Immunohistochemical Subtype Conversion After Neoadjuvant Chemotherapy and Its Impact on Breast Cancer Survival: A Systematic Review and Meta-analysis

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Abstract

Background: Neoadjuvant chemotherapy (NAC) may alter tumor biology, leading to immunohistochemical (IHC) subtype conversions between diagnosis and residual disease. The prognostic impact of such changes remains unclear. This systematic review and meta-analysis evaluated the effect of NAC-induced IHC subtype conversion on overall survival (OS) and disease-free survival (DFS) in patients with residual disease (non-pCR).

Methods: This study was registered in PROSPERO (CRD42024558811). PubMed, EMBASE, and Cochrane Library were searched through 2025 for studies reporting IHC subtype conversions after NAC and associated survival outcomes in non-pCR patients. Eligible studies included randomized trials and observational cohorts of adult women with primary breast cancer. Two reviewers independently selected studies and extracted data. Risk of bias was assessed using the Newcastle-Ottawa Scale and Cochrane tool. Pooled risk ratios (RRs) were calculated using random-effects models. Heterogeneity was quantified with I^2, and publication bias was assessed by Egger's test.

Results: **Twenty-five retrospective studies (n=5,263 non-pCR patients) were included.** Mean patient age ranged from 46–54 years, and tumors were predominantly T2–T3. **IHC subtype conversion occurred in 20% [95% CI: 0.17–0.24]**, with high heterogeneity (I^2=89.8%). **Common conversions included luminal-to-TNBC (35%), luminal-to-HER2+ (25%), HER2+-to-luminal (20%), and TNBC-to-luminal (20%). Patients without subtype conversion had significantly better OS (RR=1.13 [95% CI: 1.01–1.26], p=0.03; I^2=62%). Luminal tumors showed the greatest OS benefit without conversion (RR=1.19 [1.01–1.41], p=0.04)**, while HER2+ (RR=1.11 [0.95–1.31], p=0.19) and TNBC (RR=0.98 [0.84–1.16], p=0.85) showed no significant OS impact. DFS was not significantly affected by conversion overall (RR=0.95 [0.80–1.14], p=0.58; I^2=79%). Sensitivity analysis confirmed OS findings. Egger's test revealed no publication bias for OS (p=0.33) but suggested bias for luminal DFS (p=0.044).

Conclusion: **IHC subtype conversion after NAC occurs in 1 in 5 patients with residual disease and is associated with worse OS—particularly in luminal breast cancer.** Routine post-NAC IHC reassessment should be considered to improve prognostication and guide adjuvant treatment. Prospective studies with standardized reporting are needed to validate these findings and refine treatment algorithms.

Introduction

Breast cancer remains the most frequently diagnosed cancer in women worldwide, accounting for approximately 2.3 million new cases annually. Despite advances in early detection and systemic therapy, breast cancer continues to be a leading cause of cancer-related death. Over recent decades, breast cancer management has shifted from uniform treatment approaches to precision medicine paradigms, fundamentally transforming patient outcomes.

Neoadjuvant chemotherapy (NAC) has become a cornerstone in the management of both locally advanced and early-stage breast cancer, enabling breast-conserving surgery, assessing tumor biology in vivo, and providing prognostic information through pathological complete response (pCR) evaluation. Immunohistochemistry (IHC) plays a central role in breast cancer characterization through evaluation of estrogen receptor (ER), progesterone receptor (PR), and HER2, guiding clinical decisions regarding endocrine therapy, HER2-targeted treatment, and chemotherapy.

However, NAC can substantially modify biomarker expression, with reported conversion rates ranging from 8% to 55%, most commonly involving hormone receptors and HER2. These dynamic shifts have direct implications for treatment eligibility and prognosis. Despite increasing recognition of biomarker conversion, its clinical significance remains poorly defined, with no consensus on prognostic value or standardized guidelines for treatment modification. This systematic review and meta-analysis evaluated the prevalence, patterns, and prognostic significance of IHC biomarker conversion following NAC to clarify whether reassessment of ER, PR, and HER2 status should be integrated into routine clinical practice.

Methods and Materials

Study Design and Protocol Registration

This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 statement to ensure methodological rigor and transparent reporting. The review protocol was developed prospectively and formally registered in PROSPERO (CRD42024558811), with methodology predetermined and documented to minimize bias and enhance reproducibility.

Search Strategy

A comprehensive systematic literature search was conducted across multiple electronic databases including PubMed/MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar from database inception through June 2025, with no language restrictions. The search strategy was developed in collaboration with a medical librarian and utilized Medical Subject Headings (MeSH) terms and free-text keywords including: ("breast neoplasms" OR "breast cancer") AND ("neoadjuvant therapy" OR "neoadjuvant chemotherapy") AND ("immunohistochemistry" OR "biomarkers" OR "receptor conversion") AND ("estrogen receptor" OR "progesterone receptor" OR "HER2") AND ("survival" OR "prognosis" OR "mortality").

Eligibility Criteria

Studies were eligible if they involved adult women (≥18 years) with histologically confirmed invasive breast cancer who received neoadjuvant chemotherapy followed by surgical resection, with assessment of immunohistochemical biomarker expression (ER, PR, HER2) both before and after treatment, documentation of biomarker conversion status, reporting of survival outcomes (OS and/or DFS), minimum sample size of ≥50 evaluable patients, and adequate methodological quality. Studies were excluded if they involved only metastatic breast cancer, lacked paired pre- and post-treatment biomarker assessments, had insufficient survival data or follow-up, were case reports/series with <50 patients, focused exclusively on neoadjuvant endocrine therapy without chemotherapy, or had substantial missing data.

Study Selection and Data Extraction

The study selection process was conducted independently by two reviewers using a standardized approach. Initial screening involved review of titles and abstracts using predefined eligibility criteria. Data extraction was performed using a comprehensive, standardized form designed specifically for this review, piloted on five included studies to ensure completeness and reproducibility.

Quality Assessment

Risk of bias was evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool, which evaluates seven domains:

(1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported result.

Each domain was independently assessed by two reviewers and classified as low, moderate, serious, or critical risk of bias.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.0) with the meta, metafor, and survival packages. Random-effects models were employed for all analyses using the DerSimonian-Laird method. Pooled proportions with 95% confidence intervals were calculated for biomarker conversion rates. Primary analysis compared survival outcomes using Risk Ratios (RR) with 95% confidence intervals between patients with and without biomarker conversion. Statistical heterogeneity was quantified using I^2 statistic (25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity), Cochran's Q test (p<0.10), and Tau². Publication bias was evaluated using funnel plots and Egger's regression test. Statistical significance was set at p<0.05 for all analyses except heterogeneity testing (p<0.10). All tests were two-sided, and multiple comparison adjustments were applied using the Bonferroni correction when appropriate.

Results

The systematic literature search identified 295 records across five databases. After removing 113 duplicate and automatically generated records, 182 unique records underwent initial screening. Following title and abstract review, 142 reports were sought for full-text retrieval, of which 100 were successfully obtained and assessed for eligibility. After comprehensive full-text review, 76 studies were excluded due to inadequate survival outcome reporting, resulting in 24 studies included in the final systematic review and meta-analysis [8, 10, 14-35].

The study selection process is summarized in Figure 1 PRISMA Flowchart diagram [13, 36].

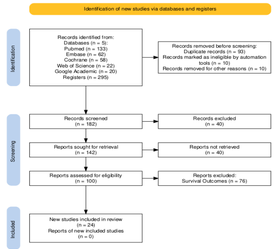


Figure 1. Prisma Flowchart.

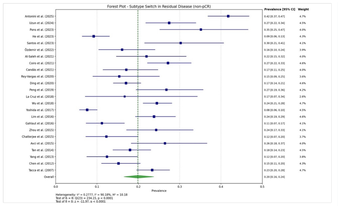


Figure 2. Forest Plot of Immunohistochemical Subtype Conversion Prevalence in Breast Cancer Patients with Residual Disease After NAC

Prevalence of Immunohistochemical Subtype Conversion

The pooled analysis revealed an overall prevalence of 0.20 (95% CI: 0.16-0.24), indicating that approximately 20% of patients with residual disease experienced molecular subtype conversion following neoadjuvant chemotherapy. Substantial heterogeneity was observed across studies (I^2 = 90.18%, p < 0.0001), likely reflecting differences in patient populations, treatment protocols, and biomarker assessment methodologies (Figure 2).

Survival Outcomes Meta-Analysis

Patients without molecular subtype conversion demonstrated a statistically significant survival advantage with a risk ratio of 1.13 (95% CI: 1.01-1.26, p = 0.03), indicating a 13% higher chance of survival compared to those experiencing biomarker conversion. Moderate heterogeneity was observed (I^2 = 62.0%, Tau² = 0.01, p = 0.01), and Egger's test showed no evidence of publication bias (p = 0.33). Disease-free survival analysis revealed no statistically significant difference between groups (RR: 0.95, 95% CI: 0.80-1.14, p = 0.58) with substantial heterogeneity (I^2 = 79.0%, Tau² = 0.04, p = 0.0002) and no publication bias (p = 0.25). Figure 3 presents the forest plots of survival outcomes associated with biomarker conversion in breast cancer.

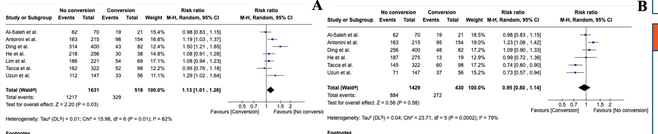


Figure 3. Forest plots of survival outcomes all breast cancer conversion. (A) Overall Survival; (B) Disease-Free Survival (DFS).

Discussion

To our knowledge, this is the first systematic review and meta-analysis to evaluate the prevalence, patterns, and prognostic implications of IHC biomarker conversion following NAC in breast cancer. Approximately 20% of patients with residual disease experience IHC subtype conversion after NAC, and biomarker stability is associated with superior OS, particularly in luminal tumors. Patients without biomarker conversion had a 13% higher chance of OS (RR: 1.13; 95% CI: 1.01–1.26; p = 0.03), with a more pronounced effect in luminal subtypes (RR: 1.19; 95% CI: 1.01–1.41; p = 0.04). These findings confirm the clinical relevance of reassessing ER, PR, and HER2 on surgical specimens, as changes directly influence adjuvant therapy decisions [38].

Hormone receptor loss emerged as the most significant pattern, consistently associated with worse survival [39], while receptor gain may enable additional therapeutic opportunities. Although HER2 conversion did not significantly impact OS, the transition from HER2-positive to HER2-low has relevant therapeutic implications in the era of antibody–drug conjugates [40].

Our findings highlight an unresolved clinical dilemma: how should adjuvant therapy be adapted when biomarker profiles change after NAC? No consensus exists regarding the management of patients who lose HR or HER2 expression or gain HER2 positivity in residual disease. These scenarios demand clarification on whether standard adjuvant therapies remain effective or require modification.

By integrating data from nearly 6,000 patients, our meta-analysis strengthens the evidence that biomarker conversion is frequent and clinically meaningful. It also exposes the absence of high-level evidence to guide adjuvant treatment decisions, underscoring the need for prospective studies evaluating therapy adaptation according to post-NAC receptor status.

Biomarker conversion likely reflects tumor heterogeneity and chemotherapy-induced clonal selection rather than pure phenotypic transformation [3,31]. This "unmasking" mechanism may explain worse outcomes in cases of HR or PR loss and supports systematic retesting.

High heterogeneity (I^2 = 90.2%) was observed, related to differences in IHC thresholds, NAC regimens, and population backgrounds—most studies (58%) originated from Asia, limiting external validity. Furthermore, few studies addressed modern therapeutic contexts, including immunotherapy [42–44] or HER2-low classification.

Importantly, no included studies detailed how adjuvant treatments were adapted after biomarker conversion. For luminal tumors, ER loss after NAC raises uncertainty about the benefit of continuing endocrine therapy, while HER2-positive tumors converting to HER2-negative pose a similar therapeutic dilemma. The prognostic impact appears subtype-dependent, being more deleterious in ER+/HER2– tumors that convert to triple negative.

Current ASCO guidelines do not mandate post-NAC IHC reassessment [45]; however, our data support its routine use, particularly to identify patients converting to triple-negative phenotype, associated with poor prognosis [39]. Future research should prioritize prospective validation with standardized IHC protocols and evaluate whether therapy modification based on receptor changes improves outcomes. Incorporating complementary biomarkers such as TILs [46] and molecular predictors may further refine individualized treatment strategies.

Conclusions

This systematic review and meta-analysis show that IHQ biomarker conversion occurs in about 20% of breast cancer patients with residual disease after neoadjuvant chemotherapy. Biomarker stability—especially in luminal subtypes—is linked to improved overall survival, reinforcing its prognostic value. Reassessment of ER, PR, and HER2 on surgical specimens is essential, as post-NAC changes can modify treatment eligibility and guide adjuvant therapy. In the era of precision oncology, routine post-NAC IHC profiling should guide risk stratification and optimize care. **Prospective studies must confirm whether adapting treatment based on these changes improves survival.**

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