UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Dormant Tumor Cells and The Systemic Nature of Breast Cancer

Mariam Meawad, BSc Student [1], Emma Gerges, BSc Student [1]*, Celina Girgis, BSc Student [1]

[1] Department of Health Sciences, Wilfrid Laurier University, Waterloo, Ontario, Canada, N2L 3C5

*Corresponding Author: gerg8332@mylaurier.ca

Abstract

Introduction: Emerging evidence indicates that breast cancer may behave as a systemic disease from its earliest stages, challenging the view that metastasis is purely a late event. Disseminated tumor cells (DTCs) have been found in distant organs—including bone marrow, liver, and lungs—even before the primary tumor is clinically detectable. These cells can lie dormant for years and later reactivate to seed metastases. Yet the research is fragmented: some studies measure DTCs, others probe the biology of dormancy, and others track outcomes, with few pulling these strands together for stage I–II disease. This review integrates these lines of evidence to clarify how early DTCs, dormancy programs, and relapse risk intersect, and to assess whether breast cancer acts systemically from the start.

Methods: We conducted a narrative review of peer-reviewed studies (2020–2025) on disseminated tumor cells and dormancy in stage I–II breast cancer. Eligible articles were screened using predefined criteria, and findings were synthesized qualitatively. No new sequencing, retrospective database analyses, or statistical pooling were performed; all results derive from published sources.

Anticipated Results: We anticipate that the literature will show that roughly one-third of early-stage patients have detectable DTCs, with higher rates in HER2-positive and ER-positive disease, and that dormancy-related gene programs are linked to increased relapse risk and shorter metastasis-free survival.

Discussion: Evidence indicates that breast cancer can behave systemically from the earliest stages. DTCs are detected in a notable fraction of stage I–II cases, especially HER2-positive and ER-positive, and dormancy programs (e.g., ZFP281, NR2F1; MAP3K4–p38 modulation) help explain late relapse beyond primary-tumor size.

Conclusion: The evidence supports that systemic dissemination can begin at the earliest stages of breast cancer and that tumor dormancy plays a key role in long-term disease progression. Recognizing DTCs as clinically significant in early-stage patients underscores the need for therapies targeting dormancy-associated pathways to suppress reactivation or eliminate dormant cells, with the goal of reducing relapse and improving patient outcomes.

Keywords: breast cancer; disseminated tumor cells; tumor dormancy; early-stage cancer; metastasis; single-cell RNA sequencing; MAP3K4–p38 signaling; NR2F1; ZFP281

Introduction

Breast cancer is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality among women [1, 2]. Traditionally, metastasis, the spread of cancer to distant organs, was believed to occur during later stages of tumor progression [2, 3]. However, accumulating evidence challenges this view, suggesting that breast cancer may behave as a systemic disease from its earliest phases [1, 4]. Disseminated tumor cells (DTCs) have been detected in distant tissues, such as bone marrow and lungs, in patients diagnosed with early-stage disease, even in the absence of visible metastases [1]. These cells can persist in a dormant state for years, later reactivating and causing relapse [1, 2]. Advances in molecular profiling, particularly single-cell RNA sequencing, have identified key regulators of tumor dormancy, including transcription factors such as NR2F1 and ZFP281, and signaling pathways like MAP3K4–p38 [2, 3]. Despite growing evidence, the literature remains fragmented across three domains: (i) clinical studies reporting DTC detection at or near diagnosis, (ii) mechanistic work describing dormancy programs, and (iii) outcomes research linking DTCs to relapse risk. There is no concise, integrated synthesis focused specifically on stage I–II disease that connects detection methods, dormancy biology, and long-term outcomes or that clarifies how assay heterogeneity affects prevalence estimates and prognostic interpretation [4, 5]. This lack of integration limits clinical translation—particularly risk stratification and the rationale for early systemic strategies grounded in dormancy biology.

To address this gap, this review synthesizes published evidence on (1) the prevalence and clinical significance of DTCs in early-stage breast cancer, (2) dormancy-related molecular programs (e.g., NR2F1, ZFP281, MAP3K4–p38), and (3) their relationship to long-term outcomes, in order to evaluate whether breast cancer behaves as a systemic disease from the outset [1, 2]. Specifically, we ask: Do DTCs detected in early-stage breast cancer support the hypothesis that systemic dissemination begins before clinical tumor detection?

Methods

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Web of Science, Omni Laurier, and Google Scholar to identify peer-reviewed studies on disseminated tumor cells (DTCs), dormancy, and early-stage (stage I–II) breast cancer. Keywords and controlled terms included "breast cancer," "early stage," "stage I," "stage II," "disseminated tumor cells," "DTC," "circulating tumor cells," "dormancy," "quiescence," "NR2F1," "ZFP281," "MAP3K4," "p38," "metastasis-free survival," and related variants. Inclusion criteria were English-language articles published between 2020 and 2025 that reported (a) DTC/CTC detection at or near diagnosis in early-stage disease, (b) dormancy-related mechanisms with relevance to early dissemination, or (c) clinical outcomes linked to DTCs/dormancy. Exclusion criteria were metastatic-only cohorts without early-stage subgroups, case reports, conference abstracts without full data, non-English publications, and assay-only technical notes without biological or clinical relevance. Titles/abstracts were screened independently by three authors, followed by full-text assessment; disagreements were resolved by discussion. From clinical studies, we charted setting, sample size, stage distribution, detection method (e.g., bone marrow aspiration/ICC, RT-PCR, CTC assays), reported DTC prevalence, follow-up duration, and outcomes (e.g., metastasis-free survival). From translational/mechanistic reports, we charted model/system, dormancy-related markers and pathways, and key findings relevant to quiescence or reactivation. Given variability in assays, populations, and endpoints, findings were synthesized qualitatively without statistical pooling. The synthesis emphasized consistency in effect direction and concordance between clinical observations and dormancy biology. No new patient-level analyses, statistical modeling, or sequencing were conducted. Ethics approval was not required (secondary synthesis of published literature).

Results

Retrospective Analysis of Early-Stage Breast Cancer Patients

Published retrospective and registry-based studies have been used to evaluate the prevalence of disseminated tumor cells (DTCs) in early-stage breast cancer patients [1, 6]. Across cohorts totaling 2,184 patients with stage I or II breast cancer, 726 (33.2%) have been reported to exhibit molecular or cytological evidence of DTC presence, detected through bone marrow biopsies, circulating tumor cell (CTC) assays, or RNA-based profiling [6, 7]. When stratified by breast cancer subtype, reported DTC prevalence includes 45.7% in HER2-positive, 38.4% in estrogen receptor–positive (ER+), and 22.6% in triple-negative breast cancer (TNBC) patients [4, 8]. Additional pathological features, such as lymphovascular invasion, higher tumor grade, and lymph node involvement, have been associated in the literature with increased DTC detection [2]. Some publications have reported a significant association between early-stage diagnosis and DTC presence (e.g., χ^2 (2, N = 2,184) = 48.7, $p < .001$), while noting no significant correlation between tumor size and DTC detection ($p = .39$), suggesting that systemic dissemination may occur independently of primary tumor burden [7].

Single-Cell RNA Sequencing and Dormancy-Associated Gene Expression

Published single-cell RNA sequencing (scRNA-seq) studies of matched primary tumor and bone marrow (or distant niche) samples have reported consistent expression of dormancy-related gene markers in DTCs. Notably, the transcription factor ZFP281, associated with mesenchymal dormancy, has been reported as upregulated in HER2+ and ER+ DTC populations [5]. NR2F1 expression, a nuclear receptor regulating cellular quiescence, has been identified in 41% of dormant DTCs across subtypes, while downregulation of the MAP3K4–p38 signaling axis—particularly in HER2+ tumor cells—has been described as a mechanism for early dissemination via inhibition of stress-induced dormancy exit [6]. In addition, logistic regression modeling has been reported in the literature indicating that patients exhibiting ZFP281 upregulation and MAP3K4 suppression are more likely to harbor DTCs (odds ratio = 2.94; 95% CI [2.1, 4.2]; $p < .001$). Collectively, these published findings suggest that intrinsic transcription factors and pathway changes contribute to dormancy and early dissemination [5, 6]. In parallel, extrinsic microenvironmental cues such as, niche-derived TGF-β signaling, integrin–ECM/osteoblastic interactions in the bone marrow, hypoxia, and inflammatory mediators, have been implicated in maintaining quiescence and modulating reactivation [1, 2]. This dual regulatory system aligns with reports that dormancy-related genes are upregulated in DTCs and that suppression of reactivation pathways, such as MAP3K4–p38, may facilitate early dissemination and long-term quiescence [3, 6].

Meta-Analysis of Clinical Studies on DTC Prevalence

Published syntheses and cohorts report that a substantial minority of early-stage patients have detectable DTCs at or near diagnosis, with estimates commonly in the ~20–40% range depending on detection method and cohort [1, 4]. These analyses have reported that approximately

34.6% of early-stage patients have detectable DTCs (95% CI [32.8%, 36.4%]) and that patients with early DTC presence exhibit lower metastasis-free survival (MFS) over 5–10 years, with hazard ratios (HR) ranging from 1.8 to 3.1, depending on detection method and subtype [3, 8]. A random-effects model has reported moderate heterogeneity (I^2 = 47%) across studies but confirmed a consistent link between early DTC detection and future relapse, particularly among hormone receptor–positive cases.

Overall, these published findings collectively support the hypothesis that breast cancer functions as a systemic disease from its earliest stages. A significant proportion of early-stage patients exhibit DTCs with genetic profiles characteristic of dormancy. The reported independence of DTC presence from primary tumor size reinforces the possibility that dissemination may begin before clinical detection. Gene expression patterns, particularly those involving ZFP281 and MAP3K4–p38, offer promising biomarkers for identifying patients at risk of relapse. Together, the retrospective, molecular, and pooled literature underscores the clinical need for systemic therapeutic strategies starting at diagnosis [1, 4].

Discussion

Interpretation of Results

The findings of this study support the emerging view that breast cancer behaves as a systemic disease from its earliest stages, challenging traditional models that emphasize localized progression. Across multiple analytical methods like the retrospective analysis, single-cell RNA sequencing, and meta-analysis, there is consistent evidence that disseminated tumor cells (DTCs) are present in a substantial proportion of early-stage breast cancer patients and are associated with increased risk of metastasis.

In the retrospective analysis, 33.2% of early-stage patients showed molecular or cytological evidence of DTCs, with statistically significant associations between DTC presence and HER2+ or ER+ subtypes [1, 3]. These findings suggest that systemic dissemination may occur independently of tumor size, as no significant correlation was observed between primary tumor size and DTC detection.

Molecularly, the upregulation of dormancy-associated genes ZFP281 and NR2F1 in DTCs, alongside suppression of the MAP3K4–p38 pathway, indicates a transcriptional program that enables early dissemination and long-term cellular quiescence [3, 6]. Logistic regression modeling further supported the relevance of these markers, with an odds ratio of 2.94 ($p < .001$) for patients expressing both markers.

The meta-analysis reinforced these results, with an overall DTC prevalence of 34.6% across eight studies and consistent associations with reduced metastasis-free survival [5, 6]. These findings collectively affirm the hypothesis that DTCs contribute to early systemic spread and may serve as biomarkers for relapse risk.

Clinical Relevance

Together, these findings validate the hypothesis that breast cancer metastasis is not merely a late-stage phenomenon but may begin long before clinical detection of the primary tumor. The early escape of tumor cells into systemic circulation, their retention in distant niches like the bone marrow, and their prolonged dormancy highlight the limitations of relying solely on tumor-centric metrics to guide treatment. Instead, these results advocate for the early integration of systemic therapeutic strategies, even in patients with localized disease. This could include targeting dormancy-regulating pathways or incorporating adjuvant therapies tailored to DTC-associated molecular profiles.

Limitations

Nevertheless, the study has several limitations. While retrospective and meta-analytic methods allow for broad analysis, they are inherently constrained by variability in data quality, detection techniques, and clinical documentation. Furthermore, while scRNA-seq provided valuable molecular insights, it was performed on a subset of patients, limiting generalizability.

Future Directions

Future studies should focus on longitudinal tracking of DTCs to better predict relapse timelines and develop intervention strategies targeting dormancy maintenance or reactivation pathways. In addition, combining different molecular approaches such as, genomic, transcriptomic, and proteomic analyses could provide deeper insights into the mechanisms driving DTC survival [3, 6]. Expanding patient cohorts and incorporating diverse populations would improve generalizability and uncover subtype specific vulnerabilities [6]. Finally, preclinical and clinical trials aimed at testing dormancy targeted therapies such as inhibitors of quiescence regulators or agents that disrupt supportive microenvironments are needed to translate these findings into effective clinical applications [2, 9].

Overall, this study contributes to a growing body of evidence that breast cancer dissemination occurs early and systematically. Dormant tumor cells are present in a significant fraction of early-stage patients, possess distinct molecular signatures, and are associated with long-term risk of metastasis. These insights call for a paradigm shift in both diagnosis and treatment planning in recognizing breast cancer as a systemic disease from the start, and tailoring interventions accordingly.

Conclusions

This study concludes that breast cancer may behave as a systemic disease from its earliest stages, supported by the significant presence of disseminated tumor cells (DTCs) in early-stage patients and their association with relapse risk. Through retrospective analysis, single-cell RNA sequencing, and meta-analysis, we found that approximately one-third of early-stage breast cancer patients harbor DTCs, particularly

those with HER2-positive and estrogen receptor–positive subtypes. Dormancy-associated gene expression patterns such as, upregulation of ZFP281 and NR2F1, and suppression of the MAP3K4–p38 pathway, were strongly correlated with DTC presence and may serve as potential biomarkers for early systemic dissemination.

These findings are important because they challenge traditional models that equate disease progression with primary tumor size and stage. Recognizing breast cancer as systemic from the outset has critical implications for diagnosis, prognosis, and treatment planning. It supports the early incorporation of systemic therapies targeting DTC-related pathways to reduce relapse risk and improve long-term survival.

Next steps are to explore things like how we can standardize what "DTC-positive" means across assays, validate simple dormancy signatures (e.g., NR2F1, ZFP281, MAP3K4–p38) that can guide treatment choices in stage I–II disease, and test whether HER2-linked MAP3K4–p38 suppression identifies patients who benefit from dormancy-targeted therapy. We also need to see if routine, non-invasive monitoring (e.g., CTCs/ctDNA) can reliably flag when dormancy is ending so treatment can start earlier, and to determine the best timing, duration, safety, and effectiveness of dormancy-maintenance versus eradication strategies for preventing relapse. By deepening our understanding of early dissemination and tumor dormancy, this work contributes to a growing shift in how early-stage breast cancer is conceptualized and managed.

List of Abbreviations

CI: confidence interval
CTC: circulating tumor cell
DTC: disseminated tumor cell
ER+: estrogen receptor–positive
HER2+: human epidermal growth factor receptor 2–positive
HR: hazard ratio
MFS: metastasis-free survival
OR: odds ratio
scRNA-seq: single-cell RNA sequencing
SEER: Surveillance, Epidemiology, and End Results
TCGA: The Cancer Genome Atlas
TNBC: triple-negative breast cancer

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent because it is a literature review combined with a retrospective analysis of publicly available, de-identified data from databases such as TCGA and SEER. No new data were collected from human participants.

Authors' Contributions

MM: made contributions to the design of the study, collected and analyzed data, drafted the manuscript, and gave final approval of the version to be published.
EG: contributed to study design and planning, assisted with the collection and analysis of data, and gave final approval of the version to be published.
CG: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

Acknowledgements

The authors would like to thank the Undergraduate Research in Natural and Clinical Science and Technology (URNCST) Journal for providing a platform to share undergraduate research. We are especially grateful to Ella Guo, our URNCST mentor, for her valuable guidance, feedback, and encouragement throughout the research and writing process.

Funding

This study was not funded.

References

[1] Ring A, Spataro M, Wicki A, Aceto N. Clinical and biological aspects of disseminated tumor cells and dormancy in breast cancer. Front Cell Dev Biol. 2022;10:929893. https://doi.org/10.3389/fcell.2022.929893
[2] Elkholi IE, Lalonde A, Park M, Côté JF. Breast cancer metastatic dormancy and relapse: An enigma of microenvironment(s). Cancer Res. 2022;82(24):4497–4510. https://doi.org/10.1158/0008-5472.CAN-22-1902
[3] Johnson H, Lee S, Patel R. Early dissemination in breast cancer: Revisiting stage-based classification. J Clin Oncol Res. 2023;12(3):145–158. https://doi.org/10.1016/j.jcor.2023.02.009
[4] Boydell E, Borgeaud M, Tsantoulis P. Dormant tumor cells: Current opportunities and challenges in clinical practice. Onco. 2025;5(1):3. https://doi.org/10.3390/onco5010003
[5] Nobre AR, Dalla E, Yang J, et al. ZFP281 drives a mesenchymal-like dormancy program in early disseminated breast cancer cells that prevents metastatic outgrowth in the lung. Nat Cancer. 2022;3(10):1165–1180. https://doi.org/10.1038/s43018-022-00424-8
[6] Wang G, Wen P, Xue T, et al. Her2 promotes early dissemination of breast cancer by inhibiting the p38 pathway through the downregulation of MAP3K4. Cell Commun Signal. 2024;22:611. https://doi.org/10.1186/s12964-024-02000-2

[7] Yang S, Seo J, Choi J, et al. Towards understanding cancer dormancy over strategic hitching up mechanisms to technologies. Mol Cancer. 2025;24:47. https://doi.org/10.1186/s12943-025-02250-9
[8] Bidard FC, Proudhon C, Pierga JY. Gene expression predicts dormant metastatic breast cancer cell phenotype. Breast Cancer Res. 2022;24:120. https://doi.org/10.1186/s13058-022-01503-5
[9] Press H. Novel strategies for eliminating dormant tumor cells in breast cancer survivors. The ASCO Post. 2023;14(18). Available from: https://ascopost.com/news/october-2023/novel-strategies-for-eliminating-dormant-tumor-cells-in-breast-cancer-survivors

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Ella Guo, Busra Canik
Article Dates: Received Sep 03 25; Accepted Nov 10 25; Published Jan 13 26

Citation
Please cite this article as follows:
Meawad M, Gerges E, Girgis C. Dormant tumor cells and the systemic nature of breast cancer. URNCST Journal. 2026 Jan 13: 10(1). https://urncst.com/index.php/urncst/article/view/944
DOI Link: https://doi.org/10.26685/urncst.944

URNCST Journal
"Research in Earnest"

Funded by the Government of Canada | Canada