Exploring New Targets and Publication Tendency of Triple Negative Breast Cancer: A 20-Year Bibliometric Analysis

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Abstract

Background: Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, and it lacks an efficient target treatment. Here, we aimed to gain knowledge on the development of TNBC research and explore potential treatment strategies.

Methods: We analyzed 14,389 publications on TNBC from the Web of Science (WOS) over the past 20 years, from 2000 to 2020, using bibliometric methods. We evaluated the publication tendency of TNBC and the contributions of different countries. Institutions and journals with the highest number of TNBC publications were screened. Finally, the research focus of the TNBC publications were also analyzed.

Results: TNBC publications have significantly increased in the past 20 years, with elevated relative research interest (RRI). The USA has the most TNBC-related publications with high quality, and China is the country with the most rapid growth tendency in TNBC publications. The University of Texas System is the institution with the most TNBC publications. Breast Cancer Research and Treatment is the journal that published the most TNBC-related publications. The top 30 publications with high citations are also listed. The researches focusing on TNBC in the past 20 years were separated into four main clusters: tumor biology, TNBC therapies, treatment sensitivity, and gene mutations. The research focus in TNBC ranked by appearing years reflects the development of TNBC treatment strategy, showing that targeting tumor immunity is now the main focus in TNBC research.

Conclusions: Using bibliometric analysis, we initially revealed the increasing interest in TNBC research and summarized the publication tendency of TNBC. We also reported focused topics screened from publications in the past 20 years, indicating the main problems and research objectives of TNBC for the first time. Immune-related topics are becoming the focus of TNBC research.

Introduction

By 2020, breast cancer has become the malignant tumor with the highest prevalence in women worldwide (1). Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are the three most widely used markers for classifying breast cancer. The role of hormone and hormone receptors in breast cancer was first reported in 1896 (2). HER2 expression in breast cancer was reported in the 1980s (3). In the late 1990s, the HER2 agent trastuzumab was the first agent approved for HER2+ breast cancer. After that, the concept of triple-negative breast cancer (TNBC) with ER, PR, and HER2, which all appeared negative, has gradually attracted more attention.

TNBC is a breast cancer with the poorest prognosis, accounting for approximately 15% of all breast cancers (4). Contrary to other types of breast cancer, TNBC therapy lacks effective treatment targets and mainly relies on chemotherapy. Although there have been various preclinical or clinical studies attempting to identify new TNBC targets, the poor prognosis of TNBC has not improved significantly. Thus, identification of new potential targets based on existing research is urgently needed.
Bibliometric analysis is a scientific method to evaluate publications quantitatively and qualitatively, which helps to gain knowledge of the research trend in specific terms (5). As an analytical method, bibliometric analysis of certain diseases can also guide clinical strategy and translational research.

Here, in order to gain knowledge on TNBC research tendency and explore potential targets of TNBC from research focus, a bibliometric analysis of publications about TNBC recorded in the Web of Science (WOS) database was conducted. Because the concept of TNBC was put forth nearly 20 years ago, we analyzed publications about TNBC in the past 20 years to obtain a comprehensive knowledge of the development of TNBC research.

**Methods**

**Data sources and search methods**

Web of Science database (https://www.webofscience.com) was used for collecting publications about triple negative breast cancer in the past 20 years (Figure 1). We screened original articles about triple negative breast cancer under condition of TS= (triple negative breast cancer) AND Language=English, from 2000 to 2020. All information of included publications was downloaded on June 7, 2021 in order to avoid daily renewal of Web of Science.

**Data collection**

All data including publication year, title, abstract, authors, institutions, countries, citation information about publications in terms of triple negative breast cancer are collected from Web of Science. Softwares including Graphpad Prism (8.1.1), VOSviewer (v 1.6.16), Microsoft Excel 2016, R (v 3.6.3) and Adobe Illustrator (v 21.0.0.0) are used for analysis and plotting.

**Bibliometric analysis**

After downloading all the publication information, we evaluated the relative research interest (RRI) of triple-negative breast cancer in different years in all fields and in the field of breast cancer. Publications published by different countries in different years are also listed, whose increasing/decreasing tendency was predicted by the following formula: \( f(x) = ax^3+bx^2+cx+d \). R package “Remap” was used for visualizing the accumulated publication number and tendency in different countries. VOSviewer was used to screen keywords in all publications and the clusters among different keywords (6). Moreover, keywords with high occurrence frequency were also exhibited following time series to obtain knowledge of the main concerns in different periods.

**Results**

**Growing attention on TNBC research**
Relative research interest (RRI) is an index for evaluating the proportion of publications on a specific topic in all publications, reflecting the importance and weight of a certain topic. Here, we calculated the RRI of TNBC in all publications and in publications on breast cancer (Figure 2A), which shows that the RRI of TNBC in all publications continuously increased over the past 20 years. In addition, the RRI of TNBC in breast cancer publications also significantly increased from 2000 to 2020, indicating that TNBC research is attracting increasing attention. The number of publications on TNBC also increased each year (Figure 2B).

**Contribution of different countries to TNBC publications**

Four countries with the most TNBC-related publications, namely, USA, China, Italy, and Germany, account for more than half of all TNBC publications (Figure 2B). According to the cumulative publication numbers of different countries (Figure 2C), all continents have countries that contribute to TNBC publication. The USA, China, Italy, Germany, South Korea, France, Japan, England, Canada, and India are the 10 countries with the highest number of publications.

In terms of the citations of the 10 countries with the most publications (Figure 2D), publications about TNBC from the USA have the highest total citations, accounting for 37.2% of global citations. The USA also showed the highest H-index (171). England and Canada are two countries with the highest average citations, with average citation of each publication of 55.33 and 53.96, respectively (Figure 2D).

**Tendency of increase in publication in different regions**

The number of publications on TNBC increases each year and is predicted to increase continuously over the next five years (Figure 3A). The growth trend curve (Figure 3B) and growth coefficient (Supplementary Figure 1) were predicted in the 10 countries with the most accumulated publications on TNBC. The number of publications in all 10 countries is increasing. Despite the USA having the highest number of publications, China has the most rapid growth tendency in the past 20 years, as well as in the next five years.

**Institutions and journals publishing articles on TNBC**

Among 14,715 institutions participating in TNBC publications, the top 20 institutions (Figure 4A) publishing the most about TNBC accounted for 44.46% of all TNBC publications. The University of Texas System is the institution with the most publications on TNBC (726 publications, 5.0%). The top 20 institutions are mainly located in countries with large populations. Among the top 20 institutions, there are 13 US institutions, three Chinese institutions, two French institutions, one institution from the United Kingdom, and one Korean institution.

In terms of journals, among all 2095 journal publications about TNBC, the top 20 journals (Figure 4B) with the most cumulated publications account for 31.23% of all publications on TNBC. The journal with the most articles on TNBC is Breast Cancer Research and Treatment (635 publications, 4.41%).
The top 30 publications with the highest citations are listed in Table 1. Publications with high citations cover the description of the features of TNBC, milestone treatments for the development of TNBC, such as clinical trials on PARP inhibitor and anti PD1/PDL1 treatment and classic biomarkers in the induction or prognosis prediction of TNBC-like TILs.

**Hotspots in TNBC studies**

To obtain knowledge on the topics of focus in the TNBC studies, we collected keywords that appeared in publications and screened keywords that appeared more than 100 times. The relationships among these words are shown in Figure 5. The hot topics were clustered into four main clusters (Figure 5A), namely tumor biology of TNBC, TNBC therapies, TNBC treatment sensitivity, and TNBC gene mutations. In the 90 keywords with high occurrence (Supplementary Table 1), apoptosis (1416 times), migration (1051 times), mutation (1005 times), cell proliferation (972 times), neoadjuvant chemotherapy (835 times), surgery (811 times), EGFR (633 times), heterogeneity (590 times), cell death (557 times), and cytotoxicity (549 times) are the 10 words with the highest occurrence (Supplementary Table 1). Ranking by average appearing year, immune checkpoint inhibitor, PDL1, IncRNA, tumor microenvironment, nanoparticle, TILs, macrophage, ROS, reactive oxygen species, and cytotoxic effects were the 10 most popular keywords.

**Discussion**

The lack of expression of three vital markers in triple-negative breast cancer relies mainly on chemotherapy and has a worse prognosis. To find further classification and potential targets of TNBC, more attention has been focused on TNBC. In this research, in order to guide further exploration of TNBC, we initially evaluated TNBC research tendency in the past 20 years in large amounts, covering nearly all publications from the first appearance of TNBC definition to the latest research.

1. **Publication tendency and region contribution of TNBC publications**

With the development of breast cancer target exploration, HR and HER2 have become essential biomarkers for the classification and treatment of breast cancer. After endocrine therapy in HR+ breast cancer and anti-HER2 treatment appeared in the late 1900s and brought significant benefits to breast cancer treatment (7, 8), scientists and clinical doctors started to notice the subtype of breast cancer with neither HR expression nor HER2 amplification. After 2007, the number of publications about TNBC started to increase (9). To date, the number of TNBC publications has reached nearly 3000 per year and is still increasing. Generally, the RRI of TNBC in all publications and breast cancer has increased continuously over the past 20 years, indicating that TNBC has become an area of focus in breast cancer research. TNBC studies covered various countries, among which the USA published the most studies with the highest H index, which indicates its significant contribution to TNBC studies. Although China is the country with the highest increasing speed and the second highest publication number of TNBC publications, the citation and H-index are relatively lower than those of the top 10 countries. Thus, China should improve the quality of publications to make research more efficient. The increasing speed of research in China is possibly due to the increasing incidence of breast cancer, at a rate higher than the
global rate (10), and the greater support from the Chinese government for breast cancer research (11). Nevertheless, Chinese research still needs to develop quality, including more population in the regular national cancer registries, and promote long-term follow-up of breast cancer cohorts.

2. Focus of TNBC publications in different periods reflects the development of TNBC management

According to the publication focus of TNBC in the past 20 years, TNBC research can be divided into three phases. Before 2015, TNBC studies mainly focused on regulating treatments, including effective chemotherapy. As the main effective treatment for TNBC at that time, various publications focused on a suitable combination of different chemotherapy regimens for adjuvant chemotherapy, neoadjuvant chemotherapy, or chemotherapy for metastatic TNBC. Platinum, taxane, carboplatin, anthracycline, cyclophosphamide, and fluorouracil are the key cytotoxic regimens mentioned in various publications. To date, these chemotherapies play an essential role in TNBC treatment. However, these chemotherapy strategies are usually administered to other subtypes of breast cancer. Thus, TNBC specific treatment strategies are still lacking. It was not until recently that randomized controlled trials (RCTs) on TNBC-specific chemotherapy have been reported. At that time, the chemotherapy response of different regimens in TNBC has been mentioned in publications as well. The GEICAM/2003-11_CIBOMA/2004-01 trial published in January 2020 revealed that adding capecitabine in (neo)adjuvant chemotherapy significantly increased DFS in patients with early TNBC(12). The PATTERN trial(13) published in September 2020 mentioned paclitaxel-plus-carboplatin as an efficient choice for adjuvant chemotherapy compared with CEF-T (cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel). Furthermore, platinum-based neoadjuvant chemotherapy showed a significant response in TNBC (14, 15) which is one of the most cited publications (Table 1). The phase II GeparSixto trial (16) reported in 2014 showed a significantly higher response rate after adding carboplatin in taxane, anthracycline, and bevacizumab combination in TNBC patients. Phase III clinical trials, CBCSG010, published in June 2020 indicated that capecitabine, epirubicin, and cyclophosphamide can improve prognosis without additional side effects compared with three cycles of docetaxel followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide in adjuvant chemotherapy for TNBC (17). Nevertheless, it should be noted that RCTs, especially phase III clinical trials, take a long time, from designing to reporting results. There may be a delay in the publication of clinical trials and focus on the day.

To 2016–2017, publications about TNBC focused more on genomic and drug resistance mechanisms for existing treatments. During this period, BRCA mutation and identification of PARP inhibitors in TNBC led to a peak in studying target in terms of DNA damage and DNA repair and many other topics at the cell level, such as apoptosis and pathways. In 2009, The New England Journal of Medicine published a phase I study indicating that monotherapy with the PARP inhibitor olaparib has antitumor function and fewer side effects compared with standard therapy in human cancer, including breast cancer with germline BRCA mutation (18). Later, in 2011, a phase II study published in the Lancet Oncology (19) confirmed the safety and tolerability of olaparib in advanced TNBC patients without BRCA1/2 mutations. Although this study did not observe efficacy in these patients without BRCA1/2 mutations, it was still one of the most
cited publications (Table 1) that led to further phase III clinical trials. In the same year, another PARP inhibitor, iniparib, also underwent phase II clinical trials (20) with high citation counts (Table 1), showing that iniparib combined with chemotherapy can improve the prognosis of metastatic TNBC patients. However, the phase III study of iniparib (21) published in 2014, did not meet the prespecified criteria of primary endpoints. It was not until 2017 that the phase III OlympiAD study (22) on olaparib laid the foundation for PARP inhibitor therapy in advanced HER2- breast cancer with germline BRCA mutation. Despite clinical trials on PARP inhibitors in TNBC, many RCTs on chemotherapy have also analyzed different responses to treatment in different gene mutation groups, which is another reflection of the importance of genomic evaluation in TNBC. For example, the INFORM trial published by the Journal of Clinical Oncology in May 2020 found a similar response to single-agent cisplatin and doxorubicin combined with cyclophosphamide (AC) in neoadjuvant chemotherapy of TNBC with BRCA mutation (23). Moreover, many studies have explored the regulation of the BRCA/HDR pathway in order to identify potential targets for TNBC (24) (Table 1).

After 2018, the immune response in TNBC gradually attracted more attention, showing topics such as tumor infiltrating lymphocytes (TILs), programmed cell death ligand 1 (PDL1), immune checkpoint, and macrophages. Moreover, the appearance of nanoparticles in TNBC also indicates that new materials combined with existing regimens, such as nab-paclitaxel, may provide new opportunities for improving TNBC treatment (25, 26). In this period, TNBC treatment targeting the immune checkpoint was the most focused topic. In 2014, a highly cited publication focused on PDL1 in TNBC (27). Subsequently, many clinical trials and related researches on anti PD1/PDL1 therapy in TNBC have been conducted. In most cited publications, two clinical trials on anti PD1/PDL1 therapy in TNBC published in 2018 reached the top 10 cited. One of two publications is KEYNOTE-012 (28), a phase Ib clinical trial of pembrolizumab, a PD1 inhibitor in TNBC. KEYNOTE-012 shows that pembrolizumab has sufficient tolerance for advanced TNBC. Another phase III clinical trial revealed the efficacy of the anti PDL1 regimen of atezolizumab and nab-paclitaxel therapy in advanced TNBC (29). In 2019, atezolizumab combined with nab-paclitaxel was successfully approved by the FDA for PDL1 positive unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) (30). Nevertheless, atezolizumab combined with nab-paclitaxel did not show improved prognosis in mTNBC according to the IMPassion130 trial (31). However, researchers still noticed the benefit of this combination in mTNBC with PD-L1 positivity. Given that atezolizumab and nab-paclitaxel showed efficacy in neoadjuvant chemotherapy of TNBC (32), targeting immune checkpoints still has potential for further exploration in TNBC.

In terms of immune treatment biomarkers, tumor infiltrating lymphocytes (TILs), on which PD1 is mainly expressed, is another highly focused topic in terms of immune topic in recent years. TILs have been found to be associated with both prognosis and response to neoadjuvant chemotherapy in TNBC (33-35). Further research is needed to confirm the role of TILs in TNBC.

Despite TNBC targets and treatment strategies listed above, there are more novel potential TNBC targets such as ERK, AKT, autophagy, IncRNA, and EGFR, some of which have targeted regimens and are
undergoing clinical trials. Cetuximab, an anti-EGFR antibody together with carboplatin, was evaluated in stage IV TNBC and failed to observe any benefit (36).

Publication focus in TNBC reflects the tendency of more individual and variable diagnosis methods and treatment strategies for TNBC. It is expected that more effective strategies targeting TNBC will appear in the future and will improve prognosis of TNBC patients.

**Conclusions**

Here we collected publications about triple negative breast cancer in the past 20 years. It shows that relative interest of TNBC is continuously increasing. USA and China are two countries with the most TNBC related publications and highest growth rate of publications. Breast Cancer Research and Treatment is the journal with the most TNBC related publications. Immune related topics are now becoming the main focus of TNBC research.

**Abbreviations**

TNBC, triple negative breast cancer, WOS, Web of Science, RRI, relative research interest, ER, estrogen receptor, PR, progesterone receptor, HER2, human epidermal growth factor receptor 2, RCTs, randomized controlled trials, TILs, tumor infiltrating lymphocytes, PDL1, programmed cell death ligand 1.

**Declarations**

**Conflicts of Interest**

The authors declare that they have no competing interests with the contents of this article.

**Authors' Contributions**

Conception and design: XN Sheng, HJ Dai, Administrative support: XN Sheng, XY Ma, YG Song, Provision of study materials or patients: XN Sheng, HJ Dai, Collection and assembly of data: XN Sheng, HJ Dai, Data analysis and interpretation: XN Sheng, Manuscript writing: All authors, Final approval of manuscript: All authors.

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**Availability of data and materials**
The source of original data is presented in the method part from Web of Science database (https://www.webofscience.com).

**Ethical Statement**

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1 Thirty TNBC related publications with the most citations.
| No. | Title                                                                 | Corresponding author | Journal                             | Year | Citations |
|-----|----------------------------------------------------------------------|----------------------|-------------------------------------|------|-----------|
| 1   | Triple-negative breast cancer: Clinical features and patterns of recurrence | Narod, SA            | CLINICAL CANCER RESEARCH            | 2007 | 2547      |
| 2   | Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies | Pietenpol, JA        | JOURNAL OF CLINICAL INVESTIGATION   | 2011 | 2630      |
| 3   | Triple-Negative Breast Cancer                                        | Foulkes, WD          | NEW ENGLAND JOURNAL OF MEDICINE     | 2010 | 2000      |
| 4   | Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer | Pusztai, L           | JOURNAL OF CLINICAL ONCOLOGY        | 2008 | 1677      |
| 5   | The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes | Carey, LA            | CLINICAL CANCER RESEARCH            | 2007 | 1348      |
| 6   | Descriptive analysis of estrogen receptor (ER)negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype - A population-based study from the California Cancer Registry | Bauer, KR            | CANCER                              | 2007 | 1351      |
| 7   | The clonal and mutational evolution spectrum of primary triple-negative breast cancers | Aparicio, S          | NATURE                              | 2012 | 1217      |
| 8   | Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer | Schmid, P            | NEW ENGLAND JOURNAL OF MEDICINE     | 2018 | 1191      |
| 9   | Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study | Nanda, R             | JOURNAL OF CLINICAL ONCOLOGY        | 2016 | 1025      |
| 10  | Prognostic markers in triple-negative breast cancer                  | Rakha, EA            | CANCER                              | 2007 | 888       |
| 11  | Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype | Nielsen, TO          | CLINICAL CANCER RESEARCH            | 2008 | 846       |
| 12  | Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease | Gianni, L            | NATURE REVIEWS CLINICAL ONCOLOGY    | 2016 | 828       |
| ID | Title                                                                 | Author(s) | Journal                         | Year | Pages |
|----|----------------------------------------------------------------------|-----------|---------------------------------|------|-------|
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**Figures**
21,435 publications in WOS

Excluded reviews, case reports, corrections, meeting abstracts, biography, books, news item, editorial material and others (n=7046)

14,389 publications in WOS

Figure 1
Flow chart of choosing triple negative breast cancer related publications included in this study

Figure 2
Publication tendency of TNBC related publications and country contribution from 2000 to 2020. (A) Relative Research Interest (RRI) of TNBC related publications in all publications or publications about breast cancer in different years. (B) Number of publications from different countries in different years. (C) Cumulative distribution of countries publishing TNBC related researches. (D) Quality of publications from the top 10 countries with the most TNBC related publications reflected by citation number and H-index.

Figure 3
Increasing tendency of TNBC related publications. (A) Number of global TNBC publications in different years and predicting curve. (B) Number of TNBC publications from 10 countries with the most TNBC publications in different years and their predicting curves.

Figure 4
Institution and journal with the most TNBC related publications. (A) Top 20 institutions with the most publications about TNBC and their proportion. (B) Top 20 journals with the most publications about TNBC and their proportion.
Figure 5

Network of keywords with high occurrence in TNBC related publications. Connecting curve between different keywording indicated the appearance of two keywords in the same publication. (A) Keywords with high occurrence are clustered into 4 groups with different colors reflecting different topics. (B) Keywords with high occurrence are showed according to average publishing year.

Supplementary Files

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