RESEARCH PAPER

# Early Histopathological Changes in Breast Carcinomas

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***Received: 05 Apr, 2026; Revised: 27th Apr 2026; Accepted: 11th May, 2026; Available Online: 19May, 2026***

**ABSTRACT**

**Background:** Breast cancer remains the most frequently diagnosed malignancy in women globally, accounting for approximately 30% of all female cancers. Identification of early histopathological alterations is critical for timely diagnosis, risk stratification, and therapeutic intervention. Despite advances in molecular oncology, traditional histomorphological assessment remains the gold standard for definitive diagnosis. However, systematic synthesis of early microscopic changes across the spectrum of breast pathology—from proliferative benign disease through pre-invasive lesions to frank invasive carcinoma—has been insufficiently consolidated.

**Objectives:** This systematic review and meta-analysis aimed to: (1) consolidate published evidence on early histopathological changes in breast malignancies; (2) compare morphological features across benign, pre-invasive, and malignant entities; (3) quantify diagnostic markers with highest discriminatory value; and (4) construct a comprehensive comparative table for clinical and educational reference.

**Methods:** A systematic search was conducted across PubMed/MEDLINE, EMBASE, Cochrane Library, and Scopus (1990–2024). Studies reporting histopathological characteristics of early or pre-invasive breast lesions and invasive breast carcinomas were included. Two independent reviewers performed study selection, data extraction, and quality assessment using QUADAS-2 and Newcastle–Ottawa Scale. Meta-analysis was performed using random-effects models (DerSimonian–Laird method). PRISMA 2020 guidelines were followed throughout.

**Results:** From 4,312 screened records, 187 studies encompassing 96,450 patients met inclusion criteria. Nuclear pleomorphism was the single most discriminatory early feature (pooled sensitivity 82.4%, 95% CI: 78.1–86.3%). Loss of myoepithelial layer demonstrated the highest specificity for invasive carcinoma (pooled specificity 96.8%, 95% CI: 94.2–98.4%). High-grade ductal carcinoma in situ (DCIS) with comedo necrosis carried the greatest risk of progression to invasive carcinoma (OR 4.71, 95% CI: 3.44–6.45). Stromal desmoplasia, increased mitotic count (>3/HPF), and E-cadherin loss were identified as early hallmarks of malignant transition. There was moderate heterogeneity across studies ($I^2$ = 52–67%).

**Conclusions:** Early histopathological changes in breast malignancies encompass a reproducible constellation of cytological, architectural, and stromal alterations that are detectable before frank invasion occurs. Nuclear atypia, loss of polarity, architectural distortion, abnormal mitoses, and myoepithelial disruption / loss constitute the core diagnostic continuum. Integration of ancillary immunohistochemistry (IHC)—particularly E-cadherin, p63, smooth muscle actin, Ki-67, and hormone receptors—substantially enhances diagnostic precision. This review provides a reference compendium for pathologists, oncologists, and trainees.

**Keywords:** breast malignancy; histopathology; ductal carcinoma in situ; invasive ductal carcinoma; atypical ductal hyperplasia; flat epithelial atypia; early diagnosis; nuclear pleomorphism; desmoplasia; systematic review

**How to cite this article:** Almousa AM, Alzallal O. Early Histopathological Changes in Breast Carcinomas. Int J Drug Deliv Technol. 2026;16(55s): 1439-1446. DOI: 10.25258/ijddt.16.55s.150

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related mortality in women worldwide. According to the Global Cancer Observatory (GLOBOCAN 2022), an estimated 2.3 million new breast cancer cases were diagnosed globally, with 666,000 deaths recorded. Despite marked advances in imaging technology, molecular diagnostics, and targeted therapies, histopathological examination of tissue specimens continues to form the diagnostic cornerstone upon which all subsequent management decisions are based.

The natural history of breast carcinoma is characterised by a spectrum of morphological alterations that progressively accumulate from normalcy through benign proliferative disease, atypical hyperplasia, carcinoma in situ, and ultimately invasive carcinoma. Early recognition of pre-neoplastic and neoplastic changes not only enables timely intervention but also provides insights into tumour biology, guides prognostication, and informs the selection of systemic therapy.

Despite the well-established conceptual framework of the multi-step carcinogenesis model, the precise

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histopathological signatures distinguishing benign proliferative lesions from malignant precursors remain a source of diagnostic challenge in routine practice. Interobserver variability in the grading of lesions such as atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), and low-grade ductal carcinoma in situ (DCIS) is well documented in the literature. Systematic synthesis of the morphological criteria most reliably associated with early malignant transformation is therefore of substantial clinical and academic value.

This systematic review and meta-analysis was designed to comprehensively evaluate the existing body of literature pertaining to early histopathological changes in breast malignancies, to quantify the diagnostic accuracy of individual morphological features, and to provide a structured comparative compendium encompassing the most clinically encountered breast pathological entities.

**Background and Conceptual Framework**

**The Multi-Step Model of Breast Carcinogenesis**

The widely accepted model of breast carcinogenesis proposes a sequential progression from normal luminal epithelium through columnar cell lesions (CCL), FEA, low-grade DCIS, and ultimately to invasive carcinoma. This low-grade pathway is contrasted by an alternative high-grade pathway characterised by high-grade DCIS, predominantly driven by HER2 amplification and TP53 mutation, which does not necessarily pass through recognised precursor stages.

At the molecular level, early malignant transformation is accompanied by cumulative genetic alterations including chromosomal instability, loss of heterozygosity (LOH), epigenetic silencing of tumour suppressor genes, and dysregulation of cell cycle checkpoints. Histopathologically, these molecular events translate into recognisable morphological alterations affecting cellular architecture, nuclear morphology, stromal composition, and proliferative activity.

**Spectrum of Non-Invasive and Invasive Breast Lesions**

For the purposes of this review, the following entities are considered along the continuum of breast pathology:

- Usual Ductal Hyperplasia (UDH): a benign proliferative lesion with low malignant potential;
- Flat Epithelial Atypia (FEA): a putative precursor lesion characterised by columnar cell change with low-grade nuclear atypia;
- Atypical Ductal Hyperplasia (ADH): shares morphological and molecular features with low-grade DCIS but is defined by extent and distribution criteria;
- Lobular Carcinoma In Situ (LCIS): classically regarded as a risk indicator, though the pleomorphic variant is treated as a direct precursor;
- Ductal Carcinoma In Situ (DCIS): a non-obligate precursor to invasive carcinoma stratified by nuclear grade and presence of comedo necrosis;
- Invasive Ductal Carcinoma, No Special Type (IDC-NST): the most common invasive malignancy, accounting for approximately 75% of cases;
- Invasive Lobular Carcinoma (ILC): characterised by single-file infiltration and E-cadherin loss;
- Special-type carcinomas (mucinous, tubular, metaplastic, cribriform): each with distinct morphological and prognostic profiles.

**METHODS**

**Protocol and Registration**

The review protocol was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The PICO framework guided the formulation of the research question: Population (patients with breast tissue specimens or breast pathology), Intervention/Index test (histopathological examination), Comparator (normal or benign breast tissue), and Outcome (identification of early malignant histopathological changes).

**Search Strategy**

A comprehensive and reproducible electronic search was conducted across the following databases: PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science Core Collection. The search was restricted to studies published between January 1990 and December 2024 and limited to English, Arabic, French, and German language publications. The following Medical Subject Headings (MeSH) and free-text terms were employed:

- ("breast neoplasm*" OR "breast carcinoma" OR "breast cancer" OR "mammary carcinoma")
- AND ("histopatholog*" OR "morpholog*" OR "histolog*" OR "microscop*")
- AND ("early change*" OR "precursor" OR "pre-invasive" OR "in situ" OR "atypical hyperplasia" OR "nuclear grade" OR "DCIS" OR "LCIS" OR "ADH")

Reference lists of included studies and relevant systematic reviews were also manually screened to identify additional eligible publications. Grey literature, conference proceedings, and institutional reports were searched via OpenGrey and ProQuest Dissertations & Theses.

**Eligibility Criteria**

Studies were considered eligible if they: (i) included histopathological analysis of breast tissue from human

subjects; (ii) reported morphological characteristics of at least one non-invasive, or invasive breast lesion; (iii) had a sample size of ≥30 patients; and (iv) employed standardised pathological assessment criteria (WHO Classification of Tumours of the Breast, 5th edition or equivalent). Studies were excluded if they: (i) were purely molecular or genomic without concurrent histomorphological analysis; (ii) included only animal models; (iii) were case reports or case series with fewer than 10 cases; (iv) were duplicate publications.

**Study Selection and Data Extraction**

Two independent reviewers (A.M.A. and O.A.) screened titles and abstracts using Covidence systematic review software. Full-text articles were retrieved for all potentially eligible studies, and final inclusion decisions were made jointly. Disagreements were resolved by consensus or consultation with a third reviewer. Data extraction was performed on a pre-piloted standardised form encompassing: study design, geographic setting, sample size, patient demographics, diagnostic criteria employed, histopathological features reported, IHC markers used, and outcomes.

**Quality Assessment**

The methodological quality of diagnostic accuracy studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool, evaluating four domains: patient selection, index test, reference standard, and flow and timing. Cohort and cross-sectional studies were assessed using the Newcastle–Ottawa Scale (NOS). Risk of bias was rated as low, high, or unclear for each domain.

**Statistical Analysis**

Meta-analytic pooling was performed using the random-effects model (DerSimonian–Laird method) to account for anticipated between-study heterogeneity. For diagnostic accuracy meta-analysis, summary sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and diagnostic odds ratios (DOR) were calculated using a bivariate mixed-effects model. Summary receiver operating characteristic (SROC) curves were generated, and the area under the SROC curve (AUC) was reported. Heterogeneity was assessed using Cochran's Q statistic and the $I^2$ index. $I^2$ values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively. Publication bias was evaluated using the Deeks' funnel plot asymmetry test. All statistical analyses were performed using R (version 4.3.1) with the 'meta', 'mada', and 'metafor' packages.

## RESULTS

**Study Selection and Characteristics**

The initial database search yielded 4,312 unique records after deduplication. Following title and abstract screening, 842 full-text articles were retrieved. Of these, 187 studies fulfilled the inclusion criteria and were included in the systematic review; 124 studies provided sufficient quantitative data for inclusion in the meta-analysis. The included studies represented data from 96,450 patients across 34 countries. Publication dates ranged from 1990 to 2024, with 63% published after 2010. Study designs included: retrospective cohort studies (n=104), prospective cohort studies (n=38), cross-sectional studies (n=27), and case-control studies (n=18). Geographic representation spanned Europe (38%), North America (27%), Asia (21%), the Middle East (7%), and other regions (7%).

**Early Cytological Changes**

Nuclear pleomorphism was the most consistently reported early feature across non-invasive and invasive lesions. Pooled sensitivity for nuclear pleomorphism in distinguishing malignant from benign breast tissue was 82.4% (95% CI: 78.1–86.3%), with specificity of 74.2% (95% CI: 69.8–78.5%). Increased nuclear-to-cytoplasmic (N:C) ratio was reported in 94% of included DCIS studies and 98% of IDC studies.

Loss of cellular polarity was observed as an early change in both ductal and lobular in situ lesions. Prominent nucleoli were identified as a reliable marker of high-grade lesions, with a pooled sensitivity of 71.3% (95% CI: 65.4–76.8%) for high-grade DCIS. Abnormal mitotic figures—including tripolar, ring-form, and asymmetric mitoses—were present in 88% of high-grade DCIS and 96% of grade 3 invasive carcinomas.

**Architectural and Structural Alterations**

Loss of the myoepithelial layer was the most specific histological indicator of invasive carcinoma, with a pooled specificity of 96.8% (95% CI: 94.2–98.4%) and a positive likelihood ratio of 18.7 (95% CI: 12.3–28.4). IHC markers confirming myoepithelial loss (p63, smooth muscle actin, calponin) demonstrated higher discriminatory accuracy than haematoxylin and eosin (H&E) alone (AUC 0.97 vs 0.81, $p<0.001$).

Stromal desmoplasia—characterised by dense collagenous stroma with activated myofibroblasts—was identified in 89% of invasive carcinomas but only 12% of in situ lesions. Peritumoural lymphovascular invasion, identified in 34.7% of invasive carcinomas, was strongly associated with axillary lymph node metastasis (OR 4.2, 95% CI: 3.1–5.7). Basement membrane disruption, as assessed by type IV collagen and laminin staining, was detectable at the earliest stages of microinvasion.

**Necrosis, Calcification, and Intraluminal Changes**

Comedo-type necrosis was present in 52.3% of high-grade DCIS cases and was associated with a significantly higher risk of disease recurrence following breast-conserving surgery (OR 2.84, 95% CI: 2.11–3.82). Microcalcifications detectable on mammography corresponded to specific histological subtypes: laminated (psammomatous) calcifications were

predominantly associated with low-grade DCIS, while amorphous, granular calcifications were characteristic of comedo-type high-grade DCIS. Intraluminal secretions with apocrine-type change were noted in FEA and some low-grade DCIS lesions.

**Immunohistochemical Correlates of Early Malignancy**

E-cadherin expression was lost in 96.4% of lobular carcinomas (both in situ and invasive), confirming its role as a hallmark of lobular differentiation and a reliable IHC discriminator from ductal lesions. High Ki-67 labelling index (>30%) was associated with high-grade DCIS, grade 3 IDC, and triple-negative breast cancer, and served as an independent predictor of early recurrence (HR 2.31, 95% CI: 1.74–3.07). HER2 overexpression was identified in 15–20% of invasive carcinomas and was strongly associated with HER2-enriched molecular subtype and comedo-DCIS.

Oestrogen receptor (ER) positivity was demonstrated in over 95% of FEA and ADH cases, suggesting a shared hormonal milieu along the low-grade pathway. Loss of ER expression in high-grade lesions was associated with basal-like and triple-negative phenotypes. P53 overexpression (surrogate for TP53 mutation) was identified in 67% of high-grade DCIS and 74% of grade 3 IDC cases.

**Heterogeneity and Publication Bias**

Moderate-to-high heterogeneity was observed for most pooled estimates ($I^2$ range: 52–67%), attributable to variability in reference standards, patient demographics, specimen processing, and diagnostic criteria. Subgroup analysis by geographic region, study design, and WHO classification edition used reduced heterogeneity to acceptable levels ($I^2 < 40\%$) for nuclear grade and myoepithelial markers. The Deeks' funnel plot test revealed no significant publication bias for the primary outcomes ($p > 0.10$).

**Comprehensive Comparative Table of Early Histopathological Changes**

Table 1 provides a systematic comparison of early histopathological features across the principal non-invasive and invasive breast pathological entities encompassed in this review. Features are evaluated across nineteen morphological, structural, and immunohistochemical parameters. Abbreviations are explained in the legend below the table.

**Table 1. Comparative Early Histopathological Features Across Non-Invasive and Invasive Breast Pathological Entities**

| **Histopathological Feature** | **NON-INVASIVE LESIONS** | | | | **INVASIVE MALIGNANT LESIONS** | | | |
|---|---|---|---|---|---|---|---|---|
| **Feature** | **DCIS** | **LCIS (Classic)** | **ADH** | **FEA** | **IDC** | **ILC** | **Mucinous Ca** | **Metaplastic Ca** |
| Cell Size | Variably enlarged | Small, uniform | Mild enlargement | Slightly enlarged | Moderate–markedly enlarged | Small–medium | Medium, uniform | Variable; large |
| Nuclear Pleomorphism | Low–High grade | Low grade (uniform) | Low–intermediate | Low–intermediate | Moderate–high | Low–moderate | Low–moderate | High (spindle/squamoid) |
| Nuclear Membrane | Irregular (HG) | Smooth, round | Slightly irregular | Slightly irregular | Irregular, thickened | Irregular | Smooth to mildly irregular | Highly irregular |
| Nucleoli | Inconspicuous (LG) to prominent (HG) | Inconspicuous | Inconspicuous | Inconspicuous–small | Prominent (HG) | Inconspicuous | Small, inconspicuous | Prominent |
| Chromatin Pattern | Fine–coarse (grade dep.) | Clumped, dark | Fine, evenly distributed | Fine, open | Coarse, irregular | Fine to coarse | Pale, vesicular | Coarse, hyperchromatic |
| Mitotic Activity | Rare (LG) to numerous (HG) | Rare to absent | Rare | Rare | Moderate–high (HG) | Low | Low–moderate | Variable, often high |
| Cell Polarity | maintained or Lost | Lost | Maintained | Maintained | Lost | Lost | Maintained | Lost |
| Architecture / Growth Pattern | Solid, cribriform, | Discohesive lobular | Cribriform or micropapi | Flat/columnar epithelium | Irregular infiltrative nests/cords/t | Single-file pattern | Nests/clusters in extracell | Sheets; squamoid/spindle |

| | micropapillary, papillary | pagetoid spread | llary; 2 cell pops | with atypia | ubules | | ular mucin pools | differentiation |
|---|---|---|---|---|---|---|---|---|
| Basement Membrane / Invasion | Intact (in situ) | Intact (in situ) | Intact | Intact | Disrupted; stromal invasion present | Disrupted; single-file invasion | Disrupted | Disrupted |
| Stromal Changes | Periductal fibrosis | Minimal | Mild periductal fibrosis | Minimal | Desmoplastic, dense fibrosis | Desmoplastic fibrosis | Abundant extracellular mucin | Desmoplastic stroma; chondroid/osseous |
| Necrosis | Comedo-type (HG DCIS) | Absent | Absent | Absent | Present (HG) | Rare | Rare | Focal |
| Calcification | Laminated (LG), amorphous (HG) | Absent/rare | Absent/rare | Psammomatous or absent | Dystrophic; variable | Rare | Absent or rare | Absent or rare |
| E-Cadherin Expression | Positive | Negative (loss) | Positive | Positive | Positive | Negative (loss) | Positive | Variable |
| Ki-67 Proliferation Index | Low (LG) to high (HG) | Low | Low–moderate | Low | Moderate–high | Low–moderate | Low–moderate | High |
| ER/PR Status | ER+ (LG), ER- (HG) | ER+ | ER+ | ER+ | Variable (luminal A/B: ER+; TN: ER-) | ER+ | ER+ | ER-/HER2- (often triple-neg) |
| HER2 Overexpression | Positive (HG comedo) | Negative | Negative | Negative | Overexpressed (15–20%) | Rare | Rare | Negative (>90%) |
| Apocrine Features | May be present (LG) | Absent | Absent | May be present | Occasional | Rare | Absent | Absent |
| Myoepithelial Layer (p63/SMA) | Present | Present | Present | Present | Absent | Absent | Absent | Absent |
| Lobular Involvement / Pagetoid Spread | Absent typically | Hallmark feature | Absent | Absent | Absent | Common | Absent | Absent |

***Table 1 Legend.*** DCIS = Ductal Carcinoma In Situ; LCIS = Lobular Carcinoma In Situ; ADH = Atypical Ductal Hyperplasia; FEA = Flat Epithelial Atypia; IDC = Invasive Ductal Carcinoma (No Special Type); ILC = Invasive Lobular Carcinoma; LG = Low Grade; HG = High Grade; HG dep. = grade dependent; ER = Oestrogen Receptor; PR = Progesterone Receptor; SMA = Smooth Muscle Actin; TN = Triple Negative; Ca = Carcinoma.

## DISCUSSION

### Nuclear and Cytological Changes as Earliest Indicators

Our meta-analysis confirms that nuclear pleomorphism, increased N:C ratio, and loss of cellular polarity represent the earliest and most consistently identifiable features of malignant transformation in the breast. These findings are consistent with the conceptual framework proposed by Page and colleagues and subsequently refined in the WHO Classification of Tumours of the Breast. Nuclear atypia grades 1 through 3 underpin the Nottingham Grading System, which remains the most widely validated prognostic tool in routine pathological practice.

An important and clinically challenging distinction is between ADH and low-grade DCIS. Both lesions exhibit cytologically similar cells with low-grade nuclear features; however, the key discriminating features—notably extent (spanning more than two complete duct spaces or measuring >2 mm) and architectural uniformity—continue to generate interobserver variability. Our pooled data suggest that a rigid application of extent criteria combined with IHC for cytokeratin 5/6 (expressed in UDH but absent or

reduced in ADH/low-grade DCIS) significantly improves reproducibility.

**Myoepithelial Layer Disruption as the Critical Inflection Point**

Perhaps the most clinically decisive early histopathological event in breast malignancy is the loss of the myoepithelial cell layer. This event marks the transition from in situ to invasive carcinoma and is irreversible. Our meta-analysis demonstrates that IHC-confirmed myoepithelial loss is the single most specific indicator for invasive disease (pooled specificity 96.8%). The dual-marker approach using p63 (nuclear) and smooth muscle actin or calponin (cytoplasmic) is now well-established and our pooled data support its routine application in diagnostically challenging cases.

It is noteworthy that incomplete or attenuated myoepithelial layers may be encountered in sclerosing adenosis, radial scars, and some forms of benign complex sclerosing lesions, which can closely simulate invasive carcinoma on H&E. This emphasises the critical role of IHC confirmation before diagnosing invasion in morphologically ambiguous specimens.

**Stromal Desmoplasia and the Tumour Microenvironment**

Desmoplastic stromal reaction represents a paradigmatic early change at the leading edge of invasive breast carcinoma and reflects a complex interplay between tumour cells and activated cancer-associated fibroblasts (CAFs). Our analysis reveals that periductal fibrosis in DCIS may represent a pre-invasive form of this stromal remodelling process. The transition from periductal concentric fibrosis in DCIS to diffuse desmoplasia in IDC likely involves transforming growth factor-β (TGF-β) signalling pathways, matrix metalloproteinase (MMP) activity, and cross-linked collagen deposition. These stromal changes are not merely passive accompaniments of malignancy but active drivers of invasion and metastasis.

**Flat Epithelial Atypia and the Low-Grade Pathway**

FEA has attracted substantial attention as the morphological embodiment of the earliest recognisable neoplastic step along the low-grade pathway. Although long-term follow-up data demonstrate that pure FEA carries a relatively low absolute risk of subsequent invasive carcinoma (approximately 3–5% at 10 years), its consistent molecular resemblance to low-grade DCIS and tubular carcinoma—shared LOH at chromosomes 16q, 17p, and 11q13; universal ER positivity; and absence of E-cadherin alteration—underscores its biological significance. Our meta-analysis supports the clinical practice of complete excision when FEA is identified on core needle biopsy due to co-existing higher-risk lesions found at subsequent surgery in 15–30% of cases.

**Lobular Versus Ductal Pathways: The Role of E-Cadherin**

The consistent loss of E-cadherin—the transmembrane glycoprotein responsible for homotypic cell adhesion—in lobular neoplasia fundamentally distinguishes the lobular pathway from all other breast entities. Our meta-analysis confirms near-universal E-cadherin loss in both LCIS and ILC (96.4%). The molecular consequence of CDH1 gene inactivation is complete disruption of adherens junctions, resulting in the characteristic discohesive single-cell infiltration and pagetoid spread that define lobular morphology. Pathologists encountering diagnostically ambiguous cases—particularly pleomorphic LCIS versus solid-type DCIS—should routinely employ E-cadherin IHC, as treatment implications significantly differ.

**High-Grade DCIS and Risk of Invasive Progression**

High-grade DCIS with comedo necrosis carries the highest risk of synchronous microinvasion and subsequent invasive recurrence among all non-invasive lesions. Our pooled odds ratio of 4.71 (95% CI: 3.44–6.45) for progression from high-grade DCIS to invasive carcinoma is concordant with natural history studies and surgical pathology data. The presence of HER2 amplification, TP53 mutation, and a high Ki-67 index within DCIS appears to define a molecularly aggressive subset that warrants close surveillance or surgical intervention. The optimal management of high-grade DCIS—particularly the debate surrounding omission of surgery in older, lower-risk patients—remains an active area of clinical investigation.

**Special-Type Carcinomas: Mucinous and Metaplastic Carcinomas**

Among special-type invasive carcinomas, mucinous (colloid) carcinoma is characterised by tumour cells floating in abundant extracellular mucin pools, with low nuclear grade, low mitotic activity, and generally favourable prognosis. Metaplastic carcinoma, in contrast, is an aggressive triple-negative malignancy in which the neoplastic epithelium undergoes divergent differentiation into squamous, spindle, chondroid, or osseous elements. The histopathological recognition of these distinct entities is important, as they require different prognostic frameworks and, in the case of metaplastic carcinoma, typically exhibit relative resistance to conventional chemotherapy.

**LIMITATIONS**

This systematic review is subject to several limitations. First, moderate-to-high heterogeneity between included studies limits the precision of pooled estimates. Second, the majority of included studies were retrospective in design, introducing potential selection and information bias. Third, there was significant variability in the IHC panels, antibody clones, scoring systems, and cut-off values used across studies, particularly for Ki-67 and HER2. Fourth, this review focussed predominantly on

female breast cancer; male breast cancer, which accounts for approximately 1% of all cases, was not separately analysed. Fifth, evolving diagnostic entities such as encapsulated papillary carcinoma and tall cell carcinoma with reversed polarity were inadequately represented in the included literature.

## CONCLUSIONS

This systematic review and meta-analysis provides the most comprehensive synthesis to date of early histopathological changes across the spectrum of breast carcinomas. Our findings confirm that the transition from normal breast tissue to invasive carcinoma is accompanied by a reproducible and recognisable constellation of morphological changes that can be detected at early stages with standard haematoxylin and eosin staining, substantially augmented by targeted IHC.

The key early histopathological indicators of malignant transformation are: (1) nuclear pleomorphism with irregular nuclear membranes and prominent nucleoli; (2) increased mitotic activity, especially abnormal mitoses; (3) loss of cellular polarity and architectural distortion; (4) disruption or loss of the myoepithelial cell layer; (5) stromal desmoplasia and peritumoural fibrosis; (6) comedo-type necrosis in high-grade DCIS; and (7) E-cadherin loss in lobular neoplasia. Comprehensive IHC profiling—including E-cadherin, p63, SMA, Ki-67, ER, PR, and HER2—remains indispensable in diagnostically challenging cases and for prognostic subclassification.

The comparative histopathological table presented in this review (Table 1) is intended to serve as a practical reference tool for diagnostic pathologists, oncologists, breast surgeons, trainees, and educators. Future high-quality prospective studies should aim to standardise histopathological criteria, IHC protocols, and reporting frameworks to reduce diagnostic heterogeneity and optimise patient outcomes.

### Author Contributions

A.M.A.: Conceptualisation, study design, systematic search, data extraction, quality assessment, statistical analysis, manuscript writing, and final approval. O.A.: Study selection, data extraction, quality assessment, critical revision of the manuscript, and final approval. All authors have read and agreed to the published version of the manuscript.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Conflicts of Interest

The authors declare no conflict of interest.

### Institutional Review Board Statement

As this is a systematic review and meta-analysis of previously published studies, ethical approval and informed consent were not required. All included studies were conducted in accordance with the Declaration of Helsinki.

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