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Global Research Trends in Three-Dimensional Breast Cancer Models: A Bibliometric Analysis (2007–2025)

Tren Penelitian Global dalam Model Kanker Payudara Tiga Dimensi: Analisis Bibliometrik (2007–2025)

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Abstract

Background: Three-dimensional (3D) culture models have emerged as a promising preclinical platform for breast cancer research because they better mimic the tumor microenvironment (TME) of conventional two-dimensional cultures. With advances in tissue engineering, research related to 3D models has grown rapidly, necessitating a comprehensive evaluation of global research trends. **Methods:** A bibliometric analysis was performed using the Scopus database covering publications from 2007 to 2025, and only original research articles were included. Bibliometric indicators, including annual scientific output, leading countries, institutions, authors, journals, highly cited publications and collaboration patterns, were analyzed using Biblioshiny (R package), while keyword co-occurrence and temporal evolution were visualized using VOSviewer. **Results:** A total of 207 research articles published by 1,245 authors were analyzed. Scientific output showed a consistent annual growth rate of 13.32%, reflecting the increasing global interest in 3D breast cancer modeling. The United States was the leading contributor in publication productivity and scientific impact, while Biomaterials was the most productive journal. Highly cited publications predominantly focused on advanced tissue engineering technologies, including bioprinting, hydrogels, extracellular matrix engineering and microfluidics. Keyword co-occurrence analysis identified seven thematic clusters, while overlay visualization revealed a shift in research from conventional 3D cell culture toward more advanced tissue engineering approaches, particularly in biomaterials, tumor microenvironment reconstruction, drug screening and precision medicine. **Conclusion:** Research on 3D breast cancer models has evolved into a multidisciplinary field driven by tissue engineering innovations. This study provides a comprehensive knowledge map of the field, highlights emerging research directions and offers valuable guidance for future interdisciplinary collaborations and the development of physiologically relevant *in vitro* breast cancer models.

***Keywords*: 3D model, tissue engineering, breast cancer, tumor microenvironment, TME**

Abstrak

Latar belakang: Model kultur tiga dimensi (3D) telah muncul sebagai platform praklinis yang menjanjikan untuk penelitian kanker payudara karena model ini lebih baik dalam meniru lingkungan mikro tumor (TME) kultur dua dimensi konvensional. Seiring dengan kemajuan dalam rekayasa jaringan, penelitian terkait model 3D telah berkembang pesat, sehingga memerlukan evaluasi komprehensif terhadap tren penelitian global. **Metode:** Analisis bibliometrik dilakukan menggunakan basis data Scopus yang mencakup publikasi dari tahun 2007 hingga 2025, dan hanya menyertakan artikel penelitian asli. Indikator bibliometrik, termasuk produksi ilmiah tahunan, negara-negara terkemuka, institusi, penulis, jurnal, publikasi yang banyak dikutip dan pola kolaborasi, dianalisis menggunakan Biblioshiny (*R packet*), sementara kemunculan bersama kata kunci dan evolusi temporal divisualisasikan menggunakan VOSviewer. **Hasil:** Sebanyak 207 artikel penelitian yang diterbitkan oleh 1.245 penulis dianalisis. Produksi ilmiah menunjukkan tingkat pertumbuhan tahunan yang konsisten sebesar 13,32%, yang mencerminkan peningkatan minat global pada pemodelan kanker payudara tiga dimensi. Amerika Serikat merupakan kontributor utama dalam produktivitas publikasi dan dampak ilmiah, sedangkan Biomaterials adalah jurnal yang paling produktif. Publikasi yang banyak dikutip sebagian besar berfokus pada teknologi rekayasa jaringan tingkat lanjut, termasuk bioprinting, hidrogel, rekayasa matriks ekstraseluler dan mikrofluida. Analisis *co-occurence* kata kunci mengidentifikasi tujuh klaster tematik, sementara visualisasi *overlay* mengungkapkan pergeseran penelitian dari kultur sel 3D konvensional menuju pendekatan rekayasa jaringan yang lebih canggih, khususnya pada aspek biomaterial, rekonstruksi lingkungan mikro tumor, skrining obat dan pengobatan presisi. **Kesimpulan:** Penelitian tentang model kanker payudara 3D telah berkembang menjadi bidang multidisiplin yang didorong oleh inovasi rekayasa jaringan. Studi ini memberikan peta pengetahuan komprehensif tentang bidang ini, menyoroti arah penelitian yang muncul dan menawarkan panduan berharga untuk kolaborasi interdisipliner di masa depan dan pengembangan model kanker payudara *in vitro* yang relevan secara fisiologis.

Kata Kunci: 3D model, rekayasa jaringan, kanker payudara, lingkungan mikro tumor, TME

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Introduction

Breast cancer is a malignant disease with a large global health burden, both in terms of its epidemiology and biological complexity [1]. In 2022, this disease was recorded to cause approximately 670,000 deaths worldwide, making it the leading cause of cancer deaths in women globally [2]. Breast cancer treatment through systemic therapy, especially chemotherapy, often faces challenges in the form of chemoresistance that leads to therapy failure and poor prognosis [3]. The underlying factors for this resistance are the genetic diversity and plasticity of cancer cells, as well as the tumor microenvironment (TME) which contributes to tumor heterogeneity and determines the level of malignancy and response to cancer therapy [4]. Therefore, the development of models that better replicate the complexity of the TME more accurately is important to support the evaluation of therapy effectiveness and the development of anticancer agents, such as three-dimensional (3D) culture models.

The use of three-dimensional (3D) cell culture models in cancer research is able to provide conditions that support complex interactions between cancer cells, cancer cells with matrices and cancer cells with other cells, including stromal cells, immune cells and blood vessels [5]. Along with the development of the field of tissue engineering, three-dimensional (3D) culture models, initially dominated by simple cell aggregates (spheroids), have significantly evolved into platforms that designed to recapitulate the TME physiologically. Several types of 3D models that have been developed in cancer biology studies include scaffolds, microfluidics, bioprinting and organs-on-chips [6], [7], [8]. Each type of 3D model has its own advantages and disadvantages.

3D spheroid models have been shown to facilitate cell-cell interactions, but are limited in modeling interactions between cells and the extracellular matrix (ECM). Meanwhile, hydrogel-based models more closely resemble the natural ECM but still face challenges in gel homogenization during fabrication. Microfluidic-based models allow for dynamic regulation of fluid flow, biochemical gradients and cell-cell interactions, thus effectively recapitulating the TME, but require complex device design and fabrication techniques. Similarly, bioprinting and organ-on-chip technologies offer the complexity of mimicking physiological conditions, but their creation requires more complex equipment, costs, fabrication techniques and culture processes. On the other hand, scaffold-based models offer the flexibility to engineer TME characteristics with simpler and more affordable fabrication techniques, although scaffold structural homogeneity remains a challenge [6], [7], [8].

The selection of biomaterials also plays an important role in determining the biological and mechanical properties of 3D models. Various natural and synthetic biomaterials have been utilized, such as collagen, gelatin, fibrin, silk, chitosan, cellulose, dextran and hyaluronic acid, being one of the most widely used groups due to their good biocompatibility [9]. The varied characteristics of biomaterials allow for the availability of options for engineering the physical, mechanical and biological properties of 3D models according to the application objectives, both for studying cancer biology and evaluating therapy.

The development of various 3D models, fabrication techniques and biomaterial innovations generally reflects the convergence of various scientific disciplines, including biomaterial science, tissue engineering, cell biology and oncology, resulting in an increasingly broad and multidisciplinary research landscape [10]. The complexity and diversity of this research demonstrate the need for comprehensive mapping to identify development trends, scientific collaborations, research focuses and potential future technology development directions. Therefore, this study conducts a bibliometric analysis of the development of three-dimensional culture models for breast cancer in the context of tissue engineering applications.

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This study aims to provide a comprehensive overview of the development of three-dimensional (3D) culture model research for breast cancer in the context of tissue engineering. A bibliometric approach was conducted using the Biblioshiny R Package and VOSviewer as bibliometric data analysis and visualization tools [11]. Through the analysis of publications indexed in Scopus, this study is expected to identify research growth trends, scientific collaboration patterns, contributions from countries, institutions and authors, as well as the evolution of research themes that have developed over time [12]. In addition, the results of this analysis are expected to reveal research gaps and opportunities for the development of 3D model technology in the future, so that it can serve as a reference for researchers in designing more targeted research strategies to support the development of preclinical breast cancer models that are increasingly relevant to *in vivo* conditions.

Methods

Database and Keyword

Data related to three-dimensional (3D) cell culture models in breast cancer research were sourced from the Scopus database due to its extensive coverage of scientific literature [13]. We searched the Scopus database for articles containing the keywords: (TITLE-ABS-KEY ("breast cancer") AND TITLE-ABS-KEY ("3D model" OR "three dimensions" OR "three-dimensions" OR "cell culture" OR "tissue engineering")). The reviewed scientific literature must contain these keywords or similar terms in the title, abstract or keywords section.

Inclusion and Exclusion Criteria

The inclusion criteria used in the analysis of this study include literature sourced from the Scopus database, including original articles published in English, with a time span from 2007 to 2025. Exclusion criteria include irrelevant terms related to 3D models of cancer cells, as well as biased information, articles that are not available in full text and duplicate publications. Full texts that meet the inclusion and exclusion criteria that have been set will be analyzed further [14]. The data search flowchart is presented in Figure 1.

Data Extraction and Bibliometric Parameters

Literature from databases that meet the requirements are collected and stored in "CSV" format, then visualized using VOSviewer v.1.6.21 and R-Studio v.2025.4.5.2 for the analysis process. The visualization results are then further analyzed for bibliometric studies [15]. The parameters evaluated include publication trends, contributing countries and institutions, analysis of contributing publishers/journals, the most productive authors and their bibliographic coupling networks, analysis of the most influential articles and the impact of these articles to determine the results of the bibliometric study.

Data Cleaning and Pre-processing

Data cleaning and pre-processing were carried out using the VOSviewer thesaurus feature, alongside Notepad++ and Excel [16]. This stage aimed to normalize keywords that exhibited spelling variations or were considered equivalent within the research context. The groups of normalized keywords included: (1) "3d printing", "bioprinting" and "3d bioprinting"; (2) "3d cell culture" and "cell culture"; (3) "3d in vitro models" and "3d tumor models"; (4) "hydrogel" and "hydrogels"; (5) "scaffold" and "scaffolds"; (6) "spheroid" and "spheroids"; and (7) "3d" and "three-dimensional". In the thesaurus file, the original keywords were listed in the "label" column, while the normalized terms were listed in the "replace by" column. The compiled thesaurus list was then imported into VOSviewer for further visualization and analysis.

Mapping on VOSviewer

VOSviewer software extracts and analyzes words found in the titles, abstracts and keywords of relevant articles. The results of the analysis are displayed as a node map depicting individual terms or phrases. A manual review was performed to remove irrelevant terms. The size of each node reflects the frequency of occurrence of the word in the literature. The color of node represents the number of citations of each publication containing the term, while the proximity between two nodes indicates how often the two terms appear together [17].

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Results and Discussions

Document Types and Key Information

Based on the results obtained from the Scopus database, 330 documents were retrieved from 2007 to 2025, involving approximately 1,245 authors worldwide. The analysis revealed that 207 (62.73%) were research articles and 90 (27.27%) were reviews. Other document types included book chapters, conference papers, conference reviews, retractions, notes, erratums, editorials and data papers, totaling 33 (10%). Only research articles were selected and further analyzed in this study. Detailed information regarding the retrieved documents is presented in Table 1. The bibliometric analysis shows that the field of three-dimensional (3D) modeling research related to breast cancer experienced an annual publication growth rate of 13.32%, with an average document age of 6.67 years and an average citation rate of 50.69 citations per article. These values indicate that this field is actively developing and has a high scientific impact within the research community.

Furthermore, the analyzed dataset contained 609 author keywords and 2,965 Keywords Plus, reflecting the diversity of research topics in this field. The level of collaboration between authors was aLilso high, with an average of 6.84 authors per article and 24.15% international collaboration, indicating that research on 3D models for breast cancer is developing through multidisciplinary and cross-national collaboration networks.

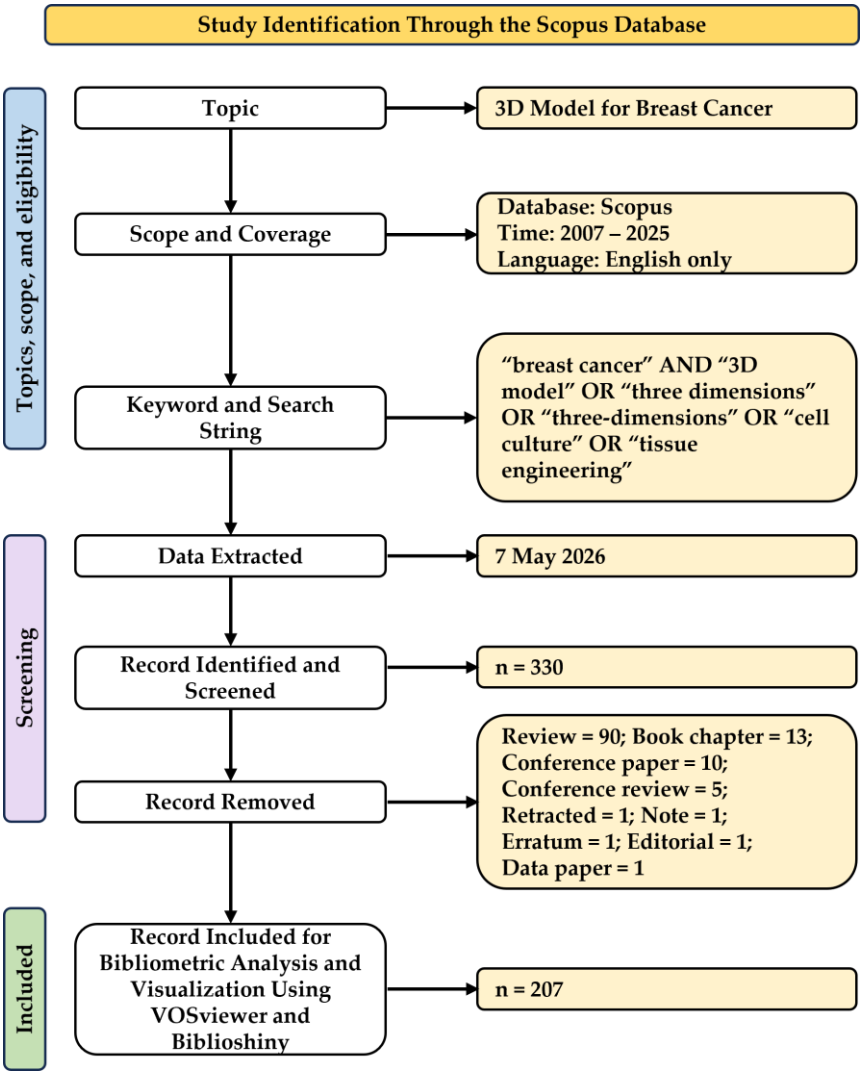

Figure 1. Flowchart of data search process methodology.

Global Publication Trends Analysis

The number of research articles related to three-dimensional (3D) models for breast cancer worldwide showed an increasing trend during the period 2007–2025 (Figure 2). At the beginning of the observation period (2007–2013), the number of publications was still relatively low and fluctuated, ranging from 1–5 articles per year. Publication productivity began to increase gradually, from 7 articles in 2014 to 12 articles in 2015

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(71.43%). After experiencing a slight decline in 2016, the number of publications increased again to 22 articles in 2018, an increase of 83.33% compared to the previous year. Publication productivity peaked in 2021 with a total of 24 articles, an 84.62% increase compared to 2020. Although the number of publications fluctuated after 2021, research productivity remained relatively high, ranging from 14 to 20 articles per year until 2025. This pattern indicates that global interest in the development of three-dimensional models for breast cancer research continues to grow.

This increasing publication trend is thought to be related to the growing global interest in three-dimensional model research for breast cancer overall. This is likely driven by technological advances in tissue engineering and the growing need for more physiological preclinical models.

Table 1. Main Information from the Three Dimensional (3D) Model Related to Breast Cancer (2007–2025).

Description	Result	Description	Result
Main Information About Data		**Authors**	
Timespan	2007:2025	Authors	1245
Sources (Journals, Books, etc)	121	Authors of single-authored docs	1
Documents	207		
Annual Growth Rate %	13.32	**Authors Collaboration**	
Document Average Age	6.67	Single-authored docs	1
Average citations per doc	50.69	Co-Authors per Doc	6.84
References	12092	International co-authorships %	24.15
Document Contents		**Document Types**	
Keywords Plus (ID)	2965	Article	207
Author's Keywords (DE)	609		

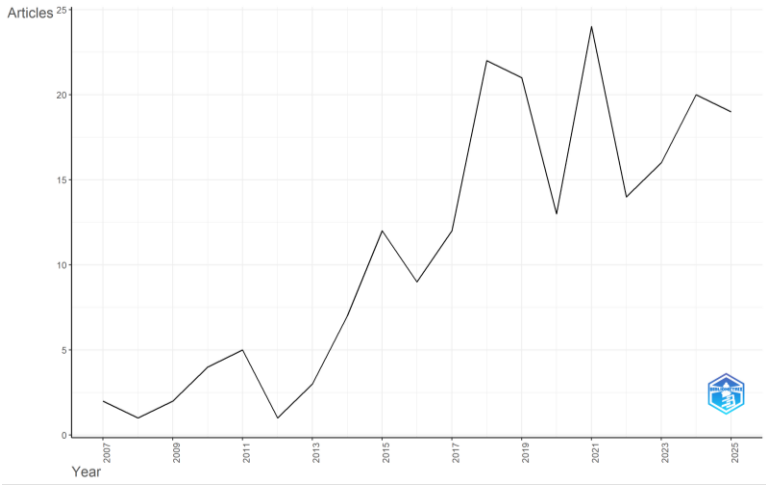

Figure 2. Annual scientific production on three-dimensional (3D) models related to breast cancer based on the number of publications (2007–2025).

Author Country and Author Affiliation of the Publication

According to Figure 3, the United States has the highest number of citations for publications on three-dimensional (3D) breast cancer models, with 3,902 citations, followed by China (1,018 citations), Germany (981 citations), Italy (387 citations) and South Korea (382 citations). Although the United States has the highest total citation count, South Korea has the highest average citations per article, with 127.3 citations per article, followed by Germany (98.1 citations per article), Italy (64.5 citations per article) and the United States (56.6 citations per article). These findings suggest that in addition to publication productivity, the quality and scientific impact of each article are also important factors in determining the impact of research on the development of the field of 3D breast cancer models. Although South Korea and Germany show high average citations, this metric should be interpreted with caution as it can be heavily influenced by a few highly cited publications, and does not necessarily reflect the overall, sustained impact of a country's entire research output.

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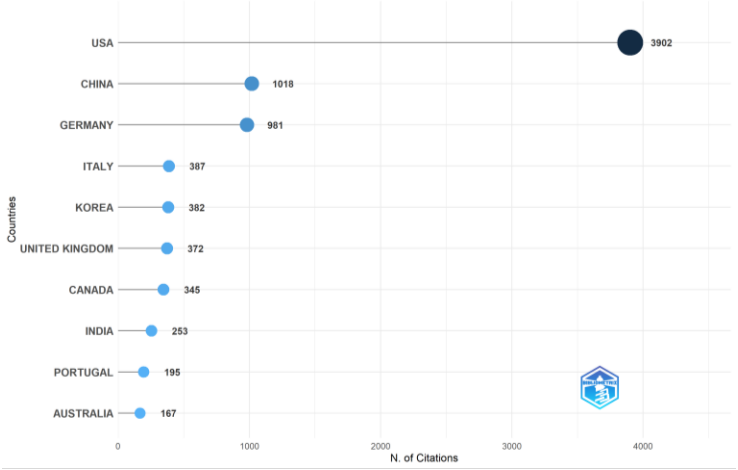

Figure 3. The countries most frequently cited in three-dimensional (3D) modeling studies related to breast cancer (2007–2025).

Figure 4 shows that the five institutions with the highest number of publications are McGill University (13 articles), the University of Washington (11 articles), the University of California (10 articles), the University of Alabama at Birmingham (9 articles) and the University of Cambridge (9 articles). The presence of several institutions from North America and Europe in the top rankings also indicates that the region remains a hub for 3D modeling development and translational research in the field of cancer.

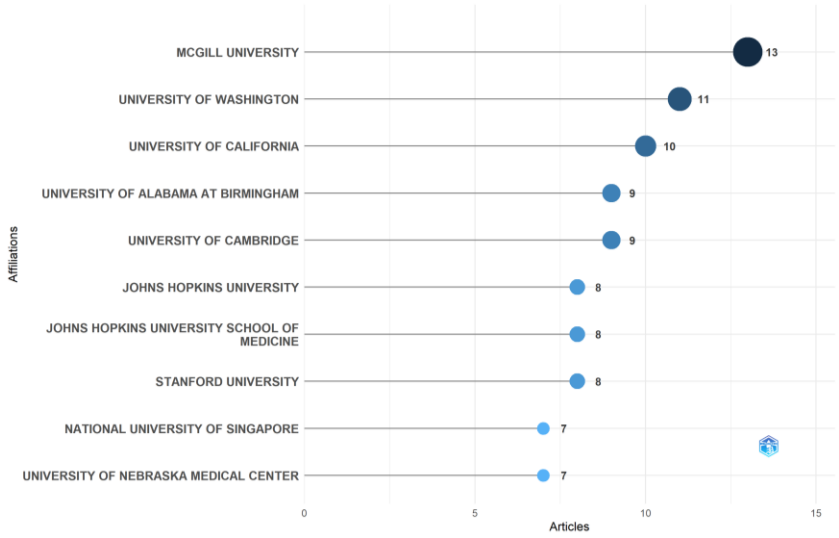

Figure 4. Institution-based publication distribution on 3D modeling research related to breast cancer (2007–2025).

Analysis of Core Journals in Three-Dimensional Breast Cancer Model Research

Based on Figure 5, "Biomaterials" is the journal that published the most research on three-dimensional (3D) models for breast cancer, with a total of 14 articles. Then, "Acta Biomaterialia" (H-Index 278 S.J.R. 2025 1.884) and "Biofabrication" (H-Index 134 and S.J.R. 1.515) each contributed 9 articles, followed by "Advanced Healthcare Materials" with 8 articles (H-Index 178 and S.J.R. 2025 2.192) and "Scientific Reports" with 6 articles (H-Index 382 and S.J.R. 2025 0.893). Several other journals actively publishing on this topic are "ACS Applied Materials and Interfaces" (H-Index 356 and SJR 2025 1.614) and "the International Journal of Biological Macromolecules" (H-Index 247 and SJR 2025 1.287) with 5 articles each, as well as "ACS Biomaterials Science and Engineering" (H-Index 117 and SJR 2025 1.041), "Cells" (H-Index 196 and SJR 2025 1.687) and "Physics in Medicine and Biology" (H-Index 231 and SJR 2025 0.821) with 4 articles each.

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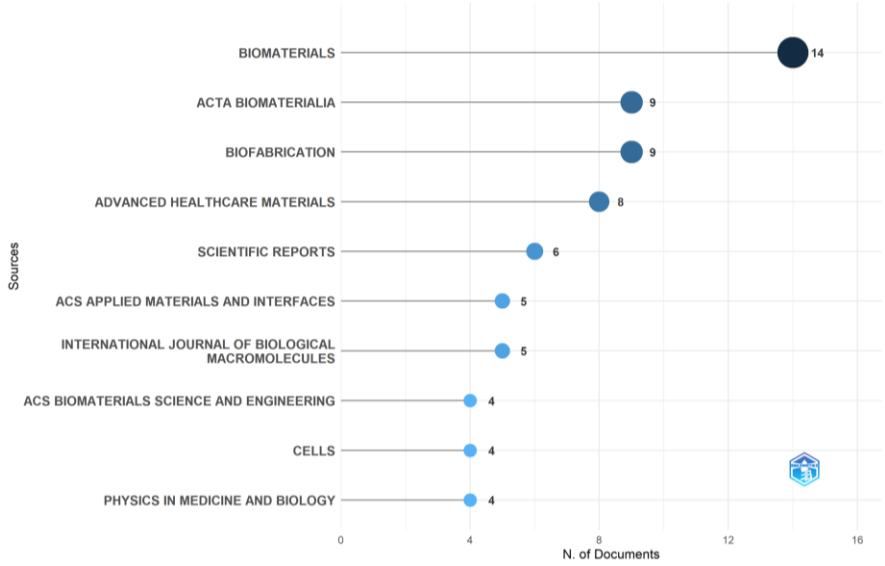

Figure 5. Top ten journals with the most publications on three-dimensional modeling research related to breast cancer (2007–2025).

The dominance of these journals indicates that research on 3D models for breast cancer is mostly published in journals focused on biomaterials, tissue engineering and biofabrication, rather than journals specifically addressing oncology. This finding indicates that the development of 3D models is not only seen as a cell culture approach, but also as the result of the integration of biomaterial engineering and design, as well as fabrication techniques to produce models that can more physiologically represent the TME. Furthermore, the presence of multidisciplinary journals such as "Scientific Reports" and "Cells" indicates that the application of 3D models has expanded into various fields, including cancer biology, drug development and translational research.

Most Prolific Author in Cancer-Related Three-Dimensional Model Research

The ten most prolific authors in publications on three-dimensional (3D) models related to breast cancer are shown in Figure 6. Liu T is the most prolific author with 6 publications. Furthermore, Li W, Sloane BF, Wang H and Wang Y each published 5 publications. In addition, Cameron RE, Hu X, Hutmacher DW, Li S and Pradhan S each produced 4 publications. These results indicate that research on 3D models for breast cancer is supported by several groups of researchers who consistently contribute to the development of this field, without any significant dominance by a single author.

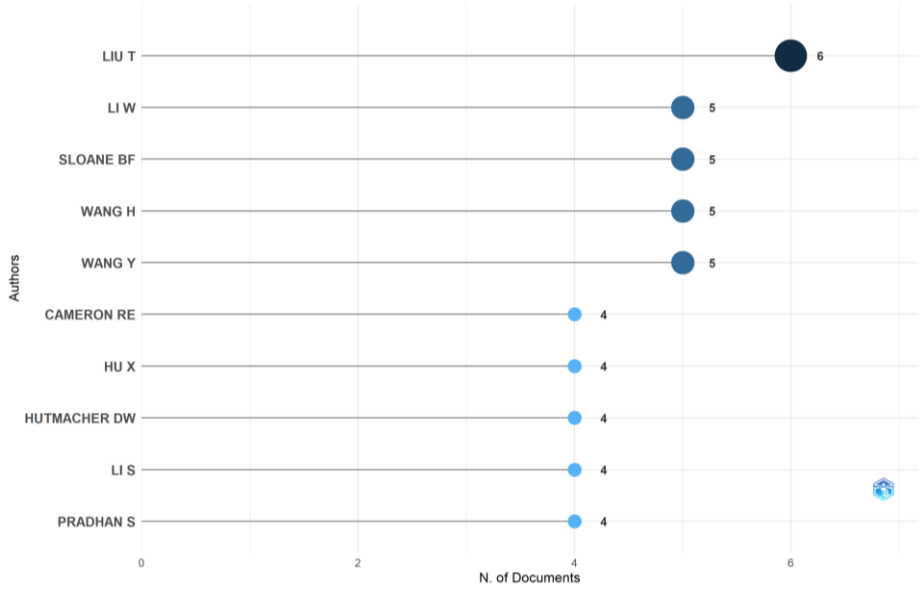

Figure 6. Distribution of the 10 most productive authors in three-dimensional modeling research related to breast cancer (2007–2025).

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Analysis of the Most Influential Publications on Three Dimensions Related to Cancer

A summary of the ten publications with the highest number of citations is presented in Table 2. The publication with the highest number of citations is the study by Ceylan et al. (2019) entitled "3D-Printed Biodegradable Microswimmer for Theranostic Cargo Delivery and Release" with 505 citations, followed by Benam et al. (2015) on engineered in vitro disease models (500 citations) and Polacheck et al. (2011) on the effect of interstitial flow on tumor cell migration (449 citations). Most of the highly cited publications were published in reputable journals, such as ACS Nano, Proceedings of the National Academy of Sciences (PNAS), Biomaterials, Acta Biomaterialia and Lab on a Chip, demonstrating the high level of interest in research in this field from the scientific community.

Overall, the most influential publications extend beyond conventional 3D culture models by incorporating advanced tissue engineering strategies, including 3D bioprinting, microfluidics, hydrogel-based systems, extracellular matrix (ECM) engineering, and organoid- and organ-on-a-chip-based platforms. Importantly, the use of patient-derived models also highlights the increasing translational relevance of advanced cancer models, bridging experimental modeling with potential clinical applications. These findings indicate that the development of 3D modeling research for breast cancer has shifted from simply establishing cell culture systems to developing preclinical platforms capable of recapitulating the complexity of the tumor microenvironment and supporting cancer biology studies, drug discovery and precision medicine.

Country Productivity Analysis and Visualization of Inter-Country Collaboration

The distribution of publication productivity by country in research on three-dimensional (3D) models for breast cancer is visualized in Figure 7. The United States has the highest number of publications, with 274 publications, followed by China (86 publications), Australia (38 publications), the United Kingdom (36 publications) and Canada (35 publications). Other countries with significant contributions include Germany (33 publications), Italy (24 publications), Iran (23 publications), France (21 publications) and Turkey (17 publications).

This geographic distribution indicates that research on 3D models for breast cancer is dominated by developed countries in North America, Europe and East Asia. Furthermore, contributions from Australia, Canada, the United Kingdom, Germany and several other European countries demonstrate that 3D model development has become a global research focus, involving various international research centers. Although contributions from developing countries remain relatively limited, this situation suggests an opportunity to expand international collaboration to promote equitable development of 3D modeling technology.

The distribution of corresponding authors by country and the pattern of international collaboration are presented in Figure 7B. The United States exhibited the highest number of corresponding-author publications, with the majority classified as Single Country Publications (SCP), while also showing a considerable proportion of Multiple Country Publications (MCP), indicating both strong domestic research capacity and extensive international collaboration. China showed a similar pattern but with a lower publication volume, whereas countries such as Germany, the United Kingdom, Canada and Australia also demonstrated active participation in international collaborative research.

Regarding international collaboration, the relationship between publication productivity and the proportion of internationally co-authored papers (MCP) showed no consistent linear relationship. The United States and China, which boast the highest publication productivity in terms of total papers, both exhibit a moderate MCP proportion of 17.4%. Conversely, countries with moderate productivity, such as Australia, Germany, Canada and Iran, show significantly higher MCP proportions, ranging from 44.4% to 50%. Meanwhile, Singapore recorded the highest MCP proportion (66.7%) despite having a relatively low publication volume. However, this pattern is not universal.

Countries such as Portugal, Japan, France and Turkey, for instance, recorded no MCPs at all, despite their relatively low publication productivity. These findings indicate that high publication productivity is not necessarily accompanied by greater international collaboration; conversely, countries with moderate or low productivity may demonstrate relatively higher levels of international engagement. Overall, these findings suggest that advances in 3D breast cancer modeling are supported by both well-established national research networks and cross-country collaborations, which facilitate multidisciplinary knowledge exchange and accelerate technological innovation in the field.

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Table 2. Top Ten of the Most Influential Publications on Three-Dimensional Models Related to Breast Cancer.

No.	Author	Title	Year	Journal	Number of Citation	Ref.
1	Hakan Ceylan, Immihan Ceren Yasa, Oncay Yasa, Ahmet Fatih Tabak, Joshua Giltinan, & Metin Sitti	3D-Printed Biodegradable Microswimmer for Theranostic Cargo Delivery and Release	2019	ACS Nano	505	[18]
2	Kambez H. Benam, Stephanie Dauth, Bryan Hassell, Anna Herland, Abhishek Jain, Kyung-Jin Jang, Katia Karalis, Hyun Jung Kim, Luke MacQueen, Roza Mahmoodian, Samira Musah, Yu-suke Torisawa, Andries D. van der Meer, Remi Villenave, Moran Yadid, Kevin K. Parker, & Donald E. Ingber	Engineered in vitro disease models	2015	Annual Review of Pathology: Mechanisms of Disease	500	[19]
3	William J. Polachecka, Joseph L. Charestb, & Roger D. Kamm	Interstitial flow influences direction of tumor cell migration through competing mechanisms	2011	Proceedings of the National Academy of Sciences	449	[20]
4	Carlos P. Huang, Jente Lu, Hyeryung Seon. Abraham P. Lee, Lisa A. Flanagan, Ho-Young Kim, Andrew J. Putnam, & Noo Li Jeon	Engineering microscale cellular niches for three-dimensional multicellular co-cultures	2009	Lab on a Chip	350	[21]
5	Xuan Zhou, Wei Zhu, Margaret Nowicki, Shida Miao, Haitao Cui, Benjamin Holmes, Robert I. Glazer, & Lijie Grace Zhang	3D Bioprinting a Cell-Laden Bone Matrix for Breast Cancer Metastasis Study	2016	ACS Applied Materials & Interfaces	286	[22]
6	Christopher S. Szot, Cara F. Buchanan, Joseph W. Freeman, & Marissa N. Rylander	3D in vitro bioengineered tumors based on collagen I hydrogels	2011	Biomaterials	266	[23]
7	Yoonseok Choi, Eunjeh Hyun, Jeongyun Seo, Cassidy Blundell, Hee Chan Kim, Eunhee Lee, Suhyun Lee, Aree Moon, Woo Kyung Moon, & Dongeun Huh	A microengineered pathophysiological model of early-stage breast cancer	2015	Lab on a Chip	205	[24]
8	Peter A. Mollica, Elizabeth N. Booth-Creech, John A. Reid, Martina Zamponi, Shea M. Sullivan, Xavier-Lewis Palmer, Patrick C. Sachs, & Robert D. Bruno	3D bioprinted mammary organoids and tumoroids in human mammary derived ECM hydrogels	2019	Acta Biomaterialia	195	[25]
9	Marta Cavo, Marco Fato, Leonardo Peñuela, Francesco Beltrame, Roberto Raiteri, & Silvia Scaglione	Microenvironment complexity and matrix stiffness regulate breast cancer cell activity in a 3D in vitro model	2016	Scientific Reports	186	[26]
10	Yoko S. DeRose, Keith M. Gligorich, Guoying Wang, Ann Georgelas, Paulette Bowman, Samir J. Courdy, Alana L. Welm, & Bryan E. Welm	Patient-derived models of human breast cancer: protocols for in vitro and in vivo applications in tumor biology and translational medicine	2013	Current protocols in pharmacology	184	[27]

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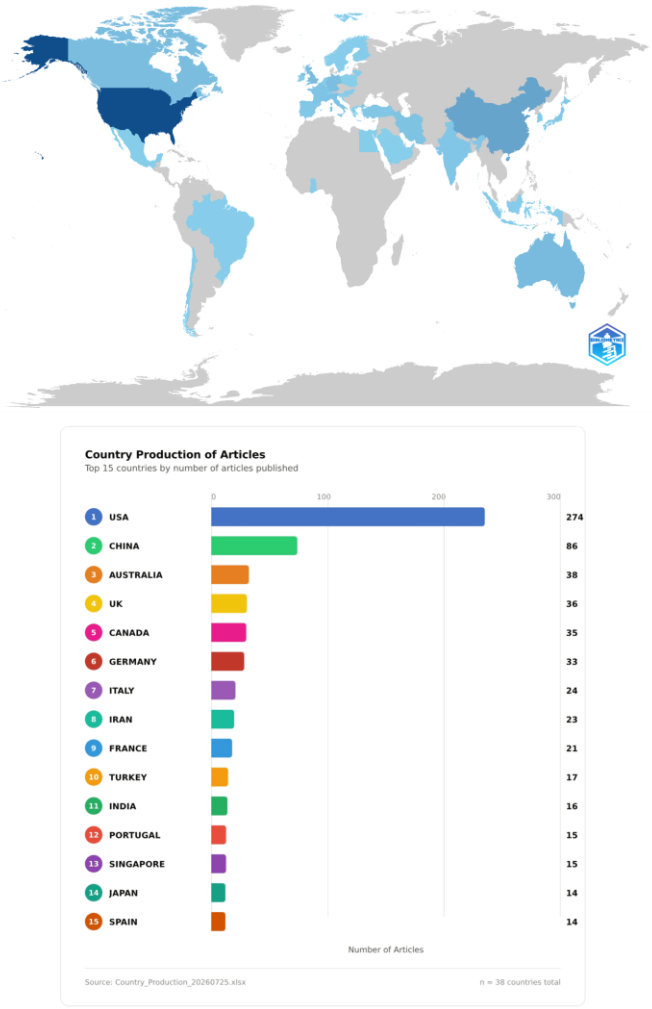

Figure 7. Distribution of publications by country on breast cancer-related 3D modeling research worldwide (2007–2025).

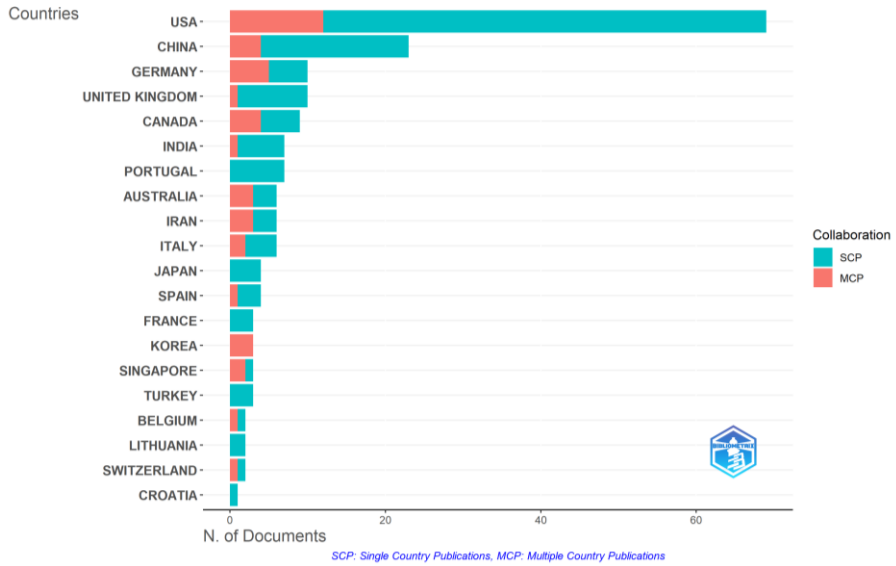

Figure 8. Visualization of the Collaborative Network of Related Countries on three-dimensional modeling research related to breast cancer worldwide (2007–2025).

Network visualization of co-occurrence

Keyword co-occurrence analysis using VOSviewer yielded seven interconnected clusters (Figure 9a), indicating that research on three-dimensional (3D) models for breast cancer is evolving through several key,

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overlapping research themes. Larger nodes indicate more frequently occurring keywords, while connecting lines (links) indicate co-occurrence relationships between keywords.

Overall, "breast cancer"was the most dominant keyword, with 38 occurrences and a total link strength (TLS) of 56, followed by "3D bioprinting"(29 occurrences, TLS = 37), "tissue engineering" (28 occurrences, TLS = 56), "3D cell culture" (22 occurrences, TLS = 31), "cancer" (13 occurrences, TLS = 31), "hydrogel" (16 occurrences, TLS = 35) and "extracellular matrix" and "tumor microenvironment" (10 occurrences each, TLS = 19). The high frequency and interconnectedness of these keywords indicate that the development of 3D models for breast cancer has expanded beyond conventional cell culture techniques into a multidisciplinary approach integrating biomaterials, tissue engineering and tumor microenvironment engineering.

Table 3. Cluster Analysis Based on Keyword Frequency.

Cluster	Most Frequently Appearing Author Keywords	Other Keywords
Red – 8 keywords	3D Bioprinting (29)	Hydrogel (16) collagen (6), drug delivery (4), breast cancer cells (3), cell migration (3), gelatin (3), mesenchymal stem cells (3)
Green – 7 keywords	Extracellular matrix (10)	Tumor microenvironment (10), 3D model (9), microfluidics (5), biofabrication (3), decellularization (3), invasion (3)
Blue – 6 keywords	Tissue engineering (28)	3D cell culture (22), spheroids (6), fibroblast (3), mechanobiology (3), organ-on-a-chip (3)
Yellow – 5 keywords	Breast cancer (38)	Scaffold (9), metastasis (8), bone metastasis (4), bone (3)
Purple – 5 keywords	Cancer (13)	Biomaterials (6), three-dimensional (9), microenvironment (5), drug discovery (3)
Light blue – 3 keywords	Angiogenesis (5)	Alginate (4), organoid (3)
Orange – 1 keywords	Drug screening (5)	–

Table 3 presents the distribution of keywords across seven clusters, revealing distinct yet interconnected research directions in the development of three-dimensional (3D) breast cancer models. Cluster 1 (red) reflects advancements in biofabrication technologies and biomaterial-based approaches for constructing physiologically relevant breast cancer models. The combination of fabrication technologies with hydrogel-based systems and cellular components demonstrates ongoing efforts to develop models capable of better replicating tumor architecture and supporting research into cancer cell behavior and therapeutic applications [28].

Cluster 2 (green) focuses on the reconstruction of the extracellular matrix and the tumor microenvironment through advanced 3D modeling approaches. This theme emphasizes the importance of replicating the structural and biochemical characteristics of the native tumor environment, with increasing use of microfluidics, biofabrication and decellularization strategies to investigate cancer invasion and associated cellular behaviors.

Cluster 3 (blue) represents the integration of tissue engineering principles with advanced 3D culture platforms. The inclusion of multicellular culture systems, stromal components, mechanobiological approaches and organ-on-a-chip technologies indicates a shift toward models that integrate the biological and physical characteristics of the tumor microenvironment. Mechanobiology highlights the influence of the tumor microenvironment's physical and mechanical properties on cancer cell behavior [29], while fibroblasts are crucial stromal components that shape the tumor microenvironment [30]. Integrating these aspects demonstrates an effort to more accurately recapitulate the complexity of the tumor microenvironment.

Cluster 4 (yellow) centers on breast cancer-related applications, specifically the use of 3D models to investigate tumor progression and metastatic behavior. Strong links to scaffold-based systems and bone metastasis indicate growing interest in developing models that replicate specific metastatic niches, particularly the bone microenvironment [31]. This reflects a broader shift from merely modeling primary tumor growth toward understanding the complex processes underlying cancer dissemination and organ-specific metastasis.

Cluster 5 (purple) represents the broader application of biomaterials and 3D modeling technologies in cancer research. This cluster links the development of biomaterial-based systems with tumor microenvironment reconstruction and therapeutic research, indicating that 3D models are increasingly positioned as multifunctional platforms capable of bridging basic cancer biology and drug discovery.

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Cluster 6 (light blue) reflects a more specialized research direction focusing on vascular-related processes within 3D cancer models. Keywords in this cluster suggest increasing efforts to integrate angiogenesis and biomimetic vascular components into tumor models, thereby enabling a more comprehensive representation of tumor progression and its interaction with the surrounding vascular environment.

Cluster 7 (orange) represents an application-oriented theme with a primary focus on drug screening. Although this cluster encompasses a single dominant theme, its emergence as a distinct cluster highlights the expanding application of 3D models in evaluating therapeutic responses. This reinforces the transition of 3D breast cancer models from mere experimental tools for studying tumor biology into platforms of direct relevance to preclinical drug evaluation.

These clustering patterns indicate that research on 3D breast cancer models is evolving from the stages of model fabrication and biomaterial development toward increasingly complex biological reconstruction and translational applications. The integration of tissue engineering, tumor microenvironment reconstruction, advanced culture platforms, metastasis modeling, angiogenesis and drug screening reflects a broader trend toward multifunctional 3D systems designed to more accurately recapitulate the complexities of the *in vivo* tumor environment.

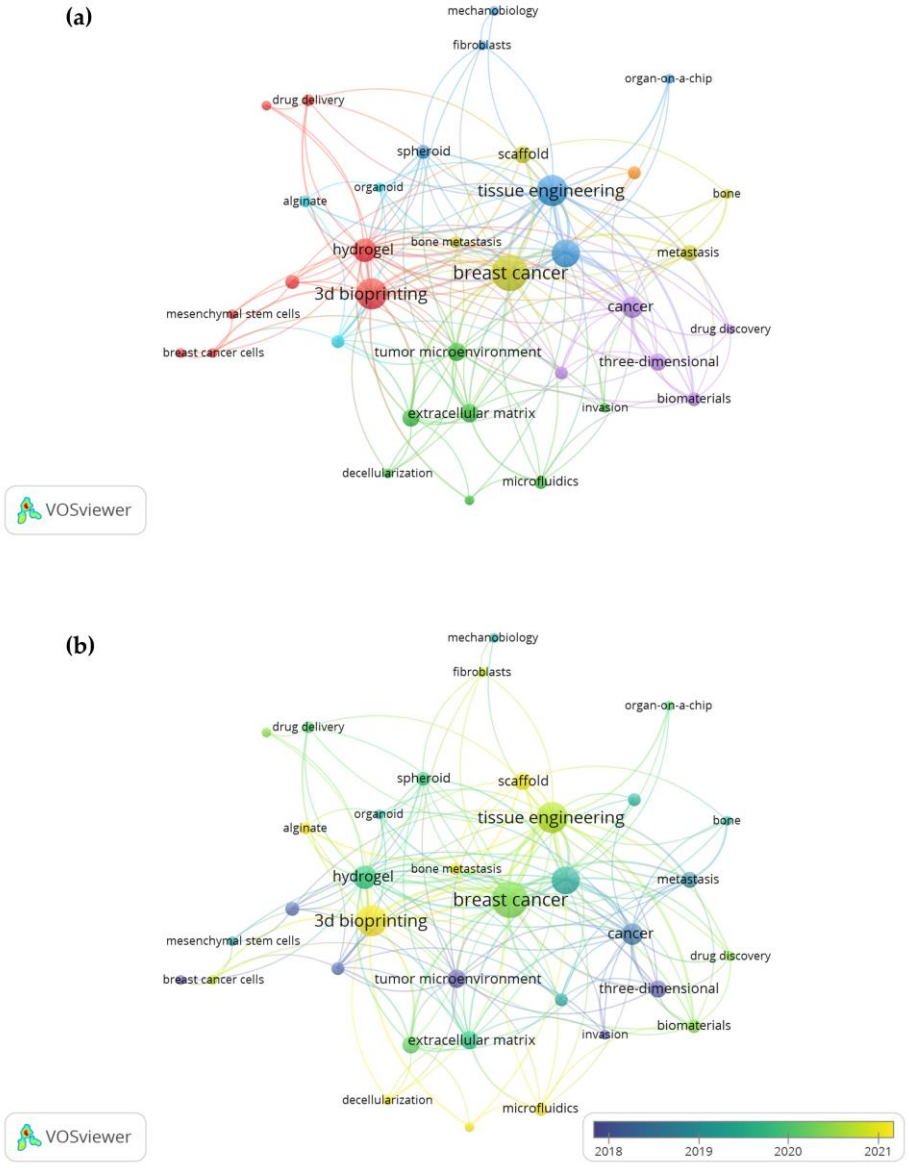

Figure 9. Visualization Keywords Authors of 3D Modeling Research Related to Breast Cancer (2007–2025): (a) Network Visualization; (b) Overlay Visualization.

Overlay visualization analysis (Figure 9b) shows a shift in research focus over time. In the initial period (2019–2020), research focused primarily on developing basic 3D culture models, extracellular matrix

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reconstruction and characterizing the tumor microenvironment. Entering the 2021–2022 period, attention began to shift toward developing tissue engineering approaches through the use of biomaterials, hydrogels and fabrication technologies. Furthermore, during the 2022–2023 period, research increasingly shifted toward the application of advanced technologies, such as 3D bioprinting, microfluidics, drug screening and mechanobiology, reflecting the evolution of 3D models from conventional culture systems into sophisticated platforms for precision medicine, drug discovery and cancer therapy evaluation.

Conclusions and Future Directions

This bibliometric study provides a comprehensive overview of the global development of three-dimensional (3D) models for breast cancer research from 2007 to 2025. The findings demonstrate a continued increase in scientific productivity, supported by international collaborations and diverse multidisciplinary contributions. The United States emerged as a leading contributor in terms of publications and scientific impact, while Biomaterials and other tissue engineering-oriented journals served as key publication platforms for this research field. Keyword co-occurrence analysis revealed that the research focus has progressively shifted from conventional 3D cell culture toward more sophisticated tissue engineering strategies involving hydrogels, scaffolds, ECM engineering, microfluidics, bioprinting and mechanobiology to better recapitulate the TME. These findings suggest that 3D breast cancer models are evolving into a growing preclinical platform for disease modeling, drug screening and precision medicine. Based on the emergence of mechanobiology and microfluidics as recent research hotspots, future studies should prioritize their integration to develop more dynamic 3D models capable of better recapitulating the physical and mechanical complexity of the TME. Furthermore, the observed geographic disparities in research contributions highlight the need for broader international collaborations and funding initiatives to support participation from underrepresented regions.

Conflict of Interest

There is no conflict of interest.

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