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Research Article

The 100 most cited articles in ESR1 mutant breast cancer: a bibliometric analysis

ESR1 mutant meme kanserinde en çok atıf alan 100 makale: bibliyometrik bir analiz

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Abstract

Aim: Breast cancer is the most frequently diagnosed cancer and one of the main causes of cancer related death in women worldwide. Around 70% of breast cancer cases are estrogen receptor positive (ER+), and many of these patients benefit from hormone based treatments. However, despite initial responses, a large number of patients eventually develop resistance, especially in the metastatic stage .This study aims to identify and analyze the 100 most cited original research articles related to ESR1-mutant breast cancer, providing insights into publication trends, leading contributors, and thematic focuses in this growing field.

Material and Methods: A systematic search was conducted on May 20, 2025, using the Web of Science Core Collection (WoSCC). The top 100 cited original research articles related to ESR1 mutations in breast cancer were selected based on citation count, excluding non-original and non-English papers. Bibliometric mapping was performed using VOSviewer software (v1.6.10).

Results: A total of 100 articles published between 2007 and 2024 were analyzed. The most cited article received 919 citations. Most publications and citations originated from the United States. Nature Genetics had the highest citation rate per article, while Clinical Cancer Research had the largest number of top-cited articles. Common keywords included "ESR1," "breast cancer," and "resistance."

Conclusion: This bibliometric analysis highlights the foundational and emerging literature on ESR1 mutations in breast cancer. It provides a valuable reference for researchers and clinicians by identifying pivotal studies and mapping the development of this research domain.

Keywords: bibliometric analysis, breast cancer, endocrine resistance, estrogen receptor 1, esr1 mutation

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Öz

Amaç: Meme kanseri, dünya genelinde kadınlarda en sık tanı konulan kanser olup kansere bağlı ölümlerin başlıca nedenlerinden biridir. Meme kanseri olgularının yaklaşık %70'i östrojen reseptörü pozitif (ER+) olup bu hastaların büyük bir kısmı hormon temelli tedavilerden fayda görmektedir. Ancak başlangıçta alınan yanıtlara rağmen, özellikle metastatik evrede birçok hastada zamanla tedavi direnci gelişmektedir. Bu çalışmanın amacı, ESR1 mutasyonlu meme kanseri ile ilişkili en çok atıf alan 100 özgün araştırma makalesini belirlemek ve analiz ederek, bu alandaki yayın eğilimleri, önde gelen katkı sağlayıcılar ve tematik odaklar hakkında bilgi sunmaktır.

Gereç ve Yöntemler: 20 Mayıs 2025 tarihinde Web of Science Core Collection (WoSCC) kullanılarak sistematik bir tarama yapılmıştır. Meme kanserinde ESR1 mutasyonları ile ilişkili, en çok atıf alan 100 özgün araştırma makalesi atıf sayılarına göre seçilmiş; özgün olmayan ve İngilizce dışındaki yayınlar çalışma dışı bırakılmıştır. Bibliyometrik haritalama VOSviewer yazılımı (v1.6.10) kullanılarak gerçekleştirilmiştir.

Bulgular: 2007–2024 yılları arasında yayımlanan toplam 100 makale analiz edilmiştir. En çok atıf alan makale 919 atıf almıştır. Yayınların ve atıfların büyük çoğunluğu Amerika Birleşik Devletleri kaynaklıdır. Nature Genetics makale başına en yüksek atıf oranına sahip dergi olurken, Clinical Cancer Research en fazla üst düzey atıf alan makaleyi yayımlayan dergi olmuştur. En sık kullanılan anahtar kelimeler arasında "ESR1", "meme kanseri" ve "direnç" yer almıştır.

Sonuç: Bu bibliyometrik analiz, meme kanserinde ESR1 mutasyonlarına ilişkin temel ve gelişmekte olan literatürü ortaya koymaktadır. Alandaki kritik çalışmaları belirleyerek ve araştırma alanının gelişimini haritalandırarak araştırmacılar ve klinisyenler için değerli bir başvuru kaynağı sunmaktadır.

Anahtar Kelimeler: bibliyometrik analiz, meme kanseri, endokrin direnç, östrojen reseptör 1, esr1 mutasyonu

Introduction

Breast cancer is a leading cause of cancer related death in women. Around 70% of breast cancer cases are estrogen receptor positive (ER+), and many of these patients benefit from hormone based treatments. However, despite initial responses, a large number of patients eventually develop resistance, especially in the metastatic stage [1].

One of the main reasons for this resistance is mutations in the estrogen receptor 1 (ESR1) gene, which have become a focus of attention in the last decade [2]. These mutations often occur in the receptor's ligand binding domain, allowing it to remain active without estrogen. As a result, cancer cells continue to grow, and treatments that block estrogen or reduce its production become less effective [2,3]. While ESR1 mutations are rare in untreated primary tumors, they are more often found in metastatic tumors, especially after treatment with aromatase inhibitors [3]. Because of this, ESR1 mutations are now seen as both a predictive marker for treatment response and a possible target for new therapies [4].

Due to their growing clinical importance, research on ESR1 mutations especially their biology, diagnosis, and treatment options has expanded rapidly. Bibliometric analysis is a useful method to examine the scientific impact of publications, identify key studies and researchers, track research trends, and help plan future work [5].

So far, no detailed bibliometric study has focused specifically on the most influential papers about ESR1 mutations in breast cancer. The aim of this study is to identify and analyze the 100 most cited original articles in this field. The results will highlight leading research, authors, institutions, countries, and journals, while also showing common research themes. These findings may help researchers, clinicians, and decision-makers better understand the current state of knowledge and shape future directions in the field of ESR1-mutant breast cancer.

Material and Methods

We conducted a systematic literature search in the WoSCC database on May 20, 2025. The search strategy included the terms: "breast cancer" AND (treat OR medic* OR remedy OR cure OR therapy) AND (mutant OR mutation) AND (ESR1 OR "estrogen receptor 1")*, which were applied to the topic field (title, abstract, and author keywords) within the Web of Science Core Collection (WoSCC). All retrieved results were exported for manual screening by the researcher.

From a total of 880 records, the 100 most cited original research articles were selected after applying exclusion criteria based on citation ranking. No time restriction was applied. Only original research articles were included. Reviews, case reports, editorials, meeting abstracts, letters to the editor, book chapters, and non-English articles were excluded. Duplicate or irrelevant records were also removed.

Table1. Overview of the top 10 most cited original research articles related to ESR1-mutant breast cancer.

No	Article title	Authors	Institution	Journal	Year	Citations
1	ESR1 ligand-binding domain mutations in hormone-resistant breast cancer	Toy et al.	Memorial Sloan Kettering	Nature Genetics	2013	919
2	Activating ESR1 mutations in hormone-resistant metastatic breast cancer	Robinson et al.	University of Michigan	Nature Genetics	2013	864
3	Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer	Fribbens et al.	Royal Marsden	Journal of Clinical Oncology	2016	544
4	Emergence of Constitutively Active Estrogen Receptor-α Mutations in Pretreated Advanced Estrogen Receptor-Positive Breast Cancer	Jeselsohn et al.	Harvard University	Clinical Cancer Research	2014	512
5	Endocrine-Therapy-Resistant ESR1 Variants Revealed by Genomic Characterization of Breast-Cancer-Derived Xenografts	Li et al.	Washington University	Cell Reports	2013	482
6	The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial	O'Leary et al.	Royal Marsden	Cancer Discovery	2018	433
7	Analysis of ESR1 Mutation in Circulating Tumor DNA Demonstrates Evolution During Therapy for Metastatic Breast Cancer	Schiavon et al.	Royal Marsden	Science Translational Medicine	2015	387
8	Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial	Chandarlapaty et al.	Memorial Sloan Kettering	JAMA Oncology	2016	381
9	Elacestrant Versus Standard Endocrine Therapy for ER+, HER2- Advanced Breast Cancer: Results From the EMERALD Trial	Bidard et al.	UNICANCER	Journal of Clinical Oncology	2022	376
10	Mutational Profile of Metastatic Breast Cancers: A Retrospective Analysis	Lefebvre et al.	Institut National de la Sante	PLOS Medicine	2016	293

For each of the top 100 selected articles, data were extracted on publication year, country of origin, journal, institution, keywords, and citation count. To identify trends and visualize relationships among keywords, countries, authors, and citations, network maps were generated using VOSviewer software (version 1.6.10). This software was used to perform bibliometric mapping and clustering analyses to better understand research dynamics in the field.

Results

After excluding non-original and review articles from the Web of Science database, a total of 216 relevant publications on ESR1-mutant metastatic breast cancer were identified. Following the removal of non-English and unrelated records, a final sample of 100 articles was selected for analysis. A noticeable increase in publications on this topic has been observed since 2016. The majority of these articles and their citations originated from the United States. The authorship-country network visualization map is presented in Figure 1.

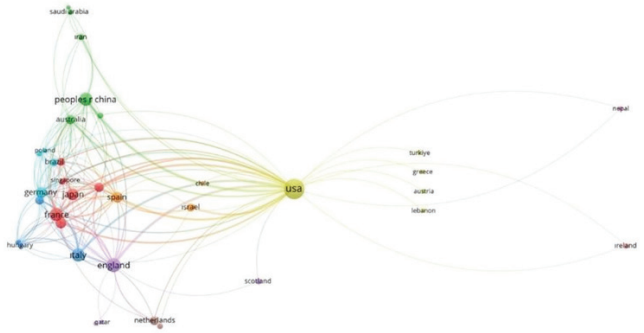

Figure 1. Network visualization map showing the collaboration between authors and their countries in ESR1-mutant breast cancer research.

The five most cited articles in this field were authored by Toy et al. (919 citations) [6], Robinson et al. (864) [4], Fribbens et al. (544) [7], Jeselsohn et al. (512) [2], and Li S et al. (482) [8]. A summary of the 10 most cited articles is provided in Table 1.

Citations per article ranged from 22 to 919, averaging 113.2. The most cited article, by Toy et al., titled "ESR1 ligand-binding domain mutations in hormone-resistant breast cancer", had 919 citations [6]. The article with the fewest citations, at 22, was authored by Page et al. and focused on circulating tumor DNA profiling across the breast cancer continuum [9].

Regression analysis of publication trends revealed a significant increase in output, from 6 articles in 2015 to 17 in 2016. In terms of citation impact per journal, Nature Genetics led with an average of 891 citations per article, indicating it as the most influential journal in this area. Among contributing authors, Takeshita T. appeared most frequently, with five publications among the top 100 cited papers [10].

The most commonly used keyword across all articles was "ESR1", followed by "breast cancer". A keyword co-occurrence map visualizing their relationships is presented in Figure 2.

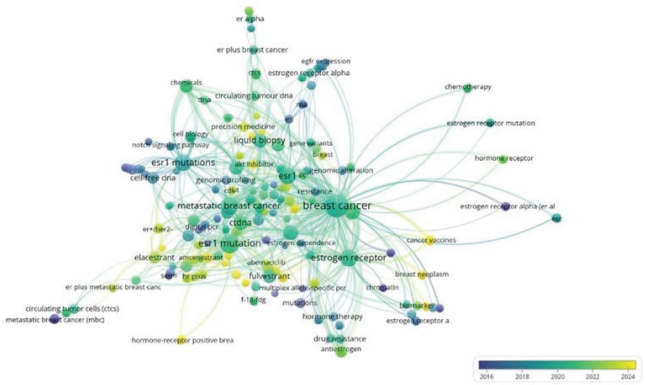

Figure 2. Co-occurrence map of author keywords showing clusters and relationships among high-frequency terms related to ESR1 mutations in breast cancer.

Discussion

Recently, ESR1 mutations have become a key mechanism of resistance to hormonal therapy in breast cancer. The increased prevalence of these mutations, particularly in metastatic disease following aromatase inhibitor exposure, has positioned ESR1 as both a predictive biomarker and a potential therapeutic target [4,11]. Bibliometric analysis offers researchers a valuable opportunity to evaluate the scientific development of a specific field from a historical perspective. Beyond identifying past and current research trends, this method also provides strategic insights for future scientific directions. In this sense, bibliometric studies serve as a practical roadmap for academic communities and healthcare decision-makers.

According to our analysis, there has been a significant rise in the number of publications since 2016, which may reflect growing awareness of the clinical importance of ESR1 mutations and the increasing availability of non-invasive diagnostic methods, such as liquid biopsy [7]. Notably, one of the most highly cited articles Toy et al. (2013), with 919 citations described ligand-binding domain mutations in ESR1 among patients with hormone-resistant breast cancer, marking a key turning point in the field [6].

Importantly, the detection of ESR1 mutations may precede radiological disease progression. The use of circulating tumor DNA analysis allows for earlier identification of emerging ESR1 mutations during endocrine therapy, potentially enabling timely therapeutic adjustments before overt clinical or radiological progression occurs. This highlights the growing role of liquid biopsy in guiding personalized treatment strategies in estrogen receptor–positive breast cancer.

Our study also showed that the most influential journals included Nature Genetics and Clinical Cancer Research, which suggests that research on ESR1 mutations garners substantial attention not only in clinical oncology but also in molecular and translational science. The repeated appearance of authors such as Takeshita et al. among the top-cited publications highlights the leadership of research teams based in Japan and the United States. The predominance of the U.S. in both publication volume and citations may be related to higher research funding levels and broader access to genomic technologies [10].

In addition to their diagnostic and prognostic relevance, ESR1 mutations are increasingly being explored as therapeutic

targets. The development of novel agents such as oral selective estrogen receptor degraders (SERDs) and ESR1 mutant-selective inhibitors is expanding treatment options in this population [12]. Our bibliometric mapping also confirmed that key terms such as "ESR1," "breast cancer," "liquid biopsy," and "resistance" frequently co-occurred, reflecting the central research themes in the literature. In recent clinical trials, oral SERDs like elacestrant have demonstrated promising efficacy against ESR1-mutated tumors [13-15].

This study has several limitations. Although we applied comprehensive search terms and citation-based selection to identify the most impactful studies on ESR1-mutant breast cancer, some important articles may have been excluded. Specifically, recently published studies that have not yet accumulated enough citations might have been underrepresented. As a result, our sample may not fully capture emerging literature that could shape the future of the field. Moreover, the dynamic landscape of ongoing studies, such as those conducted in the EMERALD trial and large scale genomic mapping, suggests that the field is rapidly evolving [13-15]. Additionally, citation-based analyses inherently favor older publications, as these articles have had more time to accumulate citations compared with more recent studies. Consequently, some recently published but potentially influential articles may be underrepresented in our analysis despite their scientific relevance.

Furthermore, the data were obtained solely from the Web of Science Core Collection (WoSCC). Therefore, relevant publications indexed in other databases such as Scopus, PubMed, or Google Scholar were not included. Future bibliometric analyses incorporating multiple databases may yield more balanced and comprehensive insights.

In conclusion, oncology is a dynamic field, continuously shaped by scientific and technological advancements. In recent years, significant progress has been made in the treatment of breast cancer, with ESR1 mutations gaining increasing attention due to their role in endocrine resistance. Bibliometric analysis serves as a valuable tool to objectively assess developments and identify trends in the literature.

By mapping key contributors, emerging keywords, and high-impact journals, this study contributes to a deeper understanding of the intellectual structure of the field. As research into ESR1 mutations continues to evolve, bibliometric analyses such as this will remain essential for navigating the expanding literature and shaping research agendas in precision oncology.

Declaration of conflicting interests

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Ethical approval

Ethical approval was not required for this study because it was based on publicly available bibliographic data and did not involve human participants or patient data.

Authors' contributions

A.Y.: Conceptualization, methodology, software, formal analysis, investigation, writing - original draft, visualization, supervision. M.E.D.: Methodology, investigation, data curation, writing - review & editing. G.T.: Formal analysis, investigation, data curation, writing - review & editing. E.K.: Formal analysis, methodology, validation, data curation, writing - review & editing. M.U.: Resources, investigation, validation, writing - review & editing.

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