

Review

Trends in Breast Cancer Epigenetics Research from 1993 to 2023: A Bibliometric Analysis

Khevin Jade Gumaru ^{1,†}, Harley Rodriguez ^{1,†}, Ourlad Alzeus G. Tantengco ^{2,*}

1. College of Medicine, University of the Philippines Manila, City of Manila, Philippines; E-Mails: kbgumaru@up.edu.ph; hmrodriguez2@up.edu.ph
2. Department of Physiology, College of Medicine, University of the Philippines Manila, City of Manila, Philippines; E-Mail: ogtantengco@up.edu.ph

† These authors contributed equally to this work.

* **Correspondence:** Ourlad Alzeus G. Tantengco; E-Mail: ogtantengco@up.edu.ph**Academic Editor:** Apostolos Zaravinos

OBM Genetics
2025, volume 9, issue 3
doi:10.21926/obm.genet.2503307

Received: January 12, 2025
Accepted: July 28, 2025
Published: August 15, 2025

Abstract

Breast cancer is a significant health problem. Epigenetic alterations that influence gene expression were implicated in breast cancer pathogenesis. Bibliometric analysis can be done to evaluate the existing literature and identify gaps and emerging trends. This bibliometric analysis aims to provide an overview of the current landscape of global breast cancer epigenetics research, identify existing networks of countries and authors' keywords, and assess the association of a country's socioeconomic indicators with its scientific productivity. A literature search was performed on SCOPUS for existing original articles published from 1993 to 2023. The metadata available from these articles was evaluated using Bibliometrix, and VOSViewer 1.6.20 was used for the network and overlay visualizations. Spearman's correlation analysis of country-specific characteristics with bibliometric indices was performed in GraphPad Prism, and a p-value < 0.05 was considered statistically significant. There are 688 publications in this field with 31,215 citations. The USA is the central country for scientific productivity regarding publications, citations, funding, affiliations, and collaborations. The trend in breast cancer epigenetics research has evolved from cancer-related genes to molecular mechanisms of epigenetic alterations to the development of



© 2025 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

therapeutics such as epigenetic drugs. The only statistically significant correlation is between research collaborations and total citations ($r = 0.649$, $p = 0.049$) and h-index ($r = 0.646$, $p = 0.049$). This study provided substantial evidence for breast cancer epigenetics research progress regarding productivity, collaborations, and citations. Administrators and policymakers can use these results for evidence-based decision-making on implementing current breast cancer epigenetics programs worldwide and for better resource allocation of these programs to augment the field toward therapeutics development.

Keywords

Breast cancer; epigenetics; epidrugs; bibliometric analysis; scientometric analysis

1. Introduction

Breast cancer is a global health problem that has grown out of control. It has become the most commonly diagnosed cancer in the world, with 2.3 million women affected and 670,000 deaths occurring globally [1, 2]. To improve survival rates, especially in low-income countries, the World Health Organization introduced the Global Breast Cancer Initiative, which focuses on health promotion, timely diagnosis, comprehensive treatment, and supportive care [3].

Alterations at the molecular level that do not change the DNA sequence but influence gene activity are known as epigenetics. The role of these epigenetic changes has been linked to many types of cancers [4]. Understanding the mechanisms of how DNA methylation, histone modifications, and miRNA expression influence the abnormal growth of breast cancer has been the center of studies over the past few years.

Bibliometric analysis can be used to evaluate the scientific productivity of breast cancer epigenetics as an emerging research field. The characteristics of existing studies (e.g., number of citations and publications, key authors and co-authorship networks) can be evaluated through bibliometrics analysis [5]. This would allow researchers to have an evidence-based assessment of the existing literature and identify existing gaps and emerging new trends for breast cancer epigenetics research.

There has been no bibliometric analysis yet for global research on breast cancer epigenetics. The closest article to a bibliometric analysis of breast cancer epigenetics is the review paper of Huang et al. [6]. This study briefly touched on the advances in breast cancer epigenetics during that time and reviewed some of the ongoing initiatives for breast cancer. The more recent bibliometric analyses for breast cancer are either region-specific or global but more particular to inflammation, metastases, diagnostic and prognostic biomarkers, or male breast cancers [6-10].

This study aims to provide an overview of the current research landscape of breast cancer epigenetics worldwide. This includes determining the characteristics of existing breast cancer epigenetics studies, particularly on recent advancements in pathophysiology, diagnosis, and treatment, identifying existing networks between countries and authors' keywords, and assessing the association of a country's socioeconomic indicators with its scientific productivity.

2. Materials and Methods

2.1 Data Source and Collection

A literature search was performed on July 12, 2024, for original research articles on breast cancer epigenetics published on the SCOPUS database before 2024. The search string used for the literature search is: (TITLE ("s adenosylmethionine" OR cpg OR epigenetic* OR epigenomic*)) OR (TITLE ((histone* OR dna OR "long interspersed") near/2 (acetyl* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) AND (TITLE ("breast cancer*" OR "breast neoplasm*" OR "breast tumor*" OR "breast malignan*")) AND (PUBYEAR > 1992 AND PUBYEAR < 2024) AND (LIMIT-TO (DOCTYPE, "ar")). The literature search, which includes the search string and the database, was patterned after other recent bibliometric studies on epigenetics [11, 12]. The keywords used for the search string were constructed with NCBI MeSH to ensure inclusion of studies titled with specific epigenetic alterations. The following information was obtained for each article: authors, year of publication, title, journal, institution, country, keywords, and citation frequency.

A total of 688 publications were retrieved from the SCOPUS database for analysis. The search was limited to article titles to ensure that the number of studies collected was adequate. Compared to other databases, the SCOPUS database has a broader coverage of peer-reviewed articles due to its larger number of indexed journals and thus was used as a source of literature for this study [13]. The number of retrieved articles does not directly correspond to the number of referenced studies because SCOPUS already provides an integrated analytical function for large-scale bibliometric assessment without the need to manually evaluate each article and incorporate each finding in this study.

The range of years, 1993 to 2023, is intentionally defined when the search function is conducted in SCOPUS. The decision to finalize 2023 as the cutoff was based on the observation that only a limited number of studies had been published in 2024 at the time of the search. The analysis relied exclusively on original research articles, as review papers are synthesized compilations of existing literature rather than primary data sources. Likewise, conference papers typically present preliminary findings rather than entirely new research.

The GDP, GDP per capita (international dollar unit), research and development (R&D) expenditure, and researchers in R&D were retrieved from the World Bank database (World Bank Data, <https://data.worldbank.org/>). The prevalence of breast cancer data was retrieved from the Global Cancer Observatory (GLOBACON; <https://gco.iarc.fr/en>).

2.2 Identification of Spatiotemporal Networks

VOSViewer 1.6.20 was used to visualize the bibliographic information obtained from SCOPUS. Network visualization was used to identify links between different countries. Overlay visualization was used to analyze the evolution of authors' keywords over time. The analysis was limited to countries with at least three publications and articles with at least 5 keywords. The Bibliometrix package of R was used to supplement the maps created from VOSViewer.

2.3 Statistical Analysis

Statistical analysis was performed on GraphPad Prism version 10. Spearman's rank correlation coefficient was used to analyze the correlation between bibliometric indices (i.e., total publications,

total citations, and h-index) with different country-specific characteristics (i.e., gross domestic product (GDP), GDP per capita, research and development (R&D) expenditure, researchers in R&D, research collaborations, and breast cancer prevalence). This is an appropriate statistical technique because country-specific characteristics are continuous and do not conform to normality assumptions, as observed by deviations when using Pearson's correlation. P-values less than 0.05 ($p < 0.05$) were considered statistically significant.

3. Results

3.1 Characteristics of Published Articles on Breast Cancer Epigenetics

Figure 1 shows the annual scientific productivity of breast cancer epigenetics research based on publications and citations. Since 1993, 688 documents on this field have been published in SCOPUS, with a total of 31,215 citations. The average number of publications and citations per year is 22.19 and 924.26, respectively.

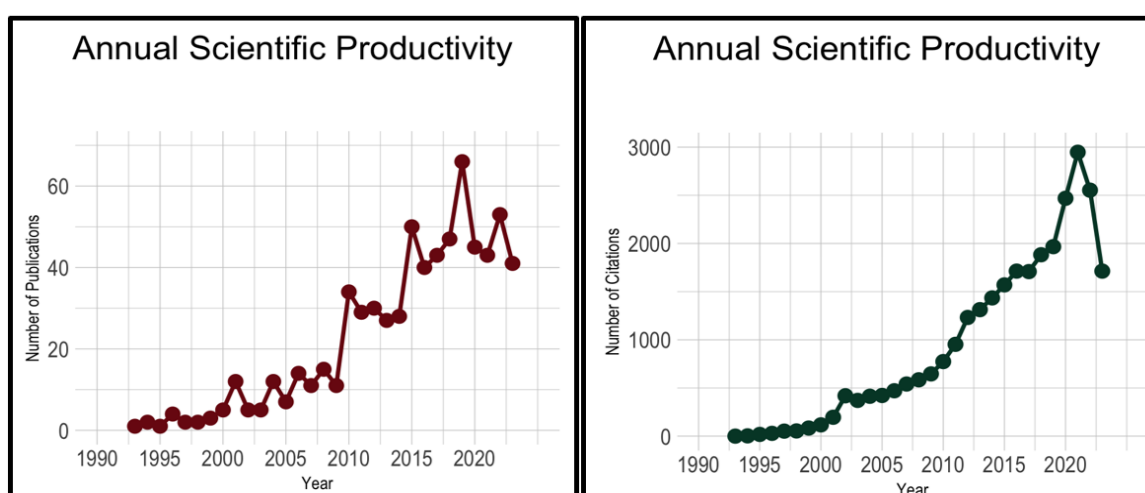


Figure 1 Annual scientific productivity of global research on breast cancer epigenetics: (A) total publications (red), (B) total citations (green).

There is a difference in the trends for the publication and citation curves, as seen in Figure 1A and 1B. The peak productivity for total citations was in 2021, with 2,947 citations. The total citations generally increased every year from 1993 to 2021, but have continuously decreased since 2021 up to the present. The trend mirrors the citation lag observed by an outdated study on breast cancer research citations, which might be attributed to the inherent citation bias towards older publications [14].

However, the trend for publications is not as consistent. The most productive year for publications on breast cancer epigenetics was in 2019, with 66 published articles. Based on the graph (Figure 1A), it was observed that there was a 20.5% increase in the number of publications in 2010.

3.1.1 Core Journal Sources

There are 12 core journal sources identified by Bradford's Law, as shown in Figure 2. The 212 articles published in these journals are noted as the most relevant sources of information for breast

cancer epigenetics research. The leading journals with the highest number of publications in this field include Cancer Research (n = 39), PLOS One (n = 25), Oncotarget (n = 23), Oncogene (n = 22), and Breast Cancer Research and Treatment (n = 18). Cancer Research had the highest total citations (n = 4,530), followed by PLOS One (n = 1,677) and Oncogene (n = 1,307) (Table S1). Among these journals, only four out of 12 journals (i.e., PLOS One, BMC Cancer, International Journal of Molecular Sciences, and Cancers) are available in open access. At the same time, the rest are either mixed open access and subscription-based or purely subscription-based.

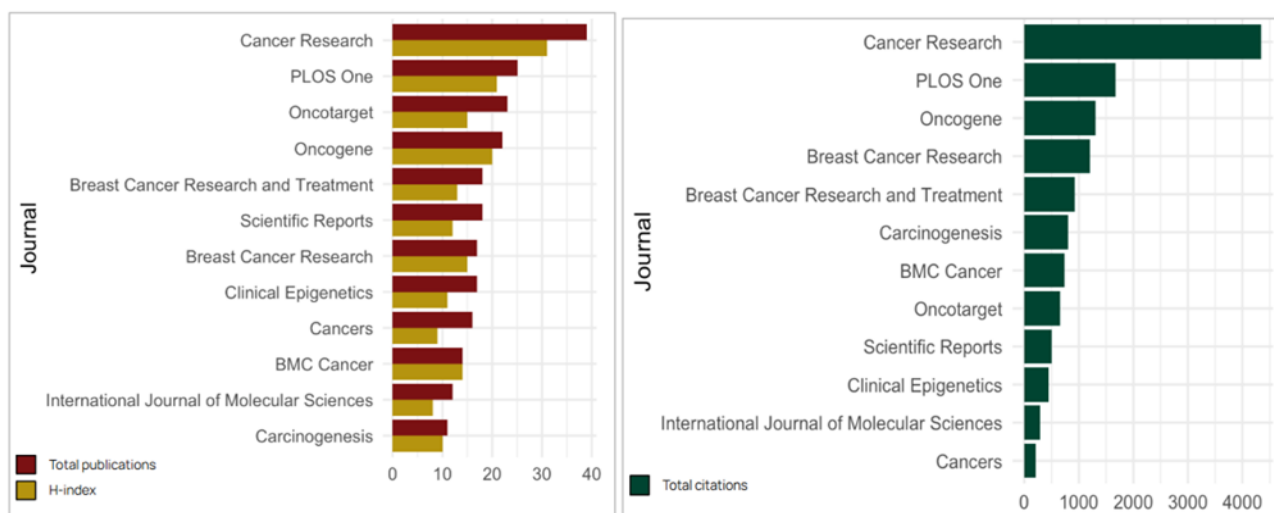


Figure 2 Core journal sources for breast cancer epigenetics research: (A) total publications (red) and h-index (yellow), (B) total citations (green).

Cancer Research has the highest number of total publications. The journal published its first article on breast cancer epigenetics in 1994 and has continued publishing 1.3 articles annually on average. The most productive years for Cancer Research were 2001 and 2010, with 4 articles published in both years. Cancer Research has the highest h-index (h = 31) among all core journal sources.

Cancer Research also has the highest number of total citations. On average, the articles in this journal are cited 145.07 times annually. The highest number of citations was attained in 2013, with 259 citations. The journal has been cited at least 157 times in the past ten years.

3.2 Countries with the Highest Scientific Productivity in Breast Cancer Epigenetics Research

The USA is the most productive country in breast cancer epigenetics research, with 292 publications and 12,878 citations, as shown in Figure 3. This was followed by China (n = 134) and the United Kingdom (n = 45). The United States had the highest total citations (n = 19,033), followed by China (n = 4,560) and the United Kingdom (n = 2,939) (Table S2). The USA started publishing in 1994 and has published 9.73 articles annually on average. The most productive year in the USA in terms of publications was 2015, with 25 articles. The USA published at least 11 articles from 2010 to 2022, but decreased to just 8 in 2023. The USA has articles published in 121 journals, with 42.81% published in the core journals identified. Most of the articles from the USA are published in Cancer Research (10.62%), Oncogene (5.14%), PLOS One (5.14%), and Breast Cancer Research (3.42%). Currently, the USA has an h-index of 77.

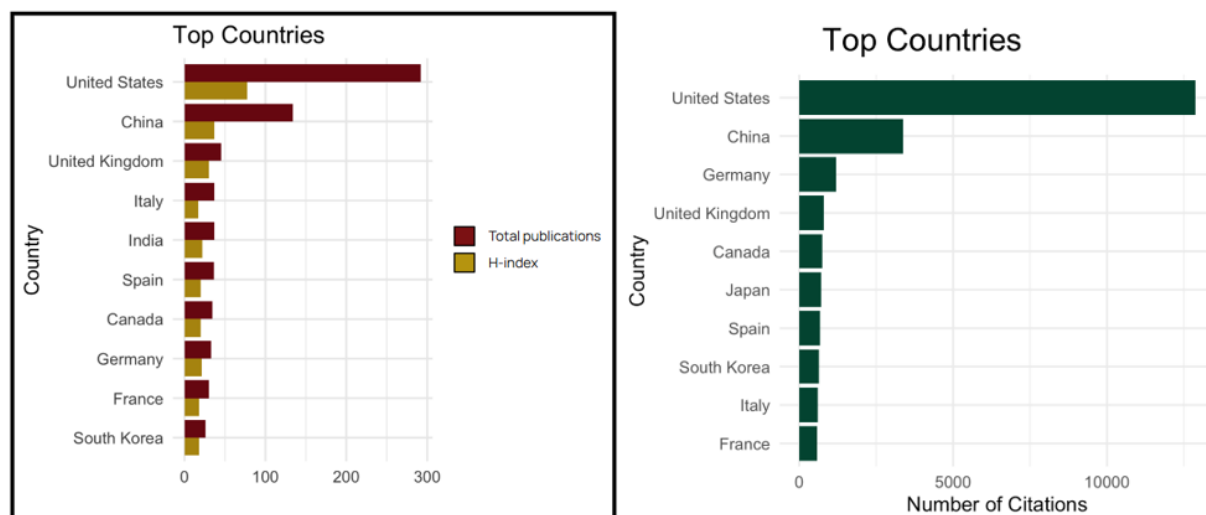


Figure 3 Countries with the highest scientific productivity on breast cancer epigenetics research: (A) total publications (red) and h-index (yellow), (B) total citations (green).

The scientific production of the USA is driven by its major funding sponsors and affiliations, which are also found among the world's top affiliations and funding sponsors. The leading institutions in this field include The University of Alabama in Birmingham, with 22 publications, followed by Johns Hopkins University School of Medicine ($n = 15$), Chinese Academy of Sciences ($n = 14$), and The Sidney Kimmel Comprehensive Cancer Center ($n = 14$). The Sidney Kimmel Comprehensive Cancer Center was the most cited, with total citations of 2175, followed by Johns Hopkins University with 1875 citations, and the University of Alabama in Birmingham with 1784 citations (Table S3). Eight out of the top 10 affiliations in the world with the most publications are from the USA.

The University of Alabama at Birmingham is the top affiliation in the world for breast cancer epigenetics research. Currently, it has an h-index of 18. Most of these documents are authored by Tollefsbol, T.O., with 18 publications and 1,523 citations. Tollefsbol, T.O., ranks first in terms of publications, citations, average citations, and h-index (Table S4). Most documents are published in the International Journal of Molecular Sciences ($n = 3$) and PLOS One ($n = 3$). The National Cancer Institute has funded 81.82% of the articles published by this institution.

Among the top 10 funding sponsors with the most publications for breast cancer epigenetics research, five are from the USA: National Cancer Institute ($n = 146$), National Institutes of Health ($n = 105$), U.S. Department of Health and Human Services ($n = 49$), American Cancer Society ($n = 11$), and Breast Cancer Research Foundation ($n = 11$). The National Cancer Institute is the top funding sponsor worldwide for breast cancer epigenetics research. It has 145 documents, 11,427 citations, and an h-index of 61.

Among the published articles, Burbee and colleagues' study had the highest total citations about the potential tumor suppressor gene RASSF1A in breast cancer (Table 1). The top three articles with the most citations [15, 16]. Hu and colleagues were affiliated with the United States. The studies of Ottaviano and colleagues found that the hypermethylation at the promoter region of the estrogen receptor gene leads to the loss of estrogen receptor expression in human breast cancer cells. At the same time, Hu and colleagues proved that epigenetic changes play a role in the tumorigenesis of breast cancer. Of note, the study of Meeran and colleagues about the effect of sulforaphane leading to the repression of the hTERT expression in human breast cancer cell lines provides a possible link to the therapeutic use of epigenetics in the treatment of breast cancer.

Table 1 Highly cited articles on breast cancer epigenetics based on total citations (TC).

	TC	Authors	Title	Year	Journal	Impact Factor	Quartile Ranking
1	736	Burbee et al. [15]	Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression	2001	Journal of the National Cancer Institute	11.816	5.703 (Q1)
2	458	Ottaviano et al. [16]	Methylation of the Estrogen Receptor Gene CpG Island Marks Loss of Estrogen Receptor Expression in Human Breast Cancer Cells	1994	Cancer Research	12.071	3.879 (Q1)
3	456	Hu et al. [17]	Distinct epigenetic changes in the stromal cells of breast cancers	2005	Nature Genetics	31.8	16.586 (Q1)
4	431	Lehmann et al. [18]	Epigenetic inactivation of microRNA gene hsa-mir-9-1 in human breast cancer	2008	Journal of Pathology	5.6	2.160 (Q1)
5	388	Huang et al. [19]	Methylation profiling of CpG islands in human breast cancer cells	1999	Human Molecular Genetics	3.1	1.560 (Q1)
6	328	Hoffman et al. [20]	microRNA miR-196a-2 and breast cancer: A genetic and epigenetic association study and functional analysis	2009	Cancer Research	12.071	3.879 (Q1)
7	301	Meeran et al. [21]	Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines	2010	PLOS One	2.9	0.803 (Q1)
8	282	Zöchbauer-Müller et al. [22]	5' CpG island methylation of the FHIT gene is correlated with loss of gene expression in lung and breast cancer	2001	Cancer Research	12.071	3.879 (Q1)

9	281	Dammann et al. [23]	Hypermethylation of the cpg island of Ras association domain family 1A (RASSF1A), a putative tumor suppressor gene from the 3p21.3 Locus, occurs in a large percentage of human breast cancers	2001	Cancer Research	12.071	3.879 (Q1)
10	268	Doherty et al. [24]	In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: An epigenetic mechanism linking endocrine disruptors to breast cancer	2010	Hormones and Cancer	4.667	0.880 (Q2)

Figure 4 illustrates the keyword co-occurrence network derived from the 100 most highly cited articles. The analysis identified three distinct thematic clusters. The red cluster, characterized by terms such as “major clinical study,” “gene silencing,” and “breast cancer,” corresponds to Clinical and Genomic Oncology. The green cluster, featuring keywords like “cell line,” “animal models,” and “epigenesis,” reflects the domain of Preclinical and Experimental Cancer Models. The blue cluster, with terms such as “gene repression,” “histones,” and “DNA methyltransferase,” represents Molecular Epigenetics, highlighting mechanistic studies of gene regulation in breast cancer.

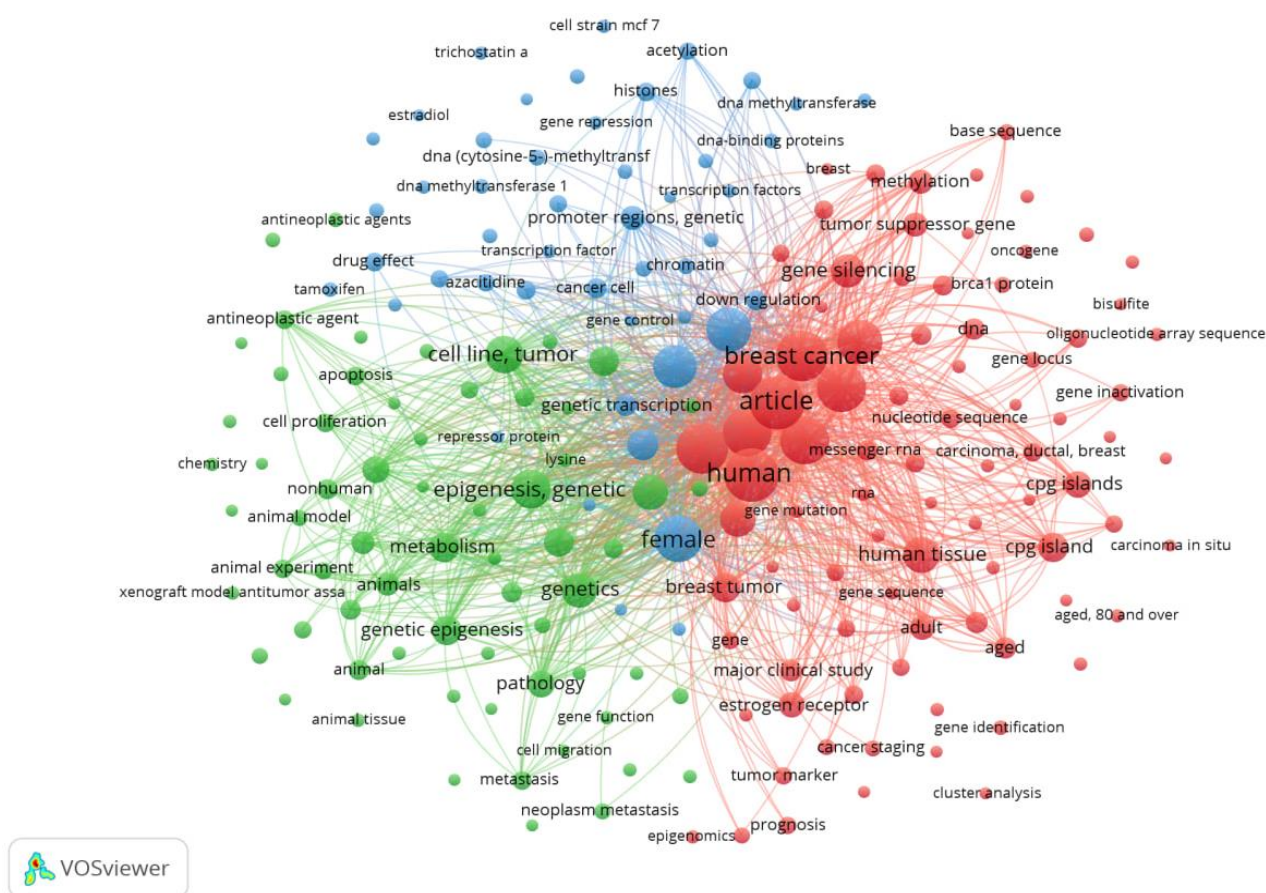


Figure 4 Network visualization of keywords used in global research on breast cancer epigenetics. The size of each circle is directly proportional to the number of articles using the keyword. The lines represent the co-occurrence of a keyword with other keywords.

3.2.1 International Collaborations on Global Breast Cancer Epigenetics Research

Figure 5 visualizes the international collaborations on breast cancer epigenetics research. This network is established based on the number of links (L) and total link strength (TLS): the links indicate the number of co-authorship links a country has with other countries, while the total link strength indicates the total strength of these links.

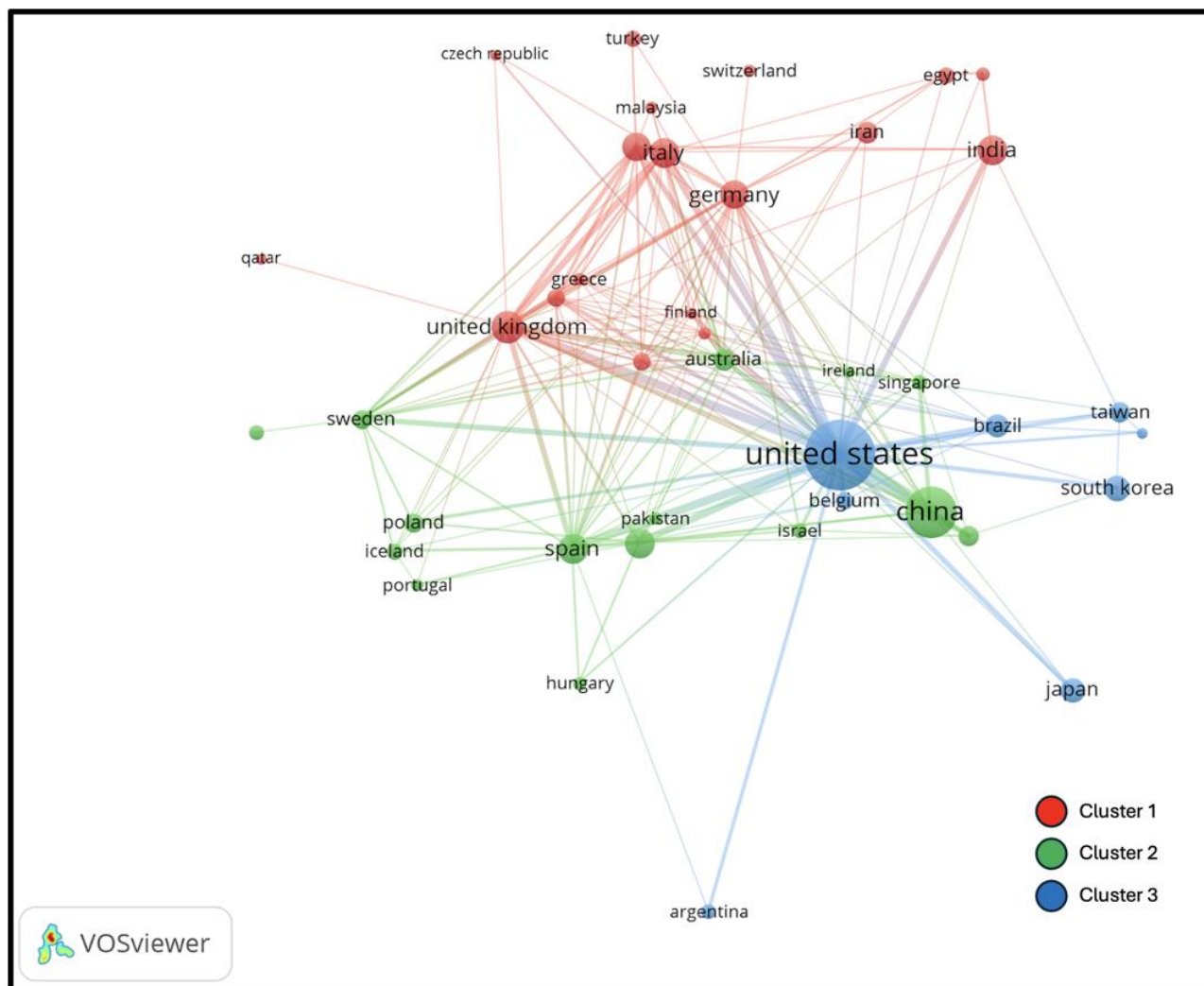


Figure 5 Network visualization for international collaborations on breast cancer epigenetics research. The size of each circle is directly proportional to the number of published articles on breast cancer epigenetics from a particular country. The lines reflect the frequency of co-authored publications between the connected countries. The colors represent the clusters of countries that collaborate frequently with one another.

This study identified three main clusters: Clusters 1, 2, and 3, which are central to the United Kingdom, China, and the USA, respectively. Cluster 1 is the largest in terms of the number of countries ($n = 18$) and has the highest average for links ($L = 10.22$), while Cluster 3 has the highest average for total link strength ($TLS = 31.25$), documents ($n = 49$), and citations ($n = 2888.88$).

The networks for Cluster 1 and Cluster 3 are of particular interest. Cluster 1 has higher links than Cluster 3 but has a lower score for total link strength. The cluster analysis results suggest that 1) the USA mainly drives the scientific production of Cluster 3, and 2) there is a strong internal collaboration within Cluster 1.

The USA plays a central role in the productivity of Cluster 3. Aside from having the highest number of publications and citations, the USA also has the highest scores for links ($L = 34$) and total link strength ($TLS = 186$) among all countries included in the analysis. This contrasts with other countries in its cluster: Argentina, Belgium, Brazil, Chile, Japan, South Korea, and Taiwan, with scores for links and total link strength of 10 and 17 at most, respectively. This further asserts the global

role of the USA in breast cancer epigenetics research, driving the productivity of a cluster with few countries and less scientific production.

Of equal importance to global productivity are the collaborations identified within Cluster 1. Notably, 12 of the 18 countries in Cluster 1 are from Europe: the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Switzerland, Turkey, and the United Kingdom. These countries alone have an average score of 11.92, which is already higher than those of Clusters 2 and 3. This would mean a strong, internal collaboration within the European bloc on breast cancer epigenetics studies.

3.2.2 Country-Level Factors Associated with Breast Cancer Epigenetics Research Productivity

This study showed that the number of research collaborations was significantly correlated with the total citations ($p = 0.049$) and h-index ($p = 0.049$) (Table 2). Other country-level factors, such as population, GDP (in billions), GDP per capita, R&D expenditure, researchers in R&D, research collaborations, and prevalence of breast cancer, did not have a significant correlation with the bibliometric indices for breast cancer epigenetics research.

Table 2 Association of socioeconomic and epidemiologic indicators with scientific productivity.

Indicators	Bibliometric indices	r	p-value
Gross domestic product (in USD, billions)	Total publications	0.620	0.061
	Total citations	0.576	0.088
	h-index	0.549	0.104
Gross domestic product per capita (in USD)	Total publications	0.018	0.965
	Total citations	0.467	0.179
	h-index	0.421	0.226
Research & Development Expenditure (% GDP)	Total publications	-0.079	0.830
	Total citations	0.370	0.296
	h-index	0.390	0.264
Researchers in R&D (per million people)	Total publications	-0.723	0.022
	Total citations	-0.188	0.607
	h-index	-0.195	0.587
Research collaborations	Total publications	0.420	0.227
	Total citations	0.649	0.049
	h-index	0.646	0.049
Prevalence of breast cancer (crude rate per 100,000)	Total publications	-0.274	0.441
	Total citations	0.188	0.607
	h-index	0.134	0.712

3.3 Most Common Authors' Keywords in Breast Cancer Epigenetics Research

The co-occurrence map for authors' keywords in breast cancer epigenetics research is shown in Figure 6. There are 47 keywords analyzed in this study. The most used keywords in this field, based on the number of occurrences (n), are "breast cancer" (n = 273) and "DNA methylation" (n = 118).

There are six keyword clusters identified, but there are no dominant themes for the keywords in each cluster across all clusters.

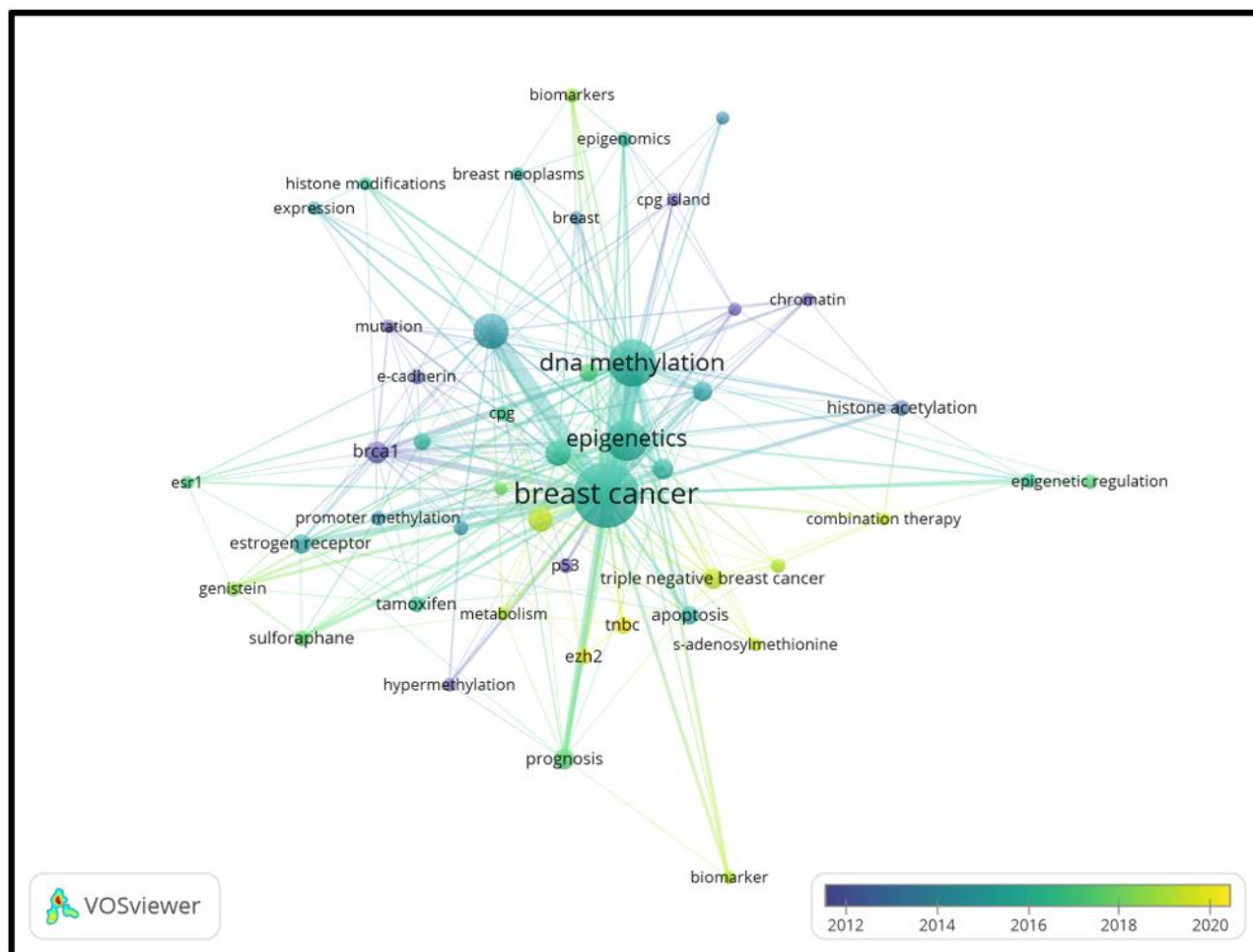


Figure 6 Overlay visualization of authors' keywords associated with breast cancer epigenetics research. The size of each circle is directly proportional to the number of articles that used the particular keyword. The lines represent the co-occurrence of keywords in published articles, with line widths directly proportional to the frequency of co-occurrence. The color gradient represents the average publication year (APY) of keywords from older (purple) to more recent (yellow).

However, a trend was observed upon analysis based on average publication year (APY). The earliest keyword used in breast cancer epigenetics studies was “trichostatin A” (APY = 2005.8). The first keywords used are keywords related to oncogenes or tumor suppressor genes: “p53” (APY = 2010.43), “brca1” (APY = 2011.32), “e-cadherin” (APY = 2012.23). The most used keyword during this time frame was “BRCA1” (n = 19).

From 2012 to 2016, the trend shifted from cancer-related genes to molecular mechanisms, particularly those related to epigenetic alterations. These include “histone acetylation” (n = 8), “promoter methylation” (n = 7), “histone methylation” (n = 7), “histone modification” (n = 10), and “methylation” (n = 56). Other epigenetics-related keywords in this time frame are “epigenetic” (n = 28), “epigenetic silencing” (n = 5), “epigenomics” (n = 7), and “epigenetics” (n = 85). The most used keywords during this time frame are “breast cancer” (n = 273) and “DNA methylation” (n = 118).

The trend has shifted from epigenetic alterations to therapeutics since 2016. This might be attributed to the emergence of prognostic studies for triple-negative breast cancer, an aggressive form of cancer. The top keywords used in this time frame are “triple negative breast cancer” (n = 15), “triple-negative breast cancer” (n = 23), “prognosis” (n = 15), and “tnbc” (n = 10). The keywords related to therapeutics that are commonly used in this time frame are “combination therapy” (n = 6), “s-adenosylmethionine” (n = 6), “decitabine” (n = 7), “genistein” (n = 7), and “sulforaphane” (n = 9).

4. Discussion

This study provided an overview of the status of global research on breast cancer epigenetics in terms of scientific productivity and ongoing international collaborations. It also analyzed emerging topics and trends in the research field and identified country-specific characteristics significantly associated with scientific productivity.

4.1 Shift in Research Trend of Breast Cancer Epigenetics Towards Therapeutics

Breast cancer is the second most common cancer worldwide, affecting 2,296,840 patients as of 2022. It is also the first most common cancer among women [25]. Among the most common causes of breast cancer are heritable alterations in normal epigenetics [26]. These alterations include genome-wide loss of DNA methylation, hypermethylation in CpG promoters of tumor suppressor genes, histone modifications, and dysregulated ncRNA networks. These alterations would result in the activation of oncogenes, suppression of tumor suppressor genes, and other gene expression changes associated with cancer tumorigenesis.

The research on breast cancer epigenetics started in the early 1990s. The first papers published on breast cancer epigenetics research explored epigenetic alterations on CpG islands and the overexpression of S-adenosylmethionine decarboxylase, a known DNA methylating enzyme, in human breast cancer cells [16, 27, 28].

However, in recent years, there has been an increase in the number of studies on breast cancer epigenetics that explored therapeutics. This can also be seen in the overlay visualization results of this study, as seen in Figure 6. The trend may be attributed to the emergence of different hurdles in breast cancer therapy: the rise of drug resistance, intra- and inter-tumor heterogeneity, and disease relapse post-chemotherapy [29].

The shift in the research trend of breast cancer epigenetics to therapeutics may be attributed to the recent emergence of multi-omics technology. This would include technologies on single-cell omics, genomics, transcriptomics, proteomics, and epigenomics that are currently utilized in the development of personalized therapeutics for different cancer subtypes [30]. With the recent keywords on breast cancer epigenetics being related to biomarker discovery, chemotherapeutic agents, and epigenomics, the use of multi-omics technology in breast cancer research may be focused on addressing the current challenges in breast cancer therapy. The shift to therapeutics due to multi-omics technology is also consistent with the results of recent bibliometric analysis in other types of cancers [31, 32].

4.1.1 Development of Epidrugs in Recent Breast Cancer Epigenetic Studies

This shift can also be attributed to the development of epidrugs. Epidrugs are novel therapeutic agents that target the reversal of aberrant epigenetic alterations commonly seen in breast cancer cells. There are different classes of drugs based on the epigenetic processes they regulate (i.e., DNA methylation, histone methylation and acetylation, tumor suppressor, and oncogenic miRNAs) [26, 33]. However, this section only discusses epigenetic drugs involved in DNA methylation (i.e., decitabine), histone methylation (i.e., EZH2, s-adenosylmethionine), and histone acetylation (i.e., trichostatin A), as these epigenetic drugs are identified in the previous keyword analysis.

DNA methyltransferase inhibitors (DMTIs) and decitabine. DNA methylation in breast cancer epigenetics is facilitated by DNA methyltransferases (DNMT), which form 5-methylcytosine upon covalent addition of methyl groups on the 5' position of the cytosine pyrimidine ring. In humans, this process is mediated by DNMT1, DNMT2, and DNMT3 and usually occurs in the promoter CpG islands [26]. Decitabine, or 5-aza-2'-deoxycytidine, is a known inhibitor of DNA methyltransferases, primarily DNMT1. Decitabine is a cytosine analog that acts as an inhibitor of DNMTs [34, 35]. This results in the inhibition of DNMT-mediated methylation post-replication. Clinical trials by the National Cancer Institute are still ongoing (e.g., NCT02957968), but the results are promising for decitabine [36]. Decitabine is also being investigated in an ongoing clinical trial (NCT03295552) for triple-negative breast cancer [37].

Histone methyltransferase inhibitors and S-adenosylmethionine. Histone methyltransferases are responsible for the methylation of histones. The polycomb group proteins (PcGs) are an essential group of histone methyltransferases. These proteins are involved in dysregulated gene expression in tumorigenesis. The PcGs have two core complexes, polycomb repressive complexes 1 (PRC1) and 2 (PRC2). PRC2 is a known methylator of histone H3 at lysine 27 [38].

The catalytic subunit of PRC2 is the zeste homolog 2 (EZH2) enhancer, which is responsible for the trimethylation of H3K27. The EZH2-mediated methylation of H3K27 is accountable for the dysregulated gene expression of many genes involved in proliferation, differentiation, and self-renewal, implicating the role of this enzyme in cancer development [33]. Many cancers have also been identified to be associated with EZH2 overexpression and gain-of-function mutations [39, 40]. Recent studies have identified the role of upregulated EZH2 in inhibiting the tumor suppressor PTEN gene in breast cancer cells [41].

Also among the keywords analyzed in this study is s-adenosylmethionine (SAM). SAM is a universal donor for methyltransferases, and several recent studies have developed competitive inhibitors of SAM that can target cells with overexpressed EZH2. Specifically, these inhibitors bind to the SAM-binding sites of EZH2, effectively inhibiting EZH2 [10]. Most of the identified SAM-competitive inhibitors are in preclinical stages, except for tazemetostat, valemetostat, GSK126, CPI-1205, CPI-0209, PF-06821497, SHR2554, and HH2583, which are currently under clinical trials. Tazemetostat is the only FDA-approved SAM-competitive inhibitor specific to EZH2 and is presently used in the treatment of advanced follicular lymphoma and epithelioid sarcoma [42].

Histone deacetylase inhibitors (HDACi) and trichostatin A. Histone deacetylases (HDACs) are involved in the post-translational modification of histones, particularly in histone deacetylation and chromatin condensation in heterochromatin formation. This results in the silencing of genes, acting

as a counterpart to acetylations mediated by histone acetyltransferases. The aberrant HDAC-mediated epigenetic regulation of tumor suppressor genes and oncogenes has been associated with different cancer hallmarks in breast cancer and other invasive cancers [43].

Trichostatin A is a known inhibitor of HDACs and has been associated with the induction of cell growth arrest, differentiation, and apoptosis in different cancer cells upon administration [44]. In breast cancer cells, trichostatin A inhibits growth upon degradation of cyclin D1 and inhibition of estrogen receptors in both ER+/- cell lines [45]. Trichostatin A also reverses epithelial-mesenchymal transition and induces apoptosis in breast cancer cells [46, 47]. However, no clinical trial has been ongoing for the use of trichostatin A.

Given the current barriers to existing chemotherapy in clinical settings, the development of new therapeutic avenues is of urgent significance. The emergence of epigenetic therapy, with its potential role in breast cancer therapeutics, provides a promising addition to existing combinations of chemotherapy, immunotherapy, and targeted therapies for patients with aggressive or chemoresistant breast cancer.

4.2 Programs and Initiatives on Breast Cancer Epigenetics

The United States serves as a hotspot for research on breast cancer epigenetics, contributing up to 41.48% of total publications and most citations. This parallels the burden of prevalence in the United States, where there has been an increase to 137 (per 100,000) age-standardized breast cancer incidence rate in 2019, prompting the need to address the global health problem of breast cancer [48]. Although the prevalence of breast cancer in Asian countries had been historically low, China had the second-highest number of publications and citations. There has been a steady increase in the incidence and mortality of breast cancer in Chinese women, and it is projected to have an 11% increase by 2030 [49].

Despite having the second-highest publications and citations, China and India lag behind the leading countries in terms of average citations or citations per publication (CPP). The later entry of both countries into breast cancer epigenetics research, compared to the US and European countries, may have contributed to this trend. However, China's steady increase in publications reflects a substantial expansion of research, accompanied by ongoing improvements in research quality. Given the global disparities in funding and infrastructure, such as the influence of initiatives from NIH grants, supporting high-quality research remains a crucial focus for China and other developing countries.

As the top funding sponsor for breast cancer epigenetic research, the National Cancer Institute established the Specialized Programs of Research Excellence (SPOREs) in 1992 to promote collaborative research on translational cancer research by providing grants to study and address human cancers. For the fiscal year 2023, SPORE grants \$4.6 million for epigenetics studies and \$11 million for breast cancer. This may have implications for interested researchers to apply for research grants that center on the epigenetics and treatment of breast cancer [50].

The National Cancer Institute was identified as a key funding sponsor in 2010, which is the same year breast cancer epigenetics research was most productive. As the top funding sponsor, the NCI funded over 12% (\$631.2 million) of its total budget to breast cancer research. This was a \$31.7 million increment from their 2009 funding [51]. In addition, beginning in October 2010, the Epigenome Project started to release data that included more than 300 maps of epigenetic changes in over 56 cell and tissue types, including several normal breast cells [6].

4.3 Policy Implications

Overall, the different programs and initiatives on breast cancer epigenetics led to an improved understanding of the mechanisms by which DNA methylation and histone modifications influence the tumorigenesis of breast cancer. Through various research grants, we were able to begin uncovering the role of epigenetics in therapeutics, particularly in the study of cancer. Although the clinical application of epidrugs is still under investigation through clinical trials, their potential impact on global policy formulation is substantial. Their implications extend beyond advancing scientific knowledge as these drugs show promise not only in cancer treatment but also in addressing a broader spectrum of diseases.

Funding agencies, pharmaceutical companies, the WHO, and the NCI will play key roles in advancing the use of epidrugs for breast cancer treatment and broader disease management. Globally, collaborative efforts will drive advancements in these implications, with identified countries leading research and application development. Although we are far from achieving the three pillars of the WHO, we have made significant progress in achieving this goal.

5. Limitations

While these results substantially contributed to the field, it is also important to acknowledge their limitations. First, this analysis mainly relied on citations and h-index as indicators of research impact. While this is partly true, as the cited studies are deemed of scholarly importance by the authors who cite them, this should not necessarily be equated with their impact in the field. This study did not account for self-citations, nor has it checked for the number of citations that are specific to some research areas only. Second, this study did not go beyond the use of citations for impact assessment. This study did not use the available altimetric data, which could have given a more holistic insight into the study's impact on media, policies, and other aspects outside of bibliometrics. Aside from this, a citation-centered analysis of an article's impact does not consider the temporal aspect of publications. The actual impact may not be fully captured by the citations of a recently published article. It may not be equated to an older article with more time to accumulate citations. Similar to the previous limitation, a high quantity of citations does not necessarily mean high quality, as this could be skewed by the preference of a body to publish in high-impact-factor journals that could easily skew an article's number of citations.

6. Conclusions

This study provided quantitative evidence for the progress of breast cancer epigenetics research globally in terms of productivity, collaborations, and citations. Administrators and policymakers can use the results of this analysis for evidence-based decision-making on the implementation of current breast cancer epigenetics programs. Particularly, this study can be used as evidence to increase collaborations with developing countries to address the burden of breast cancer across different races and countries for a better global impact. Also, the findings of this study can be used to better allocate resources for breast cancer epigenetics programs in light of current therapeutics development trends.

Author Contributions

KJG: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, visualization, writing - original draft, writing - review & editing; HR: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, writing - original draft, writing - review & editing; OAGT: Supervision, validation, writing - review & editing.

Funding

The authors declare that the research did not receive any form of external funding.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that can be construed as a potential conflict of interest.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Leading journals that published on breast cancer epigenetics.
2. Table S2: Citation analysis of publications about epigenetics and breast cancer from countries worldwide.
3. Table S3: Leading institutions that published research on breast cancer epigenetics.
4. Table S4: Leading authors who published breast cancer epigenetics.
5. Figure S1: Overview of Methods in relation to Study's Objectives.

References

1. Wilkinson L, Gathani T. Understanding breast cancer as a global health concern. *Br J Radiol*. 2022; 95: 20211033.
2. World Health Organization. Breast cancer [Internet]. Geneva, Switzerland: World Health Organization; 2024. Available from: <https://www.who.int/news-room/fact-sheets/detail/breast-cancer>.
3. World Health Organization. New global breast cancer initiative highlights renewed commitment to improve survival [Internet]. Geneva, Switzerland: World Health Organization; 2021. Available from: <https://www.who.int/news/item/08-03-2021-new-global-breast-cancer-initiative-highlights-renewed-commitment-to-improve-survival>.
4. Weinhold B. Epigenetics: The science of change. *Environ Health Perspect*. 2006; 114: A160-A167.
5. Kumar M, George RJ, Anisha PS. Bibliometric analysis for medical research. *Indian J Psychol Med*. 2023; 45: 277-282.
6. Huang Y, Nayak S, Jankowitz R, Davidson NE, Oesterreich S. Epigenetics in breast cancer: What's new? *Breast Cancer Res*. 2011; 13: 225.
7. Al-Kahtani R, Mahmood N, Aamir S, Anjum Z. Visualizing breast cancer research trends in KSA: A bibliometric analysis. *J Taibah Univ Med Sci*. 2023; 18: 1472-1479.

8. Jiang S, Meng Q, Ji F, Yin Y, Liu X, Shi W, et al. A bibliometric analysis of metastatic breast cancer: Two-decade report (2002-2022). *Front Oncol.* 2023; 13: 1229222.
9. Meng G, Xu H, Yang S, Chen F, Wang W, Hu F, et al. Bibliometric analysis of worldwide research trends on breast cancer about inflammation. *Front Oncol.* 2023; 13: 1166690.
10. Liu Y, Yang Q. The roles of EZH2 in cancer and its inhibitors. *Med Oncol.* 2023; 40: 167.
11. Nour El Huda AR, Mohd Asyraf AJ, Norlelawati AT, Siti Norain MR, Wan Muhamad Salahudin WS, Norainin Sofiya A, et al. Schizophrenia and epigenetics: A comprehensive bibliometric analysis. *Middle East Curr Psychiatry.* 2023; 30: 115.
12. Zhao Y, Ai W, Zheng J, Hu X, Zhang L. A bibliometric and visual analysis of epigenetic research publications for Alzheimer's disease (2013-2023). *Front Aging Neurosci.* 2024; 16: 1332845.
13. Hosseiniara R. General comparison of scientific databases of Scopus, PubMed, and Web of Science. *Nov Clin Med.* 2023; 2: 168-169.
14. Glynn RW, Scutaru C, Kerin MJ, Sweeney KJ. Breast cancer research output, 1945-2008: A bibliometric and density-equalizing analysis. *Breast Cancer Res.* 2010; 12: R108.
15. Burbee DG, Forgacs E, Zöchbauer-Müller S, Shivakumar L, Fong K, Gao B, et al. Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression. *J Natl Cancer Inst.* 2001; 93: 691-699.
16. Ottaviano YL, Issa JP, Parl FF, Smith HS, Baylin SB, Davidson NE. Methylation of the estrogen receptor gene CpG island marks loss of estrogen receptor expression in human breast cancer cells. *Cancer Res.* 1994; 54: 2552-2555.
17. Hu M, Yao J, Cai L, Bachman KE, Van Den Brûle F, Velculescu V, et al. Distinct epigenetic changes in the stromal cells of breast cancers. *Nat Genet.* 2005; 37: 899-905.
18. Lehmann U, Hasemeier B, Christgen M, Müller M, Römermann D, Länger F, et al. Epigenetic inactivation of microRNA gene hsa-mir-9-1 in human breast cancer. *J Pathol.* 2008; 214: 17-24.
19. Huang TH, Perry MR, Laux DE. Methylation profiling of CpG islands in human breast cancer cells. *Hum Mol Genet.* 1999; 8: 459-470.
20. Hoffman AE, Zheng T, Yi C, Leaderer D, Weidhaas J, Slack F, et al. microRNA miR-196a-2 and breast cancer: a genetic and epigenetic association study and functional analysis. *Cancer Res.* 2009; 69: 5970-5977.
21. Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. *PLoS One.* 2010; 5: e11457.
22. Zöchbauer-Müller S, Fong KM, Maitra A, Lam S, Geradts J, Ashfaq R, et al. 5' CpG island methylation of the FHIT gene is correlated with loss of gene expression in lung and breast cancer. *Cancer Res.* 2001; 61: 3581-3585.
23. Dammann R, Yang G, Pfeifer GP. Hypermethylation of the cpG island of Ras association domain family 1A (RASSF1A), a putative tumor suppressor gene from the 3p21.3 locus, occurs in a large percentage of human breast cancers. *Cancer Res.* 2001; 61: 3105-3109.
24. Doherty LF, Bromer JG, Zhou Y, Aldad TS, Taylor HS. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: an epigenetic mechanism linking endocrine disruptors to breast cancer. *Horm Cancer.* 2010; 1: 146-155.
25. World Cancer Research Fund. Breast cancer statistics [Internet]. London, UK: World Cancer Research Fund; 2022. Available from: <https://www.wcrf.org/preventing-cancer/cancer-statistics/breast-cancer-statistics/>.

26. Kim A, Mo K, Kwon H, Choe S, Park M, Kwak W, et al. Epigenetic regulation in breast cancer: Insights on epidrugs. *Epigenomes*. 2023; 7: 6.
27. van Agthoven T, Van Agthoven T, Dekker A, Foekens JA, Dorssers L. Induction of estrogen independence of ZR-75-1 human breast cancer cells by epigenetic alterations. *Mol Endocrinol*. 1994; 8: 1474-1483.
28. Manni A, Badger B, Grove R, Kunselman S, Demers L. Isolation and characterization of human breast cancer cells overexpressing S-adenosylmethionine decarboxylase. *Cancer Lett*. 1995; 95: 23-28.
29. Szczepanek J, Skorupa M, Jarkiewicz-Tretyn J, Cybulski C, Tretyn A. Harnessing epigenetics for breast cancer therapy: The role of DNA methylation, histone modifications, and MicroRNA. *Int J Mol Sci*. 2023; 24: 7235.
30. Lou W, Li Y. Research trend of lung cancer epigenetics research: Bibliometric and visual analysis of top-100 cited documents. *Heliyon*. 2024; 10: e35686.
31. Li H, Wu P. Epigenetics in thyroid cancer: A bibliometric analysis. *Endocr Connect*. 2024; 13: e240087.
32. Li S, Liang X, Shao Q, Wang G, Huang Y, Wen P, et al. Research hotspots and trends of epigenetic therapy in oncology: A bibliometric analysis from 2004 to 2023. *Front Pharmacol*. 2024; 15: 1465954.
33. Idrissou M, Sanchez A, Penault-Llorca F, Bignon YJ, Bernard-Gallon D. Epi-drugs as triple-negative breast cancer treatment. *Epigenomics*. 2020; 12: 725-742.
34. Stresemann C, Lyko F. Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine. *Int J Cancer*. 2008; 123: 8-13.
35. Chowdhury B, McGovern A, Cui Y, Choudhury SR, Cho IH, Cooper B, et al. The hypomethylating agent Decitabine causes a paradoxical increase in 5-hydroxymethylcytosine in human leukemia cells. *Sci Rep*. 2015; 5: 9281.
36. Wang H, Wang Z, Wang Z, Li X, Li Y, Yan N, et al. Decitabine induces IRF7-mediated immune responses in p53-mutated triple-negative breast cancer: A clinical and translational study. *Front Med*. 2024; 18: 357-374.
37. Lehmann U. Epigenetic therapies in triple-negative breast cancer: Concepts, visions, and challenges. *Cancers*. 2024; 16: 2164.
38. Pasini D, Di Croce L. Emerging roles for Polycomb proteins in cancer. *Curr Opin Genet Dev*. 2016; 36: 50-58.
39. Barsotti AM, Ryskin M, Rollins RA. Epigenetic reprogramming in solid tumors: Therapeutic implications of EZH2 gain-of-function mutations. *Epigenomics*. 2015; 7: 687-690.
40. Gan L, Yang Y, Li Q, Feng Y, Liu T, Guo W. Epigenetic regulation of cancer progression by EZH2: From biological insights to therapeutic potential. *Biomark Res*. 2018; 6: 10.
41. Pappas K, Martin TC, Wolfe AL, Nguyen CB, Su T, Jin J, et al. NOTCH and EZH2 collaborate to repress PTEN expression in breast cancer. *Commun Biol*. 2021; 4: 312.
42. Yang X, Xu L, Yang L. Recent advances in EZH2-based dual inhibitors in the treatment of cancers. *Eur J Med Chem*. 2023; 256: 115461.
43. Zhao H, Zhang XM, Xiao S, Wu ZR, Shi YJ, Xie MJ. HDAC11 is related to breast cancer prognosis and inhibits invasion and proliferation of breast cancer cells. *Int J Clin Exp Pathol*. 2023; 16: 172-183.

44. Zhang X, Jiang SJ, Shang B, Jiang HJ. Effects of histone deacetylase inhibitor trichostatin A combined with cisplatin on apoptosis of A 549 cell line. *Thorac Cancer*. 2015; 6: 202-208.
45. Rathinavelu A, Natarajan U. HDAC inhibition in cancer. In: *Epigenetics in organ specific disorders*. Amsterdam, Netherlands: Elsevier; 2023. pp. 63-97.
46. Sun S, Han Y, Liu J, Fang Y, Tian Y, Zhou J, et al. Trichostatin A targets the mitochondrial respiratory chain, increasing mitochondrial reactive oxygen species production to trigger apoptosis in human breast cancer cells. *PLoS One*. 2014; 9: e91610.
47. Wang X, Chen S, Shen T, Lu H, Xiao D, Zhao M, et al. Trichostatin A reverses epithelial-mesenchymal transition and attenuates invasion and migration in MCF-7 breast cancer cells. *Exp Ther Med*. 2020; 19: 1687-1694.
48. Sedeta ET, Jobre B, Avezbakiyev B. Breast cancer: Global patterns of incidence, mortality, and trends. *Am Soc Clin Oncol*. 2023; 41: 10528.
49. Lei S, Zheng R, Zhang S, Chen R, Wang S, Sun K, et al. Breast cancer incidence and mortality in women in China: Temporal trends and projections to 2030. *Cancer Biol Med*. 2021; 18: 900-909.
50. National Cancer Institute. Specialized Programs of Research Excellence (SPORes) [Internet]. Bethesda, MD: National Cancer Institute; 2024. Available from: <https://www.cancer.gov/about-nci/budget/fact-book/extramural-programs/spores>.
51. National Cancer Institute. The nation's investment in cancer research: A budget fact book [Internet]. U.S. Department of Health and Human Services, National Institutes of Health; 2010. Available from: <https://www.cancer.gov/about-nci/budget/fact-book/archive/2010-fact-book.pdf>.