

RESEARCH ARTICLE

Bibliometric analysis of hotspots and frontiers in cancer-related fatigue among ovarian cancer survivors

Yuanxia Liu¹, Qianxia Liu², Xiaolian Jiang^{1*}

1 West China School of Nursing, Sichuan University/ West China Hospital, Sichuan University, Sichuan, China, **2** Department of Laboratory, Linxia Hui Autonomous Prefecture Center for Disease Control and Prevention, Gansu, China

* jiangxiaolianhl@163.com**OPEN ACCESS**

Citation: Liu Y, Liu Q, Jiang X (2022) Bibliometric analysis of hotspots and frontiers in cancer-related fatigue among ovarian cancer survivors. PLoS ONE 17(9): e0274802. <https://doi.org/10.1371/journal.pone.0274802>

Editor: Kehinde Sharafadeen Okunade, University of Lagos College of Medicine, NIGERIA

Received: May 4, 2022

Accepted: September 3, 2022

Published: September 22, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0274802>

Copyright: © 2022 Liu et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The author(s) received no specific funding for this work.

Abstract

Objectives

To explore and analyze research hotspots and frontiers in CRF in ovarian cancer patients to provide an evidence-based basis for scholars and policymakers.

Background

Ovarian cancer is one of the most common and lethal gynecological malignancies. Cancer-related fatigue (CRF) is an annoying and pervasive side-effect that seriously affects the activities of daily living and decreases the quality of life (QoL) of cancer survivors.

Methods

The literature was retrieved from the Web of Science Core Collection (WOSCC) from inception to 2021-12-31. CiteSpace was used to discuss research countries, institutions, authors, and keywords.

Results

This study ultimately included 755 valid publications, and the number of publications showed a gradual upward trend. The countries, institutions, authors, and journals that have published the most articles and cited the most frequently were the United States, the University of Texas MD Anderson Cancer Center, Michael Friedlander and Amit M Oza, Gynecologic Oncology, and Journal of Clinical Oncology. The top three high-frequency keywords were Ovarian cancer, chemotherapy, and clinical trial. The top three keywords with the strongest citation bursts were cyclophosphamide, double-blind, and open-label.

Conclusions

Conducting multi-center, large-sample, randomized controlled clinical trials to determine whether chemotherapeutic agents have severe adverse effects and to discuss the relationship between CRF and QoL and overall survival in cancer survivors are hotspots in this field.

Competing interests: The authors have declared that no competing interests exist.

The new trends may be applying double-blind, randomized controlled trials to clarify the causes of CRF and open-label, randomized trials to determine the efficacy, safety, and tolerability of chemotherapeutic agents.

Background

Ovarian cancer is one of the most common and lethal gynecological malignancies, accounting for approximately 4% of global cancer incidence and mortality in women [1, 2]. Due to its unique anatomical site and generally vague symptoms, even in high-income countries (HICs), more than 60% of ovarian cancer are detected only in the late stage [3, 4]. Surveys conducted by the Global Burden of Diseases Cancer Collaboration note that incident cases of ovarian cancer worldwide increased from 286,000 to 294,000, and cancer deaths increased from 176,000 to 198,000 from 2017 to 2019 [5, 6]. Fortunately, with better diagnostic techniques, more and more ovarian cancer is being detected at an early stage, and early detection can significantly improve the health outcome of patients with ovarian cancer and save their lives [7]. We can learn from the latest studies that the survival rate of ovarian cancer after five years ranges from 46.2% [7] to 47.4% [3]. The absolute number of global ovarian cancer-related disability-adjusted life years (DALYs) increased by 27.5% from 2010 to 2019, reaching 5.36 million in 2019 [6].

Cancer-related fatigue (CRF) is an annoying and pervasive side-effect of cancer and cancer therapy [8, 9]. According to the definition developed by the National Comprehensive Cancer Network (NCCN), CRF is a type of fatigue that persists and cannot be relieved by rest [10]. The reported incidence of CRF varies due to the different scales chosen to assess symptoms. Studies have shown that the incidence ranges from 25% to 99% [11], with a 90% incidence in patients undergoing radiotherapy and 80% in those undergoing chemotherapy [12], and the pooled prevalence of CRF was 52% [13]. A survey showed that CRF persists for several years even after treatment ends for 25%-33% of cancer survivors [14]. CRF has adverse effects on various physiological, psychological, and social aspects and severely diminishes the QoL of cancer survivors [15]. Several studies have shown that ovarian cancer patients with CRF had poor QoL [16–18]. Relieving CRF in ovarian cancer survivors could improve their self-care ability and enhance QoL.

Bibliometric analysis is a scientific mathematical and statistical method to quantitatively explore the development of a research field, and knowledge mapping is a visual representation of bibliometric analysis [19]. The method can outline the development of a specific research field or topic from a macro perspective, clarify its research hotspots, detect its research frontiers, and provide a reference basis for the future research direction of the field or topic [20]. CiteSpace is an effective visualization tool that is widely used for knowledge mapping in the fields of medicine [21], informatics [22], and science [23].

Currently, a bibliometric analysis of CRF in people with ovarian cancer has not been published. The purpose of this study was to analyze the literature related to CRF among ovarian cancer patients published in WOSCC from 1991 to 2021 by using the visualization tool CiteSpace. To explore and analyze research hotspots and frontiers in CRF in patients with ovarian cancer to provide an evidence-based basis for scholars and policymakers.

Materials and methods

Data source

Selecting the proper database and searching thoroughly and accurately for literature related to the topic is the first step of research. The Web of Science was chosen as the data source for the

following reasons. Firstly, the Web of Science is an international multidisciplinary citation index publication on citation statistics and is recognized worldwide as the most authoritative indexing tool for scientific and technical literature, consisting of the WOSCC and other databases [24, 25]. Secondly, the Web of Science is also the largest and most comprehensive resource for academic information covering a wide range of disciplines, with data updated to reflect dynamic changes in the scientific field timely [26]. Moreover, the Web of Science has the advantage of being a bibliographic database that provides references cited in scholarly publications [27].

Data processing

The WOSCC was searched for investigating literature on CRF in women with ovarian cancer from inception to December 31st, 2021. The first article on CRF in ovarian cancer patients in the WOSCC was issued in 1991, and the literature search date was December 31, 2021; therefore, the timespan of our study was 1991.01.01–2021.12.31. The retrieval subject terms are ovarian cancer and cancer-related fatigue. A total of 768 original records were retrieved. The retrieved documents were imported into CiteSpace to remove duplicates and then independently screened by 2 researchers to exclude papers that did not fit the research topic and search strategy. After excluding editorial materials ($n = 3$), meeting abstracts ($n = 8$), and proceedings papers ($n = 2$), 693 articles and 62 reviews related to the topic were finally obtained.

Data analysis

CiteSpace is a Java application and bibliometric software developed by Professor Chaomei Chen [28]. CiteSpace applies co-citation analysis theory and pathfinder network algorithms to extract information from scientific literature, converting the information into visualized mapping knowledge maps and presenting the research evolution, hotspots, and frontiers of a given area [29, 30].

In this study, CiteSpaceV5.8 R3 visualization software was used for keyword extraction, keyword burst detection, and clustering analysis. Keyword burst detection and keyword clustering analysis were performed using the g-index algorithm. Each node in the map represents a keyword, and a line between two nodes indicates a connection between two nodes [31]. The larger the node, the more frequently the keyword appears. Node centrality represents the connection between a node and other nodes, as well as the position and role of a node in the whole network [30, 32]. If the centrality of a node is higher than 0.1, it means that the node has a relatively core position in the network [33]. In the timeline diagram, the red part of the green timeline represents the starting and ending years of the cited keywords, and "strength" represents the strength of the cited keywords [34].

Results

Analysis of annual publications

The volume of scientific literature publications could reflect the dynamic process of research ups and downs and reflect the level of scientific research in a particular field [35]. With 755 sorted and detected papers as samples, the publication volume of literature in the 31 years from 1991 to 2021 was statistically analyzed in the time dimension, mapping out the chronological distribution of relevant studies (Fig 1).

Three research articles in this area were published in 1991. Sandra et al. conducted a small-scale (twelve ovarian cancer patients in the test group and twelve healthy adult women in the control group) descriptive study indicating no clear link between fatigue and diseases or

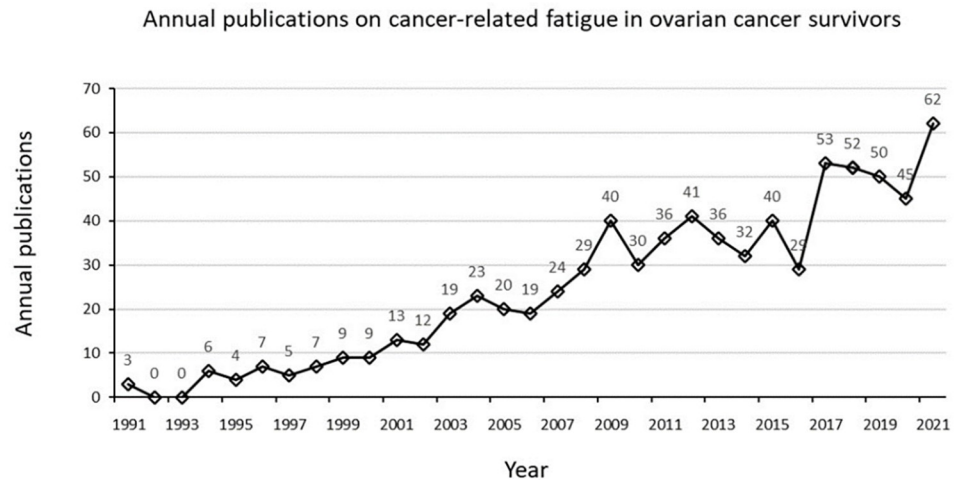


Fig 1. Annual publications on cancer-related fatigue in ovarian cancer survivors.

<https://doi.org/10.1371/journal.pone.0274802.g001>

treatments in ovarian cancer survivors undergoing chemotherapy [36]. P. J. Disaia et al. found that concurrent use of chemotherapeutic agents and interferon in patients with ovarian cancer led to severe fatigue [37]. Michele A. Hood and Rebecca S. Finley did not specify whether having cancer or chemotherapy affected fatigue in ovarian cancer patients treated with fludarabine [38]. Since then, research on this theme has begun to sprout.

Performance of countries /regions

The country was set as node type and time slice was set as 1 year, and 755 records of CRF in ovarian cancer patients published from 1991 to 2021 were analyzed to generate a collaborative country network map with 61 nodes, 375 links, and a density of 0.2049 (Fig 2). Each node in the figure represents a country (or a region), and the size of the node is proportional to the papers published by countries [39]. The links between nodes represent cooperation between countries, and the thickness of the links is positively correlated with the number of articles issued.

The top 10 active countries in this research field ($n \geq 40$) are listed in Table 1. Combining Fig 2 and Table 1 and counting the total number of publications in CiteSpace showed that 1,236 papers were published in 61 countries, with 938 papers published in the ten most active countries, far exceeding the total literature related to the topic. It showed strong links between research countries and frequent cooperation between researchers in this field. The top 10 countries accounted for 75.9% of the total publications, while the United States had the most publications with 426, accounting for 34.5% of the total publications. The United States, Australia, Italy, and France have a centrality of over 0.1.

Performance of institutions

With the institution as the node type and time slice of 1 year, 755 records of CRF in ovarian cancer survivors were analyzed to generate a knowledge map (Fig 3). Pathfinder and pruning sliced networks were used to present a more intuitive and understandable map. 634 institutions studied CRF in ovarian cancer patients. Each node in Fig 3 represents an institution, and the size of the node is proportional to the papers published by institutions. The links between nodes represent cooperation between institutions, and the thickness of the links is positively correlated with the number of articles issued.

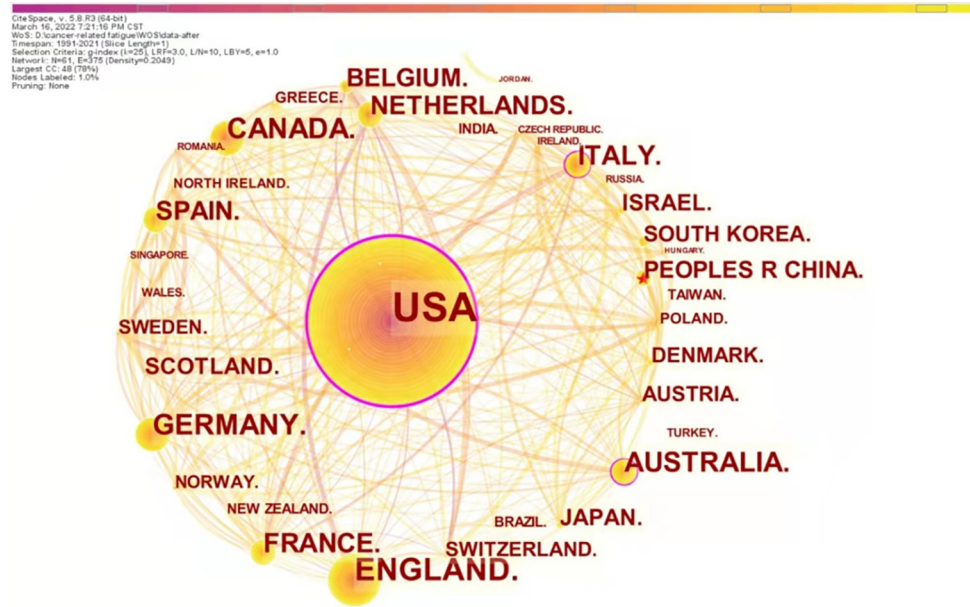


Fig 2. Map of research countries in cancer-related fatigue in ovarian cancer survivors.

<https://doi.org/10.1371/journal.pone.0274802.g002>

The top 10 productive institutions are listed in Table 1. Combining Fig 3 and Table 1 and counting the total number of publications in CiteSpace, 634 institutions published 1512 papers, far exceeding the total literature related to the theme. Among these research institutions with more than 20 publications were the University of Texas MD Anderson Cancer Center, Dana-Farber Cancer Institute, The University of Oklahoma, Memorial Sloan-Kettering Cancer Center, Massachusetts General Hospital, and National Cancer Institute (NCI).

Analysis of authors

The author was set as node type, and years per slice was 1 year and generated a collaborative author map with 798 nodes, 1369 links, and a density of 0.0043 (Fig 4). As seen in Fig 4, the nodes represent the researchers in the field, and the node size is proportional to the papers published by researchers. The links between nodes reflect the collaboration between authors, and the thickness of the links is proportional to the outputs. Core authors refer to researchers

Table 1. Top 10 research countries and institutions.

Ranking	Countries			Institutions		
	Countries	Publications	Centrality	Institutions	Publications	Centrality
1	USA	426	0.24	The University of Texas MD Anderson Cancer Center	56	0.02
2	England	93	0.06	Dana-Farber Cancer Institute	47	0.13
3	Canada	66	0.09	The University of Oklahoma	34	0.02
4	Germany	64	0.09	Memorial Sloan-Kettering Cancer Center	30	0.05
5	Australia	55	0.15	Massachusetts General Hospital	29	0.04
6	Italy	51	0.12	National Cancer Institute (NCI)	22	0.02
7	France	50	0.10	The Ohio State University	19	0.00
8	Netherlands	48	0.04	Leon Berard Center	18	0.11
9	Spain	44	0.03	Texas State University	17	0.05
10	Belgium	41	0.06	Roswell Park Cancer Center	16	0.05

<https://doi.org/10.1371/journal.pone.0274802.t001>

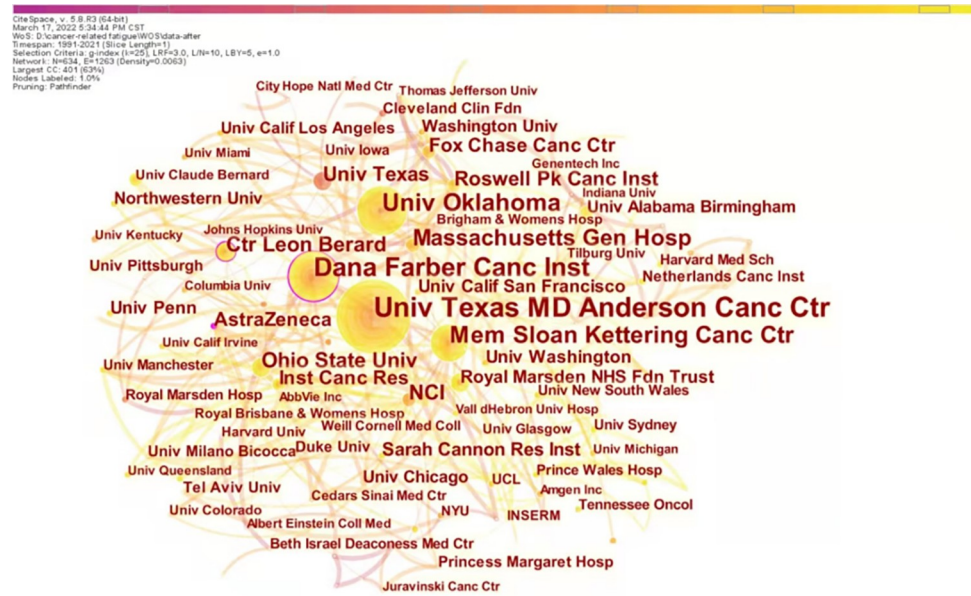


Fig 3. Map of research institutions in cancer-related fatigue in ovarian cancer survivors.

<https://doi.org/10.1371/journal.pone.0274802.g003>

with high academic attainments, extensive publications, and profound influence in a particular field. Price's Law [40] defines core authors by the number of papers published, and its calculation formula is $M = 0.749 * N_{max}^{1/2}$ (N_{max} refers to the number of papers published by the most productive author in the statistical years, and those who published more than M papers are core authors of this research area). The most productive author is Michael Friedlander and Amit M Oza, with 17 publications. According to the calculation formula, N_{max} and M for this study area were 17 and 6.4, respectively. Therefore, authors with publications of 7 or more were the core authors. The core authors in this domain are listed in Table 2. Combined to Fig 4 and Table 2, 798 authors published 755 papers, while 119 papers were published by the 11 core authors, accounting for 15.8% of the total publications in the field.

Analysis of journals and cited-journals

Since the first article on CRF in women with ovarian cancer was published in 1991, the overall trend of published articles in this area has been increasing year by year. Papers on ovarian cancer women with CRF were published in approximately 200 journals till 2021. An analysis of cited journals in CiteSpace shows that 755 papers were cited in 722 journals. Gynecologic Oncology ranked first among all journals publishing studies related to cancer fatigue in ovarian cancer patients with 142 publications and second among all co-cited journals with a frequency of 640. Gynecologic Oncology is dedicated to publishing clinical and investigative articles on female genital tract tumors. Its impact factor (IF) is 5.482, and the average number of citations per paper in this journal is 7.4. Journal of Clinical Oncology ranked second among all journals with 142 publications and second among all co-cited journals with a frequency of 457, and focused on treating various types of malignant disease. Its impact factor is 44.544, and the average number of citations per paper in this journal is 37. Articles published in Gynecologic Oncology and Journal of Clinical Oncology accounted for 25.4% of the total publications in this area. The top 10 productive journals and co-cited journals related to CRF in women with ovarian cancer are shown in Table 3.



Fig 4. Map of author network related to cancer-related fatigue in ovarian cancer survivors.

<https://doi.org/10.1371/journal.pone.0274802.g004>

Table 2. Core authors of researching CRF in ovarian cancer survivors.

Ranking	Authors	Counts	Centrality
1	Michael Friedlander	17	0.06
2	Amit M Oza	17	0.06
3	Kathleen N Moore	15	0.03
4	Isabelle Ray-Coquard	12	0.04
5	Ignace Vergote	10	0.05
6	Ursula A Matulonis	10	0.03
7	David M O'Malley	9	0.01
8	Richard T Penson	9	0.01
9	M Markman	9	0.00
10	Anil K Soon	9	0.02
11	Robert L Coleman	7	0.02

<https://doi.org/10.1371/journal.pone.0274802.t002>

Table 3. Top 10 most productive journals and co-cited journals.

Ranking	Journals	IF (2021)	Publications	Co-cited-journal	IF (2021)	Frequency
1	Gynecologic Oncology	5.482	142	Journal of Clinical Oncology	44.544	640
2	Journal of Clinical Oncology	44.544	50	Gynecologic Oncology	5.482	457
3	Clinical Cancer Research	9.619	45	Annals of Oncology	32.976	337
4	Investigational New Drugs	3.850	31	New England Journal of Medicine	91.245	335
5	International Journal of Gynecological Cancer	3.437	30	Clinical Cancer Research	9.619	299
6	Annals of Oncology	32.976	29	European Journal of Cancer	9.162	295
7	Cancer	6.860	24	British Journal of Cancer	7.640	275
8	British Journal of Cancer	7.640	20	Cancer Research	12.701	273
9	Cancer Chemotherapy and Pharmacology	3.333	18	Cancer	6.860	251
10	Supportive Care in Cancer	3.603	14	Journal of the national cancer institute	13.506	251

<https://doi.org/10.1371/journal.pone.0274802.t003>

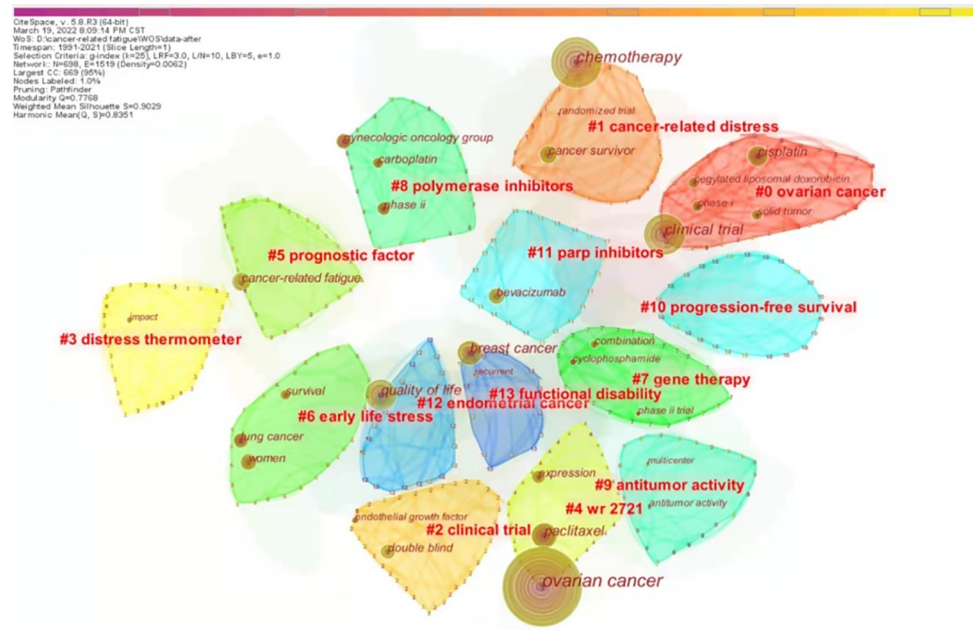


Fig 6. Map of keyword clustering in cancer-related fatigue in ovarian cancer survivors.

<https://doi.org/10.1371/journal.pone.0274802.g006>

As shown in Table 4, the subject terms of this study are cancer-related fatigue and ovarian cancer, ranking in the 8th and 1st of the top 10 keywords, respectively. Other the most frequent keywords related to our study are chemotherapy, clinical trial, quality of life, and cancer survivor. The clinical trial, QoL, and cancer survivor have high centrality (centrality > = 0.1).

In this study, the LSI algorithm recommended by Professor Chaomei Chen was applied to cluster the keywords, and the keyword clustering knowledge map is generated after adjustment and filtering, as shown in (Fig 6). According to the clarity of the network structure and clustering, CiteSpace provides the modularity (Q) index and average silhouette score to evaluate the drawing effect of the map. The average silhouette score and Q score are both between -1 and 1, and the higher the average silhouette score, the more reliable the clustering is; the higher the Q score, the better the structure of the network [41, 42]. The Q score of this study is 0.7768, and the average silhouette score is 0.9029, which can be considered that this clustering is significant and convincing.

Fig 6 shows 14 clustering modules with different color blocks to distinguish each cluster. The 14 clustered modules are labeled with #0-#13, the outline of the module is marked with the corresponding number, and the core keywords of the module are displayed within each module. The keyword font size and the circle size in front of them are proportional to the frequency of the keyword. The cluster structure and core keywords in Fig 6 reflect some of the research hotspots in CRF in ovarian cancer patients. Mainly, cluster 0 is ovarian cancer and the core keyword is clinical trial. Cluster 1 is cancer-related distress, and the core keywords are chemotherapy and cancer survivor. Cluster 4 is wr2721 with core keywords ovarian cancer and paclitaxel. Cluster 5 is prognostic factors, and the core keyword is CRF. Cluster 11 is parp inhibitors, and the core keyword is bevacizumab. Cluster 12 is endometrial cancer, and the core keyword is quality of life. Cluster 13 is functional disability, and the core keyword was breast cancer.

Top 25 Keywords with the Strongest Citation Bursts

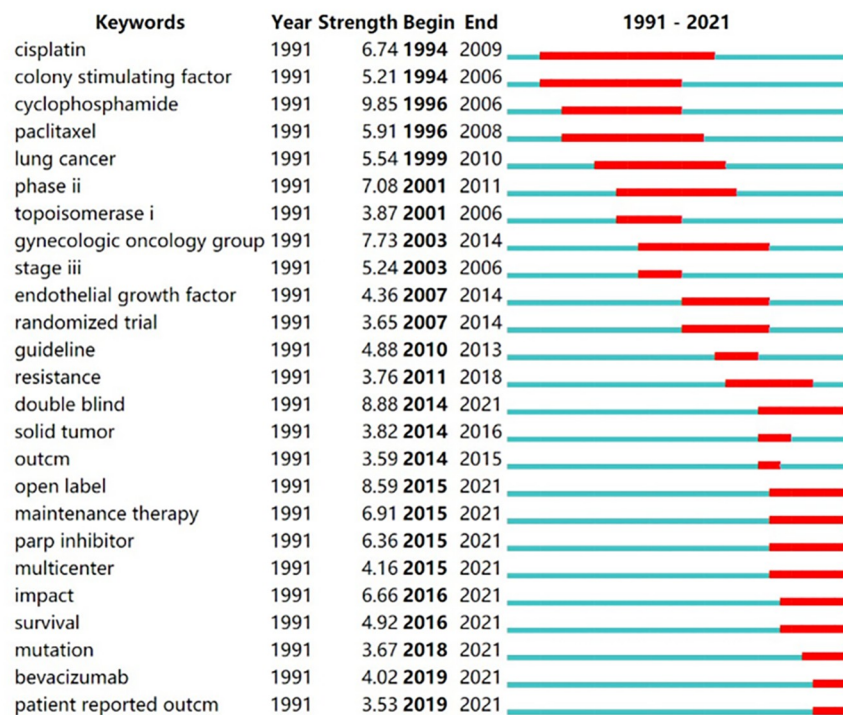


Fig 7. Map of the top 25 keywords with the strongest citation bursts.

<https://doi.org/10.1371/journal.pone.0274802.g007>

Keyword bursts

"Burst words" are keywords that suddenly increase in citation frequency within a certain period, revealing the research hotspots and frontiers in the area [43–45]. The top 25 strongest burst words and the year of begin and end of each burst word in the field of CRF in ovarian cancer survivors as shown in (Fig 7). The green line in Fig 7 displays the time window of the documents retrieved in this study, and the red color indicates the duration of a certain burst word from its beginning to its end. The first burst keywords were cisplatin and colony stimulating factor in 1994, and the keywords with the highest burst strength were cyclophosphamide, double-blind, and open-label.

Discussion

Based on the WOSCC, this study applied CiteSpace to explore the research status of CRF in ovarian cancer patients, and analyze research hotspots and frontiers by analyzing 755 papers over 31 years.

The current research status for CRF in ovarian cancer survivors

The current state of research is described in terms of annual publications, research countries, institutions, researchers, journals, and cited journals [46]. As can be seen from the annual publications in this field, there has been no research in this area for the next two years since the first paper was published in 1991. Over the next decade, research in this area showed a slow-growth trend, with consistently fewer than ten papers published per year. In the second

decade, annual publications increased significantly compared to the previous decade, with a slight decline in 2010. The volume of research literature had fluctuated considerably in the last decade, with an overall upward trend, reaching a new peak in 2021 when the annual publications increased to 62. Based on the performance of the study countries and institutions, the United States took an absolute leadership role in CRF in ovarian cancer people research with high publications (count = 426) and high centrality (centrality = 0.24), the University of Texas MD Anderson Cancer ranked first with 56 publications. Dana-Farber Cancer Institute is the most central institution for research in the area, with the highest centrality of 0.13, indicating that their literature strongly influences this research area. An analysis of researchers in this field shows 11 core authors, of which those with at least ten publications are Michael Friedlander, Amit M Oza, Kathleen N Moore, Isabelle Ray-Coquard, Ignace Vergote, and Ursula A Matulonis. Collaboration contributes to professional development and the exploration of research frontiers and should be sought to the maximum extent possible between countries, institutions, and researchers.

Papers on CRF in ovarian cancer patients have been published in approximately 200 journals, and 39.5% of the papers were published in the top five journals. The two journals with the highest publications are *Gynecologic Oncology* and *Journal of Clinical Oncology*. 62 papers were published in 45 journals in 2021, 15 of which were published in *Gynecologic Oncology*. *Lancet Oncology*, the highest impact factor among these 45 journals, which published a study of a randomized controlled trial showed that the proportion of patients with ovarian cancer accompanied with grade 3 fatigue in avelumab combination with pegylated liposomal doxorubicin (PLD) group and PLD alone group was 10 (5%) and 3 (2%), respectively [47]. It indicates that CRF is triggering increasing attention as an adverse reaction during cancer and anti-tumor treatments.

Research hotspots for CRF in ovarian cancer survivors

The co-occurrence network of high-frequency keywords represents a hot research topic in CRF in patients with ovarian cancer from 1991 to 2021. Since the search was conducted with ovarian cancer and CRF as the subject terms, although they appeared highest in the keyword co-occurrence knowledge map, it was not the focus of this paper; therefore, this was eliminated to obtain keywords with higher centrality and closer relevance to this study: chemotherapy, clinical trial, quality of life, cisplatin, paclitaxel, cancer survivor, and bevacizumab. As shown in Table 4, published articles on chemotherapy, clinical trial, and QoL were more than 100. In contrast, cancer survivor and the research on chemotherapeutic agents such as cisplatin, paclitaxel, and bevacizumab on fatigue are less studied and less published. The level of centrality is also a measure of the substantive impact that studying the hotspot can bring. The top 10 keywords with centrality greater than 0.1% were clinical trial, QoL, and cancer survivor.

Several surveys found that 43% [48]-53% [17] of patients with ovarian cancer complained of fatigue or extreme fatigue. CRF as a long-term side effect in cancer survivors negatively impacts the QoL of patients [18, 49]. Home-based exercise, good relationships, and lifestyle interventions can improve QoL and reduce fatigue in patients with ovarian cancer [50, 51]. Moreover, a randomized controlled trial study indicated that QoL was associated with overall survival in ovarian cancer patients [52]. In addition, studies have shown that chemotherapeutic agents such as cisplatin, paclitaxel, carboplatin, bevacizumab, and PARP inhibitors can also trigger fatigue in patients, and the percentage of fatigue caused ranges from 28%-35% [53-55]. Therefore, conducting multi-center, large-sample, randomized controlled clinical trials to determine whether chemotherapeutic agents have severe adverse effects in patients with ovarian cancer and to discuss the relationship between CRF and QoL and overall survival in cancer survivors are hotspots in this field.

Analysis of frontiers for CRF in ovarian cancer survivors

Analyzing keyword bursts could help researchers quickly understand the frontier or future trends in a particular field [56]. The highest strength burst keyword was cyclophosphamide with a strength of 9.85, which began in 1996 and ended in 2006. The research literature on cyclophosphamide in this period explored the effects of chemotherapeutic drug application on fatigue in patients with ovarian cancer. During the combination of different chemotherapeutic agents with cyclophosphamide, patients experienced fatigue grades ranging from grade 1 to 3, and the probability of occurrence varied from 8.3% [57] to 66% [58].

Double-blind ranked second with a strength of 8.88, which began in 2014 and persists till now. Double-blind is a vital principle in the design of randomized controlled trials, which can decrease bias due to subjective factors of subjects and researchers, although there are difficulties in its implementation [59]. We can learn from a randomized, double-blind study that ovarian cancer patients treated with two chemotherapeutic agents were more susceptible to fatigue than those treated with only one (87.7% vs. 74.1%) [60]. In another double-blind, placebo-controlled trial, the ratio of experiencing grade 1–2 fatigue and grade 3 fatigue in the trial group of patients with ovarian cancer was 62% and 4%, and the ratio of experiencing grade 1–2 fatigue and grade 3 fatigue in the placebo group was 37% and 2%, indicating that cancer itself is also a major contributor to fatigue [59].

Open-label ranked third with the strength of 8.59, which began in 2015 and continues until now. An open-label trial is a clinical trial in which both the investigators and participants know the drug or treatment being given [61]. Researchers have found that open-label placebo had a significant effect on some subjective symptoms [62]. In recent years, the application of open-label trials to determine the efficacy, safety, and tolerability of chemotherapeutic agents has become a new trend in scientific research [47, 63–65].

Strengths and limitations

To our knowledge, this is the first study to use the co-occurrence and co-citation analysis methods by CiteSpace to perform bibliometric analysis and visual display of CRF among ovarian cancer patients. Moreover, we deeply discuss the research status and explore the hotspots and frontiers in this field. There are also several limitations to this study. Due to the limitation of the bibliometric software, this study only retrieved data from the WOSCC, failing to include all research literature in the field of CRF in ovarian cancer survivors, which may be biased owing to insufficient research data. A comprehensive review of the literature to determine research hotspots and frontiers is an aspect that needs to be improved in future research.

Conclusions

In conclusion, research hotspots and frontiers in studies related to CRF in ovarian cancer patients in the past 31 years are always in dynamic change and difficult to precisely control. This review analyzes the research hotspots and frontiers in this area based on the existing literature to provide an evidence-based basis for policymakers and researchers. Conducting multi-center, large-sample, randomized controlled clinical trials to determine whether chemotherapeutic agents have severe adverse effects in ovarian cancer patients and to discuss the relationship between CRF and QoL and overall survival in cancer survivors are hotspots in this field. The new trends may be applying double-blind, randomized controlled trials to clarify the causes of cancer-related fatigue and open-label, randomized trials to determine the efficacy, safety, and tolerability of chemotherapeutic agents.

Acknowledgments

We would like to express our gratitude to those who provided help in data collecting and paper writing.

Author Contributions

Conceptualization: Yuanxia Liu.

Data curation: Yuanxia Liu, Qianxia Liu.

Formal analysis: Yuanxia Liu.

Investigation: Yuanxia Liu.

Methodology: Yuanxia Liu, Qianxia Liu, Xiaolian Jiang.

Project administration: Xiaolian Jiang.

Software: Yuanxia Liu.

Supervision: Xiaolian Jiang.

Validation: Yuanxia Liu, Qianxia Liu, Xiaolian Jiang.

Visualization: Yuanxia Liu.

Writing – original draft: Yuanxia Liu.

Writing – review & editing: Yuanxia Liu, Qianxia Liu.

References

1. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and Trends. *Cancer Epidemiol Biomarkers Prev.* 2017; 26(4):444–57. <https://doi.org/10.1158/1055-9965.EPI-16-0858> PMID: 28223433.
2. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. *Best Pract Res Clin Obstet Gynaecol.* 2017; 41:3–14. <https://doi.org/10.1016/j.bpobgyn.2016.08.006> PMID: 27743768.
3. Stewart C, Ralyea C, Lockwood S. Ovarian Cancer: An Integrated Review. *Semin Oncol Nurs.* 2019; 35(2):151–6. <https://doi.org/10.1016/j.soncn.2019.02.001> PMID: 30867104.
4. Takeiwa T, Ikeda K, Horie-Inoue K, Inoue S. Mechanisms of Apoptosis-Related Long Non-coding RNAs in Ovarian Cancer. *Frontiers in Cell and Developmental Biology.* 2021; 9:641963. <https://doi.org/10.3389/fcell.2021.641963> PMID: 33996797
5. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2019; 5(12):1749–68. <https://doi.org/10.1001/jamaoncol.2019.2996> PMID: 31560378.
6. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *JAMA Oncol.* 2021; 8(3):420–44. <https://doi.org/10.1001/jamaoncol.2021.6987> PMID: 34967848.
7. Chien J, Poole EM. Ovarian Cancer Prevention, Screening, and Early Detection: Report From the 11th Biennial Ovarian Cancer Research Symposium. *Int J Gynecol Cancer.* 2017; 27(9S Suppl 5): S20–s2. <https://doi.org/10.1097/IGC.0000000000001118> PMID: 29278600.
8. Nowe E, Friedrich M, Leuteritz K, Sender A, Stöbel-Richter Y, Schulte T, et al. Cancer-Related Fatigue and Associated Factors in Young Adult Cancer Patients. *J Adolesc Young Adult Oncol.* 2019; 8(3):297–303. <https://doi.org/10.1089/jayao.2018.0091> PMID: 30789284.
9. Spahrkäs SS, Looijmans A, Sanderman R, Hagedoorn M. Beating cancer-related fatigue with the Untire mobile app: Results from a waiting-list randomized controlled trial. *Psychooncology.* 2020; 29(11):1823–34. <https://doi.org/10.1002/pon.5492> PMID: 33393199.

10. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019; 17(1):64–84. <https://doi.org/10.6004/jnccn.2019.0001> PMID: 30659131.
11. Schmidt ME, Hermann S, Arndt V, Steindorf K. Prevalence and severity of long-term physical, emotional, and cognitive fatigue across 15 different cancer entities. *Cancer Med*. 2020; 9(21):8053–61. <https://doi.org/10.1002/cam4.3413> PMID: 32893501.
12. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007; 12 Suppl 1:4–10. <https://doi.org/10.1634/theoncologist.12-S1-4> PMID: 17573451.
13. Ma Y, He B, Jiang M, Yang Y, Wang C, Huang C, et al. Prevalence and risk factors of cancer-related fatigue: A systematic review and meta-analysis. *Int J Nurs Stud*. 2020; 111:103707. <https://doi.org/10.1016/j.ijnurstu.2020.103707> PMID: 32920423.
14. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014; 11(10):597–609. <https://doi.org/10.1038/nrclinonc.2014.127> PMID: 25113839.
15. Schmidt ME, Chang-Claude J, Vrieling A, Heinz J, Flesch-Janys D, Steindorf K. Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. *J Cancer Surviv*. 2012; 6(1):11–9. <https://doi.org/10.1007/s11764-011-0197-3> PMID: 22160661.
16. Stavra C, Ford A, Ghaem-Maghani S, Crook T, Agarwal R, Gabra H, et al. A study of symptoms described by ovarian cancer survivors. *Gynecol Oncol*. 2012; 125(1):59–64. <https://doi.org/10.1016/j.ygyno.2011.12.421> PMID: 22155797.
17. Sekse RJ, Hufthammer KO, Vika ME. Fatigue and quality of life in women treated for various types of gynaecological cancers: a cross-sectional study. *J Clin Nurs*. 2015; 24(3–4):546–55. <https://doi.org/10.1111/jocn.12647> PMID: 25040957.
18. Joly F, Ahmed-Lecheheb D, Kalbacher E, Heutte N, Clarisse B, Grellard JM, et al. Long-term fatigue and quality of life among epithelial ovarian cancer survivors: a GINECO case/control VIVROVAIRE I study. *Ann Oncol*. 2019; 30(5):845–52. <https://doi.org/10.1093/annonc/mdz074> PMID: 30851097.
19. Ferreira B, Diz A, Silva P, Sousa L, Pinho L, Fonseca C, et al. Bibliometric Analysis of the Informal Caregiver's Scientific Production. *J Pers Med*. 2022; 12(1). <https://doi.org/10.3390/jpm12010061> PMID: 35055376.
20. Chen Q, Wang Y, Song S, Xie G, Cheng B, Fang X. Global research trends in perioperative care for the elderly: a bibliometric and visualized study. *J Anesth*. 2022. <https://doi.org/10.1007/s00540-021-03033-4> PMID: 34994826.
21. Kiliçaslan Ö F, Nabi V, Yardibi F, Tokgöz MA, Köse Ö. Research Tendency in Lumbar Spinal Stenosis over the Past Decade: A Bibliometric Analysis. *World Neurosurg*. 2021; 149:e71–e84. <https://doi.org/10.1016/j.wneu.2021.02.086> PMID: 33662607.
22. Waqas A, Salminen J, Jung SG, Almerexhi H, Jansen BJ. Mapping online hate: A scientometric analysis on research trends and hotspots in research on online hate. *PLoS One*. 2019; 14(9):e0222194. <https://doi.org/10.1371/journal.pone.0222194> PMID: 31557227.
23. Liu X, Zhao S, Tan L, Tan Y, Wang Y, Ye Z, et al. Frontier and hot topics in electrochemiluminescence sensing technology based on CiteSpace bibliometric analysis. *Biosens Bioelectron*. 2021; 201:113932. <https://doi.org/10.1016/j.bios.2021.113932> PMID: 35065388.
24. Weismayer C. Applied Research in Quality of Life: A Computational Literature Review. *Appl Res Qual Life*. 2021:1–26. <https://doi.org/10.1007/s11482-021-09969-9> PMID: 34394765.
25. Qi S, Hua F, Xu S, Zhou Z, Liu F. Trends of global health literacy research (1995–2020): Analysis of mapping knowledge domains based on citation data mining. *PLoS One*. 2021; 16(8):e0254988. <https://doi.org/10.1371/journal.pone.0254988> PMID: 34370749.
26. Liu S, Sun YP, Gao XL, Sui Y. Knowledge domain and emerging trends in Alzheimer's disease: a scientometric review based on CiteSpace analysis. *Neural Regen Res*. 2019; 14(9):1643–50. <https://doi.org/10.4103/1673-5374.255995> PMID: 31089065.
27. Chen C. A Glimpse of the First Eight Months of the COVID-19 Literature on Microsoft Academic Graph: Themes, Citation Contexts, and Uncertainties. *Front Res Metr Anal*. 2020; 5:607286. <https://doi.org/10.3389/frma.2020.607286> PMID: 33870064.
28. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A*. 2004;101 Suppl 1(Suppl 1):5303–10. <https://doi.org/10.1073/pnas.0307513100> PMID: 14724295.
29. Synnestvedt MB, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. *AMIA Annu Symp Proc*. 2005; 2005:724–8. PMID: 16779135.

30. Chen CM. CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature. *Journal of the American Society for Information Science and Technology*. 2006; 57(3):359–77. <https://doi.org/10.3772/j.issn.1000-0135.2009.03.012>
31. Zanghieri M, Menichetti G, Retico A, Calderoni S, Castellani G, Remondini D. Node Centrality Measures Identify Relevant Structural MRI Features of Subjects with Autism. *Brain Sci*. 2021; 11(4):498. <https://doi.org/10.3390/brainsci11040498> PMID: 33919984.
32. Da W, Tao Z, Meng Y, Wen K, Zhou S, Yang K, et al. A 10-year bibliometric analysis of osteosarcoma and cure from 2010 to 2019. *BMC Cancer*. 2021; 21(1):115. <https://doi.org/10.1186/s12885-021-07818-4> PMID: 33541299.
33. Lai Y, Wang R, Chen X, Tang D, Hu Y, Cai J, et al. Emerging trends and new developments in monoclonal antibodies: A scientometric analysis (1980–2016). *Hum Vaccin Immunother*. 2017; 13(6):1–10. <https://doi.org/10.1080/21645515.2017.1286433> PMID: 28301271.
34. Luo J, Shi Y, Wang X, Zhang R, Chen S, Yu W, et al. A 20-Year Research Trend Analysis of the Influence of Anesthesia on Tumor Prognosis Using Bibliometric Methods. *Front Oncol*. 2021; 11:683232. <https://doi.org/10.3389/fonc.2021.683232> PMID: 34458138.
35. Wei Q, Shen J, Wang D, Han X, Shi J, Zhao L, et al. A bibliometric analysis of researches on flap endonuclease 1 from 2005 to 2019. *BMC Cancer*. 2021; 21(1):374. <https://doi.org/10.1186/s12885-021-08101-2> PMID: 33827468.
36. Pickardholley S. Fatigue in cancer patients. A descriptive study. *Cancer Nursing*. 1991; 14(1):13–9 PMID: 2013047
37. Disaia PJ, Gillette P. Human lymphoblastoid interferon (IFN-alpha-N1) plus doxorubicin, cyclophosphamide, and cisplatin in the treatment of advanced epithelial ovarian malignancies. A phase I-II study of the Gynecologic Oncology Group. *American Journal of Clinical Oncology-Cancer Clinical Trials*. 1991; 14(1):71–4. <https://doi.org/10.1097/00000421-199102000-00016> PMID: 1987744.
38. Hood MA, Finley RS. Fludarabine: a review. *Dicp-the Annals of Pharmacotherapy*. 1991; 25(5):518–24. <https://doi.org/10.1177/106002809102500512> PMID: 2068837.
39. Liu H, Xie YQ, Liu YZ, Nie RS, Li XL. Mapping the Knowledge Structure and Research Evolution of Urban Rail Transit Safety Studies. *IEEE Access*. 2019; 7:186437–55. <https://doi.org/10.1109/access.2019.2961434>
40. Avin C, Lotker Z, Peleg D, Pignolet YA, Turkel I. Elites in social networks: An axiomatic approach to power balance and Price's square root law. *PLoS One*. 2018; 13(10):e0205820. <https://doi.org/10.1371/journal.pone.0205820> PMID: 30356289.
41. Aryadoust V, Zakaria A, Lim MH, Chen C. An Extensive Knowledge Mapping Review of Measurement and Validity in Language Assessment and SLA Research. *Front Psychol*. 2020; 11:1941. <https://doi.org/10.3389/fpsyg.2020.01941> PMID: 33013505.
42. Newman ME. Modularity and community structure in networks. *Proc Natl Acad Sci U S A*. 2006; 103(23):8577–82. <https://doi.org/10.1073/pnas.0601602103> PMID: 16723398.
43. Zhang J, Zhang Y, Hu L, Huang X, Liu Y, Li J, et al. Global Trends and Performances of Magnetic Resonance Imaging Studies on Acupuncture: A Bibliometric Analysis. *Front Neurosci*. 2020; 14:620555. <https://doi.org/10.3389/fnins.2020.620555> PMID: 33551731.
44. Hao KJ, Jia X, Dai WT, Huo ZM, Zhang HQ, Liu JW, et al. Mapping Intellectual Structures and Research Hotspots of Triple Negative Breast Cancer: A Bibliometric Analysis. *Front Oncol*. 2021; 11:689553. <https://doi.org/10.3389/fonc.2021.689553> PMID: 35047380.
45. Chen C, Dubin R, Kim MC. Emerging trends and new developments in regenerative medicine: a scientometric update (2000–2014). *Expert Opin Biol Ther*. 2014; 14(9):1295–317. <https://doi.org/10.1517/14712598.2014.920813> PMID: 25077605.
46. You Y, Li W, Liu J, Li X, Fu Y, Ma X. Bibliometric Review to Explore Emerging High-Intensity Interval Training in Health Promotion: A New Century Picture. *Front Public Health*. 2021; 9:697633. <https://doi.org/10.3389/fpubh.2021.697633> PMID: 34368063.
47. Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncology*. 2021; 22(7):1034–46. [https://doi.org/10.1016/S1470-2045\(21\)00216-3](https://doi.org/10.1016/S1470-2045(21)00216-3) PMID: 34143970.
48. Sehoul J, Armbrust R. All aspects of gynecologic oncology aftercare using the example of ovarian cancer. *Gynakologe*. 2021; 54(2):99–106. <https://doi.org/10.1007/s00129-020-04731-y>
49. Inci MG, Richter R, Heise K, Dukatz R, Woopen H, Sehoul J. Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (HR-QoL) in Patients with Ovarian Cancer: What Is Different Compared

- to Healthy Women? *Cancers*. 2021; 13(4):631. <https://doi.org/10.3390/cancers13040631> PMID: 33562563.
50. Smits A, Lopes A, Das N, Bekkers R, Massuger L, Galaal K. The effect of lifestyle interventions on the quality of life of gynaecological cancer survivors A systematic review and meta-analysis. *Gynecologic Oncology*. 2015; 139(3):546–52. <https://doi.org/10.1016/j.ygyno.2015.10.002> PMID: 26441008.
 51. Madan R, Dracham CB, Elangovan A, Rai B, Srinivasa GY, Gupta A, et al. Quality of Life Among Ovarian Cancer Survivors: A Tertiary Care Center Experience from India. *Indian Journal of Gynecologic Oncology*. 2021; 19(1):2–7. <https://doi.org/10.1007/s40944-020-00491-8>
 52. Zhou Y, Cartmel B, Gottlieb L, Ercolano EA, Li FY, Harrigan M, et al. Randomized Trial of Exercise on Quality of Life in Women With Ovarian Cancer: Women's Activity and Lifestyle Study in Connecticut (WALC). *Jnci-Journal of the National Cancer Institute*. 2017; 109(12):dx072. <https://doi.org/10.1093/jnci/djx072> PMID: 30053074.
 53. Assi S, Barling M, Al-Hamid A, Cheema E. Exploring the adverse effects of chemotherapeutic agents used in the treatment of cervical and ovarian cancer from the patient's perspective: a content analysis of the online discussion forums. *European Journal of Hospital Pharmacy*. 2021; 28(E1):E35–E40. <https://doi.org/10.1136/ejhpharm-2019-002162> PMID: 32349988.
 54. Berton D, Floquet A, Lescaut W, Baron G, Kaminsky MC, Toussaint P, et al. Real-World Experience of Bevacizumab as First-Line Treatment for Ovarian Cancer: The GINECO ENCOURAGE Cohort of 468 French Patients. *Frontiers in Pharmacology*. 2021; 12:711813. <https://doi.org/10.3389/fphar.2021.711813> PMID: 34616296.
 55. Romanova M, Klat J. Adverse events of PARP inhibitors. *Ceska Gynekologie-Czech Gynaecology*. 2021; 86(1):54–60. <https://doi.org/10.48095/cccg202154> PMID: 33752410.
 56. Zhou H, Tan W, Qiu Z, Song Y, Gao S. A bibliometric analysis in gene research of myocardial infarction from 2001 to 2015. *PeerJ*. 2018; 6:e4354. <https://doi.org/10.7717/peerj.4354> PMID: 29456889.
 57. Havsteen H, Bertelsen K, Gadeberg CC, Jacobsen A, Kamby C, Sandberg E, et al. A phase 2 study with epirubicin as second-line treatment of patients with advanced epithelial ovarian cancer. *Gynecologic Oncology*. 1996; 63(2):210–5. <https://doi.org/10.1006/gyno.1996.0308> PMID: 8910629.
 58. Valerio MR, Tagliaferri P, Raspagliesi F, Fulfaro F, Badalamenti G, Arcara C, et al. A phase II study of pegylated liposomal doxorubicin oxaliplatin and cyclophosphamide as second-line treatment in relapsed ovarian carcinoma. *International Journal of Gynecological Cancer*. 2006; 16:79–85. <https://doi.org/10.1111/j.1525-1438.2006.00324.x> PMID: 16515572.
 59. Pujade-Lauraine E, Ledermann JA, Selle F, GebSKI V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncology*. 2017; 18(9):1274–84. [https://doi.org/10.1016/S1470-2045\(17\)30469-2](https://doi.org/10.1016/S1470-2045(17)30469-2) PMID: 28754483.
 60. Monk BJ, Brady MF, Aghajanian C, Lankes HA, Rizack T, Leach J, et al. A phase 2, randomized, double-blind, placebo-controlled study of chemo-immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: a Gynecologic Oncology Group partners study. *Annals of Oncology*. 2017; 28(5):996–1004. <https://doi.org/10.1093/annonc/mdx049> PMID: 28453702.
 61. Vergote I, Oaknin A, Baurain JF, Ananda S, Wong S, Su X, et al. A phase 1b, open-label study of trebananib in combination with paclitaxel and carboplatin in patients with ovarian cancer receiving interval or primary debulking surgery. *European Journal of Cancer*. 2014; 50(14):2408–16. <https://doi.org/10.1016/j.ejca.2014.06.010> PMID: 25037684.
 62. Meeuwis SH, van Middendorp H, van Laarhoven AIM, Veldhuijzen DS, Lavrijsen APM, Evers AWM. Effects of Open- and Closed-Label Nocebo and Placebo Suggestions on Itch and Itch Expectations. *Front Psychiatry*. 2019; 10:436. <https://doi.org/10.3389/fpsy.2019.00436> PMID: 31293458.
 63. Thein KZ, Karp DD, Tsimberidou A, Gong J, Sulovic S, Shah J, et al. Selinexor in combination with carboplatin and paclitaxel in patients with advanced solid tumors: Results of a single-center, multi-arm phase 1b study. *Investigational New Drugs*. 2021. <https://doi.org/10.1007/s10637-021-01188-1> PMID: 34562230.
 64. Thaker PH, Bradley WH, Leath CA, Jackson CG, Borys N, Anwer K, et al. GEN-1 in Combination with Neoadjuvant Chemotherapy for Patients with Advanced Epithelial Ovarian Cancer: A Phase I Dose-escalation Study. *Clinical Cancer Research*. 2021; 27(20):5536–45. <https://doi.org/10.1158/1078-0432.CCR-21-0360> PMID: 34326131.
 65. Zsiros E, Lynam S, Attwood KM, Wang C, Chilakapati S, Gomez EC, et al. Efficacy and Safety of Pembrolizumab in Combination With Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Ovarian Cancer A Phase 2 Nonrandomized Clinical Trial. *Jama Oncology*. 2021; 7(1):78–85. <https://doi.org/10.1001/jamaoncol.2020.5945> PMID: 33211063.