

Breast cancer metastasis research: current approaches and future possibilities

Priyanka Balaji¹, Shruthi Ragothaman² and Ravi Maddaly^{3,*}

¹Department of Human Genetics, Faculty of Biomedical Sciences and Technology, Sri Ramachandra Institute of Higher Education and Research, Chennai 600 116, India

²Department of Biotechnology, School of Chemical and Biotechnology, SASTRA University, Tanjore 613 401, India

³Department of Anatomy, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Chennai 602 105, India

Breast cancer (BC) remains a major global health challenge, with metastases causing nearly 90% of related deaths. Early and accurate prediction of metastatic progression is crucial yet difficult due to its biological complexity. The present review comprehensively examines key experimental and computational models that have advanced our understanding and prediction of BC metastasis. Traditional 2D cell cultures, although widely used, provide limited predictive insight. Conversely, patient-derived 3D organoids are cutting-edge preclinical models for better replicating tumor microenvironments, enhancing therapeutic prediction. Advanced microfluidic platforms demonstrate predictive accuracies up to 96% by dynamically stimulating tumor-stroma interactions. *In vivo* models, including patient-derived xenografts with engraftment rates up to 57% in aggressive tumors, closely mirror metastatic mechanisms linked to clinical outcomes, while genetically engineered mouse models offer reproducible systems for mechanistic studies. At the forefront, new-generation artificial intelligence and machine learning models integrate multi-omics, imaging, and clinical data, achieving prediction accuracies from 74% to 87%, with some models reaching 87% overall accuracy and 93% precision in metastasis risk stratification. Combining diverse models helps overcome limitations in understanding BC metastasis and is crucial for accelerating research, improving the detection of disease spread, and advancing targeted treatments for better patient outcomes.

Keywords: Breast cancer, experimental models, metastasis, organoids and histocultures, personalised medicine.

BREAST cancer (BC) represents a critical global health challenge, notably prevalent in regions such as China, the United States, and India, which together account for one-third of the world's BC burden¹. According to the latest 2025 GLOBOCAN data, BC is the most commonly diagnosed cancer among women globally and ranks second in overall cancer incidence when both sexes are considered.

In India, BC is the leading cause of cancer-related mortality reported in women. The country is projected to witness around 232,832 new BC cases, with incidence and mortality rates steadily increasing due to factors such as delayed diagnosis and underlying biological mechanisms, including cellular and molecular signalling and key driving mutations. Despite advances in awareness and screening, only about 29% of cases are detected at early stages, contributing to poor clinical outcomes. This underscores the urgent need for enhanced early detection, improved prediction of metastatic progression, and development of personalised treatment strategies.

As cancer therapy research advances, sophisticated preclinical investigations leveraging diverse models are increasingly important. Metastasis, a defining feature of BC progression, poses a major clinical obstacle demanding a comprehensive scientific understanding. Throughout tumorigenesis, the primary tumour cells undergo a series of transformative events, facilitating migration and colonisation to distant anatomical sites². This intricate process involves refinement and selection of tumour cell phenotypes, and these adaptive transitions ultimately result in the emergence of a metastatic phenotype³. Tumor cells acquire metastatic capabilities through genomic instability, compromised DNA integrity, and disrupted cell cycle regulation. Extracellular matrix (ECM) remodelling and changes in receptor and gene expression patterns characterise breast tumour progression, influencing metastatic potential within the tumour microenvironment (TME)⁴.

Utilising interdisciplinary approaches such as genomics and imaging, researchers have gained comprehensive insights into tumor behavior. Model selection varies depending on factors like tumour type, stage, genetics, and research objectives⁵. Table 1 presents an integrated comparison of multiscale models, highlighting their complementary roles in studying BC metastasis. This harmonisation of approaches underscores the strengths and limitations of each model in mimicking different aspects of metastatic progression. Ongoing efforts aim to develop more sophisticated models that mimic human tumour characteristics, advancing the boundaries of cancer research⁶. Understanding the nuanced global burden of BC, particularly in South India, underscores the

* For correspondence. (e-mail: ravim.smc@saveetha.com)