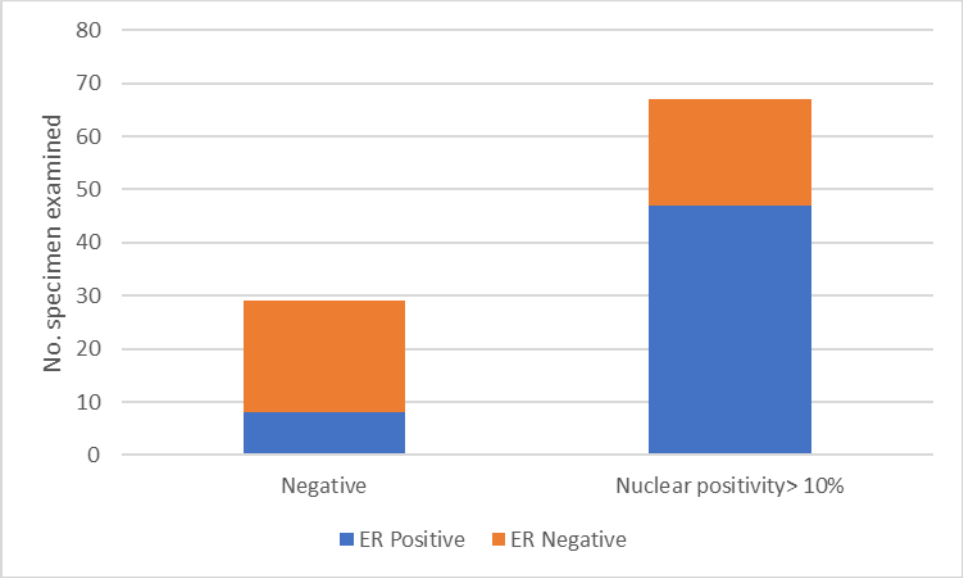
For molecular classification, HER2+ samples showed: 8 negative, 1 weak, 1 moderate, and 2 strong. Luminal A showed: 7 negative, 13 weak, 14 moderate, and 2 strong. Luminal B showed: 2 negative, 2 weak, 11 moderate, and 12 strong. TNBC showed: 13 negative, 6 weak, 1 moderate, and 1 strong. A highly significant association was observed (Fischer's Exact p = 0.000*).

Table 19: Association between different parameters and 10% Nuclear positivity - AR

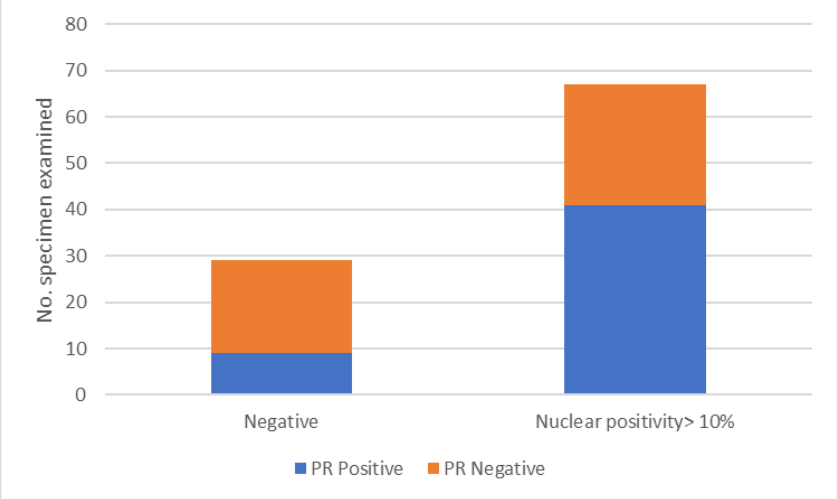
	Nuclear Positivity			Chi Square (df, p value)
LVI	**Negative**	**>10%**	**Total**	
Present	19	39	58	χ^2 =0.452, df= 1, p = >0.05
Absent	10	28	38	
TILS	**Negative**	**>10%**	**Total**	
High	10	19	29	χ^2 =0.546, df= 2, p = >0.05
Intermediate	7	15	22	
Low	12	33	45	
ER	**Negative**	**>10%**	**Total**	
Positive	8	47	55	χ^2 =14.98, df= 1, p = <0.05*
Negative	21	20	41	
PR	**Negative**	**>10%**	**Total**	
Positive	9	41	50	χ^2 =7.377, df= 1, p = <0.05*
Negative	20	26	46	
Her2 Neu	**Negative**	**>10%**	**Total**	
Positive	7	15	22	Fischer's Exact p value = 0.719
Negative	21	51	72	
Equivocal	1	1	2	

Ki67	Negative	>10%	Total	
<14%	11	35	46	χ^2 =1.660, df= 1, p = >0.05
>14%	18	32	50	
Molecular classification	**Negative**	**>10%**	**Total**	
HER2+	8	4	12	Fischer's Exact p value = 0.000*
Luminal A	7	29	36	
Luminal B	2	25	27	
TNBC	12	9	21	

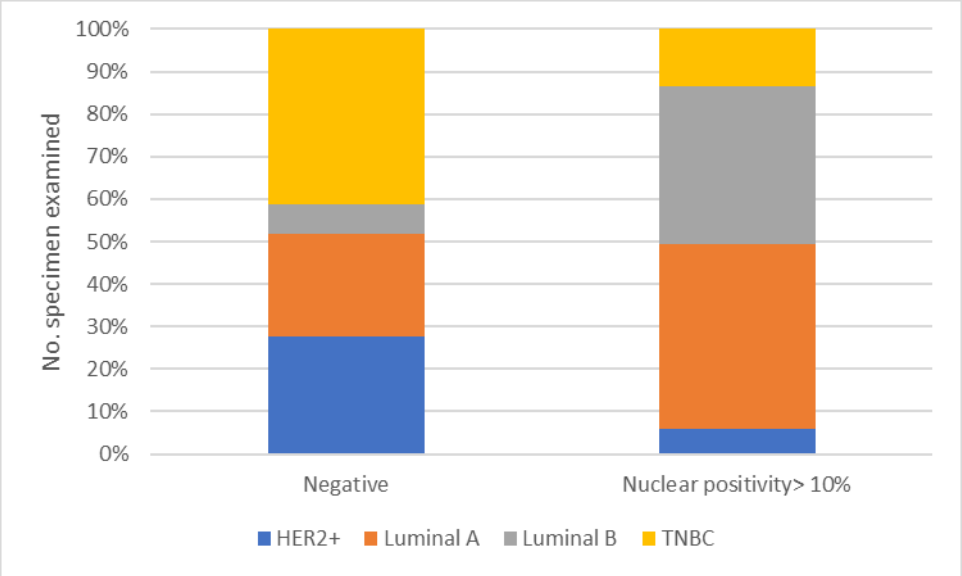
Graph 13: Number of cases in association with ER status and >10% nuclear positivity of AR



Graph 14: Number of cases in association with PR status and >10% nuclear positivity of AR



Graph 15: Number of cases in association with Molecular types and >10% nuclear positivity of AR



For lymphovascular invasion (LVI), among samples with present LVI, 19 were negative and 39 had >10% nuclear positivity. Among samples with absent LVI, 10 were negative and 28 had >10% nuclear positivity. No significant association was found ($\chi^2 = 0.452$, df = 1, p = 0.501). Regarding tumor-infiltrating lymphocytes (TILs), high TILs samples showed 10 negative and 19 with >10% nuclear positivity. Intermediate TILs showed 7 negative and 15 with >10% nuclear positivity. Low TILs showed 12 negative and 33 with >10% nuclear positivity. No significant association was observed ($\chi^2 = 0.546$, df = 2, p = 0.761).

For estrogen receptor (ER) status, ER-positive samples showed 8 negative and 47 with >10% nuclear positivity. ER-negative samples showed 21 negative and 20 with >10% nuclear positivity. A highly significant association was found ($\chi^2 = 14.98$, df = 1, p = 0.000*). Regarding progesterone receptor (PR) status, PR-positive samples showed 9 negative and 41 with >10% nuclear positivity. PR-negative samples showed 20 negative and 26 with >10% nuclear positivity. This association was statistically significant ($\chi^2 = 7.377$, df = 1, p = 0.006*).

For HER2-neu receptor status, HER2-positive samples showed 7 negative and 15 with >10% nuclear positivity. HER2-negative samples showed 21 negative and 51 with >10% nuclear positivity. Equivocal samples showed 1 negative and 1 with >10% nuclear positivity. No significant association was observed (Fischer's Exact p = 0.719). Regarding Ki67 expression, samples with Ki67 <14% showed 11 negative and 35 with >10% nuclear positivity. Samples with Ki67 >14% showed 18 negative and 32 with >10% nuclear positivity. No significant association was found ($\chi^2 = 1.660$, df = 1, p = 0.197).

For molecular classification, HER2+ samples showed 8 negative and 4 with >10% nuclear positivity. Luminal A showed 7 negative and 29 with >10% nuclear positivity. Luminal B showed 2 negative and 25 with >10% nuclear positivity. TNBC showed 12 negative and 9 with >10% nuclear positivity. A highly significant association was observed (Fischer's Exact p = 0.000*).

This comprehensive analysis of 96 infiltrating ductal carcinoma breast cancer samples reveals several key findings regarding Androgen Receptor (AR) expression and its associations with other prognostic factors. AR expression was observed in approximately 70% of the samples, as indicated by Allred score (68.75%), H-score distribution and nuclear positivity (69.79%). Significant associations were consistently found between AR expression and both ER and PR status across all three AR measurement methods (Allred score, H-score, nuclear positivity), with AR expression being significantly more common in ER-positive and PR-positive tumors. Strong statistically significant associations were observed between AR expression and molecular classification in all three AR measurement methods, with Luminal subtypes (especially Luminal B) showing the highest AR positivity, while TNBC and HER2+ subtypes showed lower AR expression. No significant associations were found between AR expression and lymphovascular invasion, tumor-infiltrating lymphocytes, HER2-neu receptor status, or Ki67 expression. Most samples were Stage II (61.46%) and Grade 1 (53.13%), with

lymphovascular invasion present in 60.42% and low tumor-infiltrating lymphocytes in 46.88%. The samples were predominantly Luminal subtypes (65.63%), with hormone receptor positivity in approximately 55% of cases and HER2 negativity in 75%. These findings suggest that AR expression is strongly associated with hormone receptor status and molecular subtypes in breast cancer, potentially indicating a hormonal interplay in tumor biology. The significant correlation with Luminal subtypes suggests AR may play a more prominent role in these subtypes. However, AR expression does not appear to be associated with morphological features like lymphovascular invasion or immune response markers like tumor-infiltrating lymphocytes. These insights could contribute to better understanding of breast cancer biology and potentially guide therapeutic approaches targeting AR in specific breast cancer subtypes.

DISCUSSION

DISCUSSION

The present study aimed to evaluate the expression of androgen receptor (AR) in infiltrating ductal carcinoma of the breast and its association with various prognostic factors. In our cohort of 96 cases, 68.75% were positive for AR expression based on Allred score, and 69.79% showed nuclear positivity of >10%. These findings are in concordance with previous reports in the literature. Nangru M et al. reported overall positivity for AR was observed in 62.22%.[86] Collins et al. reported AR positivity in 77% of invasive breast cancers in their study[84], while Park et al. found 72.9% AR positivity in their cohort of 413 patients.[106] Similarly, Niemeier et al. demonstrated AR expression in 77% of cases in their series of 189 invasive breast cancers.[107]

Demographic and Histopathological Characteristics

Our patient cohort had a median age of 53 years (range: 28-82 years), which is consistent with the general demographics of breast cancer patients as reported by Nangru M et al.[86] and Bray et al.[60]

Lymphovascular invasion (LVI) was identified in 60.42% of our cases which is higher than the 23% reported by Mohammed et al. in their series.[85] This discrepancy could be due to variations in the criteria used for defining LVI or differences in the study populations. LVI is an important prognostic factor in breast cancer, as emphasized by Rakha et al. who demonstrated its correlation with worse overall survival independent of tumor size and grade.[43]

The distribution of tumor-infiltrating lymphocytes (TILs) in our study showed that 46.88% of cases had low TILs, 22.92% had intermediate TILs and 30.21% had high TILs. Denkert et al. have highlighted the prognostic significance of TILs, particularly in triple-negative and HER2-positive breast cancers, with higher TILs being associated with improved survival.[66] Similar to our study, A study done by vellaisamy G et al.[67] did not show statistical significance with TILs.

Our study did not specifically evaluate the prognostic impact of TILs, their distribution provides important context for understanding the tumor microenvironment in our cohort.

The stage distribution in our study showed a predominance of early-stage disease, with 61.46% of cases being Stage II (IIA: 38.54%, IIB: 22.92%). This is comparable to findings by DeSantis et al. who reported that a majority of breast cancers in the United States are diagnosed at early stages due to improved screening programs.[61]

Regarding tumor grade, our study showed a higher proportion of Grade 1 tumors (53.13%) compared to Grade 2 (30.21%) and Grade 3 (16.67%). This distribution differs somewhat from that reported by Nangru et al.[86] who observed that majority of cases belonged to histologic grade 2(44.44%) followed by grade 3(40%) and similarly Rakha et al. observed Grade 1, 2, and 3 distributions of approximately 20%, 50%, and 30%, respectively, in their large cohort study.[63] The higher proportion of well-differentiated tumors in our study could potentially be attributed to differences in patient demographics, effectiveness of screening programs or variations in grading practices.

Hormone Receptor Status and Molecular Classification

In terms of hormone receptor status, 57.29% of our cases were ER-positive and 52.08% were PR-positive. A study done by Nangru M et al.[86] ER positivity was seen in 24.44% and PR positivity in 28.89% of cases. These proportions are somewhat lower than those reported by Hammond et al. who noted ER positivity in approximately 70% of invasive breast cancers.[65] The slightly lower rates in our study may reflect regional variations in breast cancer biology or potential differences in the threshold for considering a tumor hormone receptor-positive.

HER2 overexpression was observed in 22.92% of our cases with 75% being HER2-negative and 2.08% showing equivocal results. This distribution aligns with the figures reported by Slamon et al. who found HER2 amplification or overexpression in approximately 20-25% of

breast cancers.[75] The slight variations might be attributed to differences in testing methodology or interpretation criteria.

Regarding Ki67 expression, 52.08% of our cases showed high proliferation (>14%), which is consistent with the distribution reported by Goldhirsch et al. in their St. Gallen consensus.[74] Ki67 is an important marker for distinguishing Luminal A from Luminal B breast cancers and has prognostic implications as highlighted by Perou et al. [73]

The molecular classification of our cases revealed that 37.50% were Luminal A, 28.13% were Luminal B, 21.88% were Triple Negative Breast Cancer (TNBC), and 12.50% were HER2+. This distribution broadly aligns with the molecular subtype prevalence reported by Carey et al.[62] although our cohort showed a slightly higher proportion of TNBC cases compared to the approximately 15% typically reported in Western populations.

Androgen Receptor Expression and Its Associations

AR Expression and Morphological Features

Our study found no significant association between AR expression and lymphovascular invasion (LVI). Among samples with present LVI, 65.5% were AR-positive by Allred score compared to 73.7% of samples with absent LVI ($\chi^2 = 0.713$, df = 1, $p = 0.398$). Similar non-significant associations were observed using H-score ($\chi^2 = 0.791$, df = 3, $p = 0.852$) and nuclear positivity ($\chi^2 = 0.452$, df = 1, $p = 0.501$).

This finding is consistent with Gonzalez et al. who did not observe a significant correlation between AR expression and vascular invasion in their cohort of 152 breast cancer patients. However, some studies have suggested potential associations.[105] Hu et al. reported that AR-positive tumors were less likely to have LVI, although this association did not reach statistical significance in all subgroups.[104]

Similarly, our study did not find a significant association between AR expression and tumor-infiltrating lymphocytes (TILs). AR positivity by Allred score was observed in 65.5% of high TILs samples, 68.2% of intermediate TILs samples and 71.1% of low TILs samples ($\chi^2 = 0.261$, df = 2, p = 0.878). Similar non-significant associations were found using H-score (Fischer's Exact p = 0.895) and nuclear positivity ($\chi^2 = 0.546$, df = 2, p = 0.761).

The relationship between AR and TILs has not been extensively studied but our findings suggest that AR expression might not significantly influence the immune microenvironment in breast cancer. However, it is important to note that we evaluated TILs as a categorical variable (high, intermediate, low) rather than as a continuous percentage which might have limited our ability to detect subtle associations.

AR Expression and Hormone Receptor Status

One of the most significant findings in our study was the strong association between AR expression and hormone receptor status. Among ER-positive samples, 85.45% (47/55) were AR-positive by Allred score, compared to 46.34% (19/41) of ER-negative samples. This association was highly significant ($\chi^2 = 16.726$, df = 1, p = 0.000). Similarly, 82% (41/50) of PR-positive samples were AR-positive compared to 54.35% (25/46) of PR-negative samples ($\chi^2 = 8.527$, df = 1, p = 0.003).

These findings are consistent with multiple previous studies. Vellaisamy G et al. reported that AR was expressed in 73% of ER positive tumors and among ER negative tumors, AR was expressed in 29% of the tumors.[67] Collins et al. reported that 91% of ER-positive breast cancers were AR-positive compared to 43% of ER-negative tumors.[84] Park et al. similarly found a significant association between AR and ER expression, with 87.8% of ER-positive tumors expressing AR versus 34.9% of ER-negative tumors ($p<0.001$).[106] Niemeier et al. also observed AR positivity in 88% of ER-positive tumors but in only 43% of ER-negative tumors.[107]

The strong correlation between AR and ER/PR expression suggests potential interactions between these hormones signalling pathways in breast cancer. Peters et al. demonstrated that AR can inhibit ER-α activity and act as a prognostic factor in breast cancer.[82] The cross-talk between these receptors has been further elucidated by Hickey et al. who described AR as potentially having both growth-inhibitory and oncogenic roles depending on the cellular context and the presence of other hormone receptors.[72]

When evaluated using H-score, our study revealed more associations. Among ER-positive samples, 85.5% showed some degree of AR expression (weak: 23.6%, moderate: 43.6%, strong: 18.2%) compared to 46.3% of ER-negative samples (weak: 22.0%, moderate: 7.3%, strong: 17.1%). This significant association ($\chi^2 = 22.562$, df = 3, p = 0.000) suggests that not only the presence but also the intensity of AR expression correlates with ER status. Similar patterns were observed with PR status ($\chi^2 = 10.829$, df = 3, p = 0.012). These findings align with those of Yu et al. who reported significant correlations between AR intensity and both ER and PR expression.[103]

The association between AR and hormone receptors was further confirmed by nuclear positivity analysis, which showed 85.5% of ER-positive samples with >10% nuclear AR expression compared to 48.8% of ER-negative samples ($\chi^2 = 14.98$, df = 1, p = 0.000). For PR, 82.0% of positive samples showed nuclear AR expression versus 56.5% of negative samples ($\chi^2 = 7.377$, df = 1, p = 0.006).

AR Expression and HER2 Status

Interestingly, our study did not find a significant association between AR expression and HER2 status. Among HER2-positive samples, 68.2% were AR-positive by Allred score, comparable to 69.4% of HER2-negative samples (Fischer's Exact p = 0.9033). Similar non-significant associations were observed using H-score (Fischer's Exact p = 0.406) and nuclear positivity

(Fischer's Exact p = 0.719). Similar non-significant association was seen in a study done by Vellaisamy G et al.[67]

This finding contrasts with some previous reports. Chia et al.[86] demonstrated a feedback loop between AR and HER2 signalling in breast cancer, suggesting a potential correlation between their expression. Park et al. found that AR positivity was significantly associated with HER2 overexpression (p=0.019) in their cohort.[106] However, Gonzalez et al. did not observe a significant association between AR and HER2 expression, which is consistent with our results.[105]

AR Expression and Ki67

Our study found no significant association between AR expression and Ki67 proliferation index. Among samples with Ki67 <14%, 76.1% were AR-positive by Allred score compared to 62.0% of samples with Ki67 >14% ($\chi^2 = 2.213$, df = 1, p = 0.137). Similar non-significant associations were observed using H-score ($\chi^2 = 5.416$, df = 3, p = 0.144) and nuclear positivity ($\chi^2 = 1.660$, df = 1, p = 0.197).

These findings are somewhat consistent with those of Park et al. who reported that AR expression was not significantly associated with Ki67 index in their multivariate analysis.[106] However, some studies have suggested a negative correlation between AR and proliferation. Hu et al. found that AR-positive tumors generally had lower Ki67 expression, particularly in the ER-positive subgroup. The discrepancy might be related to differences in the cutoff values used for Ki67 positivity or variations in the study populations.[104]

AR Expression and Molecular Subtypes

One of the most striking findings in our study was the significant association between AR expression and molecular subtypes. Based on Allred score, AR positivity was highest in Luminal B (92.6%), followed by Luminal A (80.6%), TNBC (38.1%), and HER2+ (33.3%)

subtypes (χ^2 = 25.671, df = 3, p = 0.001). Similar patterns were observed using H-score (Fischer's Exact p = 0.000) and nuclear positivity (Fischer's Exact p = 0.000).

In contrast a study done by Vellaisamy et al. observed significantly higher AR expression in Luminal A whereas Luminal B and HER2+ tumors did not.[67]

These findings align with several previous studies. Collins et al. reported AR positivity in 88% of Luminal A, 96% of Luminal B, 59% of HER2+, and 32% of basal-like tumors.[84] Park et al. similarly found that AR expression was highest in Luminal subtypes (Luminal A: 89.5%, Luminal B: 83.1%), intermediate in HER2+ (66.7%) and lowest in TNBC (31.4%).[106] Niemeier et al. observed AR positivity in 91% of ER-positive tumors, including Luminal subtypes, compared to 50% of HER2-enriched and 36% of triple-negative tumors.[107]

The high prevalence of AR expression in Luminal subtypes, particularly Luminal B suggests a potential interplay between AR and ER/PR signalling in these tumors. Hickey et al. have proposed that in ER-positive breast cancers, AR might function as a tumor suppressor by inhibiting ER-mediated cell proliferation.[85] This is supported by Ponnusamy et al. who demonstrated that AR acts as a tumor suppressor in ER-positive breast cancer.[94]

The lower AR expression in TNBC and HER2+ subtypes in our study is consistent with the literature. However, it is noteworthy that a substantial proportion of these tumors (38.1% of TNBC and 33.3% of HER2+) still expressed AR. This finding is particularly relevant given the emerging interest in AR-targeted therapies for these subtypes. Gerratana et al. have highlighted the potential of AR as a therapeutic target in TNBC[4], while Cochrane et al.have shown that enzalutamide, an AR inhibitor, can be effective in certain breast cancer models, including TNBC.[87]

Methodological Considerations and Limitations

Our study used three methods to evaluate AR expression: Allred score, H-score, and nuclear positivity. All three methods showed consistent results, reinforcing the robustness of our findings. The use of a >10% cutoff for nuclear positivity is in line with several previous studies, including Suzuki et al. who demonstrated that this threshold is clinically meaningful for AR assessment.[91]

However, it is important to acknowledge certain limitations. Our sample size of 96 cases, while sufficient based on sample size calculations is relatively modest compared to some larger studies in the literature. Additionally, the cross-sectional design limits our ability to make inferences about causality or the prognostic impact of AR expression. Furthermore, we did not evaluate AR expression in relation to patient outcomes, which would have provided additional context for understanding its clinical significance.

Future Directions

Based on our findings and the existing literature, several areas warrant further investigation. Longitudinal studies to evaluate the prognostic impact of AR expression in different molecular subtypes would be valuable. Additionally, more detailed molecular analyses to understand the interactions between AR and other signalling pathways, particularly in Luminal B tumors where AR expression was highest in our study could provide insights into potential therapeutic targets.

The potential therapeutic role of AR in TNBC despite its lower prevalence remains an important area for exploration. Asiedu et al. used single-cell transcriptomics to identify AR signalling heterogeneity in TNBC suggesting that even within this subtype there might be specific cell populations that could benefit from AR-targeted therapies.[93]

CONCLUSION

This comprehensive analysis of 96 infiltrating ductal carcinoma samples demonstrates that Androgen Receptor (AR) is expressed in a significant proportion of breast cancers (68.75% by Allred score; 69.79% by nuclear positivity criteria). Our findings reveal strong and statistically significant associations between AR expression and both estrogen and progesterone receptor status ($p<0.001$ and $p=0.003$ respectively), confirming an important relationship between these steroid hormones signalling pathways in breast cancer.

The molecular subtype-specific distribution of AR expression is particularly noteworthy, with highest expression in Luminal B (92.6%) and Luminal A (80.6%) subtypes and considerably lower expression in TNBC (38.1%) and HER2+ (33.3%) subtypes. These distinct patterns of AR expression across molecular subtypes suggest different biological roles for AR depending on the tumor context.

Interestingly, AR expression did not significantly correlate with HER2 status, Ki67 proliferation index, lymphovascular invasion, or tumor-infiltrating lymphocytes, indicating that AR signalling may be independent of these established prognostic factors.

These results have important clinical implications, supporting the potential utility of AR as both a prognostic biomarker and therapeutic target in breast cancer. The particularly high expression in Luminal subtypes suggests AR-targeted approaches may be especially relevant in these patients. Additionally, the presence of AR in a subset of TNBC and HER2+ tumors indicates possible therapeutic opportunities in these traditionally more challenging subtypes.

Further investigations into the functional significance of AR in different molecular contexts and its impact on treatment response and patient outcomes are warranted to fully utilize AR status in personalized breast cancer management.

Summary of Findings

• A total of 96 infiltrating ductal carcinoma breast cancer samples were studied with median patient age of 53 years (range: 28-82 years).

• Stage IIA was the most common (38.54%), followed by Stage IIB (22.92%), IIIA (12.50%), IIIC (10.42%), IIIB (9.38%), IA (5.21%), and IV (1.04%).

• Grade 1 tumors were predominant (53.13%), followed by Grade 2 (30.21%) and Grade 3 (16.67%).

• Lymphovascular invasion was present in 60.42% of cases and absent in 39.58%.

• Low tumor-infiltrating lymphocytes were observed in 46.88% of cases, high in 30.21%, and intermediate in 22.92%.

• 57.29% of samples were Estrogen Receptor (ER) positive and 42.71% were negative.

• 52.08% of samples were Progesterone Receptor (PR) positive and 47.92% were negative.

• 75% of cases were HER2-negative, 22.92% were HER2-positive, and 2.08% were equivocal.

• Ki67 expression was >14% in 52.08% of samples and <14% in 47.92%.

• Molecular classification showed 37.50% Luminal A, 28.13% Luminal B, 21.88% Triple Negative Breast Cancer (TNBC), and 12.50% HER2+.

• Androgen Receptor (AR) was positive by Allred score in 68.75% of samples and negative in 31.25%.

• H-score distribution revealed 31.3% negative, 22.9% weak, 28.1% moderate, and 17.7% strong AR expression.

• AR nuclear positivity >10% was observed in 69.79% of samples and 30.21% were negative.

• A significant association was found between AR expression and ER status (p=0.000), with 85.45% of ER-positive samples showing AR positivity versus 46.34% of ER-negative samples.

• A significant association was observed between AR expression and PR status (p=0.003), with 82% of PR-positive samples showing AR positivity versus 54.35% of PR-negative samples.

• No significant association was found between AR expression and HER2 status (p=0.9033).

• No significant association was observed between AR expression and Ki67 levels (p=0.137).

• A highly significant association was found between AR expression and molecular subtypes (p=0.001), with highest AR positivity in Luminal B (92.6%), followed by Luminal A (80.6%), TNBC (38.1%), and HER2+ (33.3%).

• No significant association was found between AR expression and lymphovascular invasion (p=0.398).

• No significant association was observed between AR expression and tumor-infiltrating lymphocytes (p=0.878).

• All three methods of AR assessment (Allred score, H-score, and nuclear positivity) showed consistent associations with the clinicopathological parameters.

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