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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.5; 5-year JIF: 2.8; JIF Rank: 71/143 in gastroenterology and hepatology; JIF Quartile: Q2; and 5-year JIF Quartile: Q2. The *WJGO*'s CiteScore for 2023 is 4.2 and Scopus CiteScore rank 2023: Gastroenterology is 80/167; Oncology is 196/404.

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SCIENTOMETRICS

Bibliometric analysis of olaparib and pancreatic cancer from 2009 to 2022: A global perspective

Xu Feng, Yi-Han Chai, Ke-Xin Jiang, Wen-Bin Jiang, Wen-Chao Chen, Yu Pan

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Xu Feng, Yi-Han Chai, Ke-Xin Jiang, Wen-Bin Jiang, Wen-Chao Chen, Yu Pan, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, Zhejiang Province, China

Co-first authors: Xu Feng and Yi-Han Chai.

Co-corresponding authors: Wen-Chao Chen and Yu Pan.

Corresponding author: Yu Pan, MD, Physiotherapist, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Qingchun East Road, Shangcheng District, Hangzhou 310016, Zhejiang Province, China. panyu1013@zju.edu.cn

Abstract

BACKGROUND

Genetic screening for breast cancer gene 1 (*BRCA*)*1/2* mutations can inform breast/ovarian/pancreatic cancer patients of suitable therapeutic interventions. Four to seven percent of pancreatic cancer patients have germline *BRCA* mutations. *BRCA* genes aid in DNA repair, especially homologous recombination, which impacts genomic stability and cancer cell growth. *BRCA1* regulates the cell cycle, ubiquitination, and chromatin remodeling, whereas *BRCA2* stimulates the immune response. They predict the efficacy of platinum chemotherapy or polymerase (PARP) inhibitors such as olaparib.

AIM

To determine the trends and future directions in the use of olaparib for pancreatic cancer treatment.

METHODS

To evaluate the trends in how olaparib works in pancreatic cancer, we performed a bibliometric analysis. One hundred and ninety-six related publications were accessed from the Web of Science Core Collection and were published between 2009 and 2022. The analytic parameters included publications, related citations, productive countries and institutes, influential authors, and keyword development.

RESULTS

This study visualizes and discusses the current research, including the present global trends and future directions in olaparib and pancreatic cancer. Overall, this study sheds light on optimizing the use of olaparib in pancreatic cancer treatment,

offering valuable guidance for researchers in this field.

CONCLUSION

Our findings identified trends in olaparib and pancreatic cancer, with China and the USA leading and with global cooperation tightening. O'Reilly EM's team and Memorial Sloan-Kettering had the highest output. The *Journal of Clinical Oncology* was the most cited journal. More PARP inhibitors are emerging, and combination therapy is suggested for future therapeutic trends.

Key Words: Olaparib; Pancreatic cancer; Bibliometric analysis; Breast cancer susceptibility gene; Poly (adenosine diphosphate–ribose) polymerase

Core Tip: Breast cancer gene (*BRCA*)*1* and *BRCA2* mutations affect 4%-7% of pancreatic cancer patients and influence their response to therapies such as platinum chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib. A bibliometric analysis of 196 publications highlights growing global research interest, with China and the United States leading. The key contributors include O'Reilly EM's team and Memorial Sloan-Kettering, whereas the *Journal of Clinical Oncology* stands out for citations. Future trends point toward increased use of PARP inhibitors and combination therapies, offering valuable insights for advancing olaparib research in pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is a relatively uncommon malignant tumor that mostly originates from exocrine pancreatic ductal cells [1]. The risk factors for pancreatic cancer include smoking, obesity, alcohol abuse, diabetes, and chronic pancreatitis[2]. Approximately 60430 new diagnoses are expected in 2021 in the United States, and it is the 4th leading cause of cancer-related deaths worldwide[3]. However, as the disease has nonspecific symptoms, most patients progress to the advanced stage with no chance of surgery when first diagnosed. The current standard first-line chemotherapy regimen is FOLFIRINOX (fluorouracil, irinotecan, leucovorin, oxaliplatin), which is associated with a median progression-free survival (mPFS) of 6.4 months[4]. As metastatic pancreatic cancer is resistant to many treatments, even after radical resection, the prognosis after initial diagnosis remains poor, with a 5-year survival rate of 11%[5].

Not all pancreatic cancer patients have a low chance of survival. Approximately 4%–7% of pancreatic cancer patients harbor mutations in the genes encoding loss of function of breast cancer susceptibility gene (*BRCA*)1, *BRCA2*, or both. *BRCA1* mutations are responsible for inherited cancers, including 40% of breast cancers and over 80% of ovarian cancers [6]. *BRCA* genes play a non-neglectable role in regulating cell replication, repairing DNA damage, and normal cell growth. *BRCA* genes also act as important tumor suppressors, the encoded protein of which interacts with other tumor suppressors[7]. Cells with *BRCA* mutations are relatively sensitive to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition. If the PARP gene is inhibited, *BRCA* gene mutations in patients make homologous recombination repair unable to proceed normally, eventually leading to cell apoptosis. Therefore, *BRCA* and PARP meet the definition of synthetic lethality. When the *BRCA* gene is mutated, the DNA repair pathway depends on the PARP-1 enzyme, and PARP inhibitors prevent DNA repair and eventually die[8]. The application of PARP inhibitors in patients is expected to kill tumor cells. However, the presence of *BRCA* in normal cells can still repair DNA and allow cells to survive, so PARP inhibitors can be used as targeted drugs to selectively kill *BRCA*-mutant cells[9]. Olaparib, a PARP inhibitor, has shown promising efficacy in terms of mPFS (7.0 months *vs* 4.2 months with standard treatment) in patients with metastatic breast cancer and a g *BRCAmt*[10]. Moreover, olaparib has certain antitumor effects on patients with *BRCA* mutation–metastatic pancreatic cancer with a heavy pretreatment history, extending the mPFS from 3.8 months to 7.4 months (placebo *vs* olaparib)[11]. Olaparib became the first pancreatic cancer-targeted drug approved, bringing new hope for the survival of patients with pancreatic cancer. However, several critical knowledge gaps exist regarding olaparib and its use in treating pancreatic cancer. This calls for a comprehensive overview of the evolving landscape of olaparib research, including publication and citation trends over time. Additionally, there is a need to understand the geographical distribution of research efforts and identify the most productive countries and institutions involved in this field, along with the most influential scholars and their contributions, particularly those focusing on novel aspects such as the role of ATM variants and homologous recombination deficiency (HRD) in pancreatic cancer. Furthermore, researchers are working to understand the transition from single-agent to combination therapies involving olaparib, including the integration of immunotherapies.

Bibliometric analysis helps researchers conveniently acquire the most complete information in a complex field, providing information such as the main publishing institutions, the most influential scholars and their collaborations, the most representative research, and the keywords in a certain period. Bibliometric analysis has the advantage of mapping approaches aimed at predicting the development of future directions in some areas and is disciplined in a newly structured, transcended systemic review, which mainly concerns the development of a segment over a while[12]. Therefore, it has strengths from a global perspective, providing a more comprehensive view of the development history of certain fields[13].

Many studies have been published from 2009 to 2022 in the field of olaparib and pancreatic cancer. In this article, we provide an overview and scientific analysis of published olaparib and pancreatic cancer research *via* data obtained from the Web of Science Core Collection (WoSCC). The indices included annual changes in publications and citations, high-output countries/regions and institutions, the most influential and highly cited authors, mainstream journals, and keyword changes over time, which were demonstrated and visualized *via* several bibliometric software programs. Through this analysis, we will understand the development of olaparib and pancreatic cancer, which will help us obtain a good reference when researching studies in this field.

MATERIALS AND METHODS

Data collection

First, data from 2009 to 2022 were retrieved from the WoSCC. We collected data within one day (September 8, 2022). The search queries were set as follows: "Topic Search (TS) = (olaparib)", AND "TS = (pancreatic cancer)", AND "Language: English AND Reference Type: Article OR Review". After deleting duplicates and irrelevant papers, a total of 196 references were extracted from the WoSCC and then used to perform the bibliometric analysis. The screening process is shown in Figure 1.

Data analysis

Visual bibliometric analysis was performed *via* HisCite (version 2.1), CiteSpace (version 6.1. R2), VOSviewer (version 1.6.18), SCImago Graphica (version 1.0.23), and the Bibliometrix 4.1.0 package in R. First, the total number of publications, total local citation score, and total global citation score for each publication year, top countries, journals, authors, and institutions were analyzed by HisCite. VOSviewer was employed to visualize the collaborative network, which included countries, institutions, and authors, and a density map of keywords. With the assistance of VOSviewer, SCImago Graphica could be utilized to visualize the co-occurrence network between institutions and international collaborations of olaparib in pancreatic cancer. Cluster analysis, keyword bursts, and timeline views were obtained *via* CiteSpace. More importantly, modularity $Q > 0.3$ and weighted mean silhouette > 0.5 of cluster analysis indicate that the clustering results are sufficiently comprehensive and convincing. The Bibliometrix package is a tool designed in the R language used for bibliometric analysis and was applied to analyze the production of top authors or countries over time, the authors' *H*-index, and three-field plots of institutions, authors, and keywords.

RESULTS

Annual publication and citations

A total of 196 documents, including 138 (70.4%) original studies and 58 (29.6%) reviews associated with olaparib in pancreatic cancer, were screened from the WoSCC database. These documents received 6399 citations before September 8, 2022, with an average number of citations of 32.65 per item. The annual counts of publications and citations are shown in Figure 2. Although there was one publication in 2009 (written by Vasiliou *et al*[14]), one in 2011 (written by Vance *et al*[15]) and fewer than 10 on olaparib in pancreatic cancer published annually from 2009 to 2016, there was an overall growth trend in olaparib use among pancreatic cancer patients from 2017 to 2022. Moreover, the growth of publications has accelerated distinctly since 2020, indicating that the concept has gradually been accepted by researchers since then. In particular, the number of publications in 2020 (n = 45) was slightly greater than that from 2016 to 2019 (n = 42). The substantial surge in publications in 2020 can be attributed to several potential factors. Notably, the emergence of critical clinical trials and data releases demonstrating the efficacy and safety of olaparib in treating pancreatic cancer could have significantly fueled this growth, sparking heightened interest and subsequent publications. For example, the positive outcomes from a trial showing the efficacy of olaparib maintenance therapy in patients with metastatic pancreatic cancer and germline *BRCA* mutations contributed to a burgeoning interest in olaparib[11]. Additionally, the regulatory approvals for the application of olaparib in pancreatic cancer have reportedly escalated research activities. The approval of olaparib by the United States Food and Drug Administration (FDA) for the treatment of *gBRCAm* metastatic pancreatic adenocarcinoma on December 27, 2019, provides further rationale for the increased number of publications in this domain.

Moreover, amplified funding for pancreatic cancer research, extensive media coverage, and public awareness campaigns regarding new treatments for pancreatic cancer likely played pivotal roles in driving the upsurge in publications. It is reasonable to posit that the combined influence of these factors substantively contributed to the marked increase in publications related to olaparib in the context of pancreatic cancer. As shown in Figure 2, the annual number of citations of publications, like the number of publications, presented an overall increasing trend. For 2022, the data were

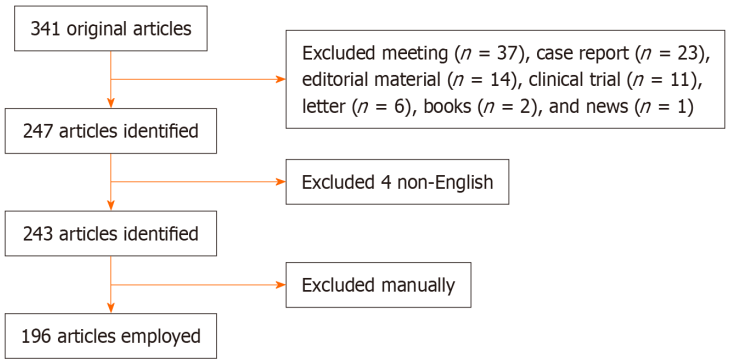


Figure 1 Flowchart of the screening process. A total of 196 references extracted from the Web of Science Core Collection were used to perform a bibliometric analysis.

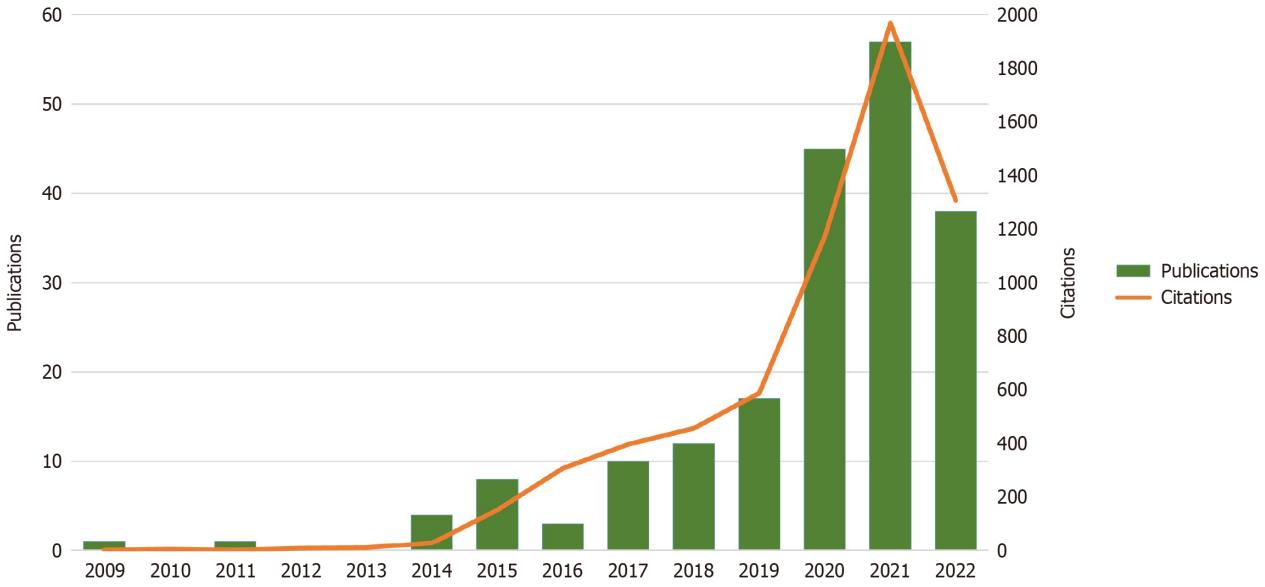


Figure 2 The number of papers published annually and the total number of citations of publications related to olaparib in pancreatic cancer. The annual number of citations of publications, similar to the number of publications, showed an overall increasing trend.

incomplete because the remaining three months were included. Therefore, the increased number of annual publications and citations highlights the potential of olaparib for the treatment of pancreatic cancer.

Countries/regions

A total of 27 countries conducted relevant studies on olaparib in pancreatic cancer patients from 2009 to 2022. First, we analyzed the production of Olaparib in five countries over time and found that the production trend in each country was rising, especially in the United States and China (Figure 3A). A adjusted geographical distribution map of global productivity is displayed in Figure 3B, where the area and color of each country are rescaled and adjusted according to the number of publications. The top 10 most prolific countries/regions associated with olaparib use in patients with pancreatic cancer are listed in Table 1. The authors from the United States published the most articles associated with olaparib in pancreatic cancer in recent years (n = 83). Next, China (n = 48) and the United Kingdom (n = 31) took second and third place, respectively. Additionally, the country with the most citations was the United States, with 4760 citations, followed by the United Kingdom, with 3748 citations, and Spain, with 2352 citations (Table 1).

Furthermore, a geographical collaboration map and cooperation network of countries/regions with a minimum of 3 publications were generated by SCImago Graphica and VOSviewer, respectively. The United States has the broadest collaboration network, mainly presenting scientific relationships with China and some European countries (Figure 3C). As shown in Figure 3D, the overvisualization of the cooperation network among countries/regions demonstrated that cooperation between countries has changed over time. The United States has collaborated most closely with some European countries, such as Germany, France, and Italy, in recent years. This may be due to shared scientific interests, funding opportunities, and historical ties. However, the United States has mainly cooperated closely with China in recent years. This increased collaboration with China underscores the growing recognition of the importance of investigating the efficacy of olaparib in Asian populations, particularly in light of genetic variations and disease prevalence. In the context of China, Chinese scientists have established extensive collaborative partnerships with Germany and France in recent

Table 1 The top 10 most popular countries/regions conducting research on olaparib and pancreatic cancer

Rank	Country	Counts	TLCS	TGCS
1	United States	83	320	4760
2	China	48	16	366
3	United Kingdom	31	241	3748
4	France	19	140	1537
5	Italy	19	124	1040
6	Germany	16	192	2254
7	Spain	12	186	2352
8	Australia	9	75	1746
9	Belgium	9	130	1391
10	Israel	9	179	2120

TLCS: Total local citation score; TGCS: Total global citation score.

years, demonstrating a keen interest in cutting-edge biotechnology and pharmaceutical development. Furthermore, earlier research endeavors and collaborations with Australia and Spain represent the diverse areas of study.

Authors

A total of 1639 authors have published 196 papers on olaparib in pancreatic cancer, and the top 20 prolific authors are presented in Table 2. All the authors came from foreign countries. Among them, O'Reilly EM, from the Memorial Sloan-Kettering Cancer Center, was the most productive author with 11 papers, followed by Golan T (n = 9), Hammel P (n = 8), Macarulla T (n = 7), Hochhauser D (n = 5), Seufferlein T (n = 5), and Van Cutsem E (n = 5). O'Reilly EM's research encompasses a wide range of topics related to olaparib in the context of pancreatic cancer. This includes investigations of olaparib's efficacy in clinical trials, its pharmacological effects, and its impact on patient outcomes. Moreover, the most cited author is Balmana J, with 1407 citations, followed by O'Reilly EM (1177 citations) and Golan T (979 citations).

We can see from the coauthorship map visualized by VOSviewer that the highly cited authors O'Reilly EM, Golan T, and Hammel P were at the center and collaborated closely (Figure 4A). The coauthorship map (Figure 4A) illustrates a close collaboration between O'Reilly EM, Golan T, and Hammel P. This suggests that their combined efforts positively influence the impact of their work. Collaborations allow for the sharing of resources, expertise, and patient populations, ultimately improving the quality and scope of research. However, some researchers were scattered independently from other researchers, especially Colle E and De Mestier L, who are in the lower left corner of Figure 4A. Therefore, the collaboration between researchers on olaparib in pancreatic cancer urgently needs to be promoted in the future. The timeline of authors who published studies on olaparib in pancreatic cancer is visualized in Figure 4B *via* the Bibliometrix package in the R language, revealing the time points at which each of the top 15 prolific authors published papers about olaparib in pancreatic cancer. As shown in Figure 4B, Lawrence TS, Morgan MA, and Parsels LA started research on olaparib in pancreatic cancer after publishing their papers in 2011 and continuing until 2021. The most prolific authors, O'Reilly EM and Golan T, began relevant research in 2015 and 2019, respectively, and continued into 2021. Most authors engaged in the study of olaparib in pancreatic cancer after 2019, and the number of publications of most authors also increased significantly in the same year. The H-index is another metric reflecting the number of publications and citations in a single number and is indicative of the authors' research achievements in this study. The highly cited authors O'Reilly EM, Golan T, and Hammel P have the highest H-indices, meaning the H-index is positively correlated with having more citations and the citation advantage of more popular authors (Figure 4C). To clarify the relationships among institutions, authors, and research fields (keywords) and promote potential cooperation between various experts from different institutions in this study, a three-field plot of institutions, authors, and keywords was generated *via* the R bibliometrix package (Figure 5), which also demonstrated that cooperation among more authors should be further enhanced.

Institutions

Four hundred and ninety-four institutions have contributed to research on olaparib in pancreatic cancer. The top 15 institutions ranked by number of publications are listed in Table 3. Most scientific research institutions were from the United States, the United Kingdom, or Israel. Among them, Memorial Sloan-Kettering Cancer Center (n = 14) in the United States was the leading institution in terms of publication outputs, followed by AstraZeneca (n = 13) in the United Kingdom. Strengthening collaboration between academic institutions and industry partners, such as AstraZeneca, is essential for translating research findings into clinical practice. These collaborations can accelerate the development of new therapeutic strategies and improve patient care. The visualization map for institutions' collaboration was generated with a minimum of 3 publications by VOSviewer, and 54 institutions formed 5 clusters with different colors, in which there were active collaborations between the institutions (Figure 6A).

Table 2 The top 20 most popular authors conducting research on olaparib and pancreatic cancer

Rank	Author	Counts	TLCS	TGCS
1	O'Reilly EM	11	135	1177
2	Golan T	9	132	979
3	Hammel P	8	130	956
4	Macarulla T	7	127	947
5	Hochhauser D	5	127	944
6	Seufferlein T	5	17	140
7	Van Cutsem E	5	127	944
8	Algul H	4	131	976
9	Brody JR	4	22	240
10	Cornelissen B	4	4	72
11	Kleger A	4	17	135
12	Lawrence TS	4	18	247
13	Morgan MA	4	18	247
14	Park JO	4	127	942
15	Parsels LA	4	18	247
16	Perkhofer L	4	17	135
17	Arnold D	3	118	919
18	Balmana J	3	68	1407
19	Biankin AV	3	5	49
20	Cavalli A	3	6	36

TLCS: Total local citation score; TGCS: Total global citation score.

The collaborative network between institutions was subsequently constructed by SCImago Graphica and VOSviewer (Figure 6B). The network revealed that the institutions in the upper left area cooperation more closely with one another than those in other areas, such as the University of Chicago, University of Paris VII, and Sungkyunkawan University. To enhance future collaborations, several areas and institutions stand out as potential targets for enhancement. First, institutions within closely integrated clusters should strive to broaden their collaboration by actively engaging with institutions outside of their immediate networks. This can involve the establishment of joint research programs, shared facilities, and collaborative grants aimed at facilitating the exchange of ideas and resources. Second, institutions located in less connected areas, such as those in the lower right region of the visualization map (Figure 6B), should be incentivized to establish new partnerships with leading institutions. This can be achieved by implementing mentorship programs, international symposia, and funding initiatives that foster cross-institutional and cross-border collaborations. In summary, collaboration among authors still needs to be strengthened in the future.

Journals

A total of 130 journals published papers focused on olaparib and pancreatic cancer. The top 10 journals ranked by publications are listed in Table 4. The top journal, *Cancers* [impact factor (IF) 2021, 6.575], published the most publications (n = 13) from 2009 to 2022, followed by Clinical Cancer Research (IF 2021, 13.801, n = 7), the *International Journal of Molecular Sciences* (IF 2021, 6.208, n = 5) and *Annals of Oncology* (IF 2021, 51.769, n = 4). Some academic journals receive a high volume of publications for several reasons. First, journals such as *Cancers*, which cover all aspects of cancer research, tend to attract many submissions because they provide a platform for a wide range of research topics. Second, well-reputed journals, as indicated by a high IF, are more likely to receive high-quality submissions, as authors want to publish in respected venues. Third, journals that align with current research trends, such as olaparib in pancreatic cancer, benefit from increased interest and activity in the field, resulting in a higher volume of submissions. Although the number of publications on olaparib in pancreatic cancer in journals was not significant, the majority of the top 10 journals had scientific influence, with high IFs 2021. The *Journal of Clinical Oncology* was the most-cited journal (1293 times) and had the highest IF (IF 2021, 50.717).

Most co-cited references

References reflect the solid foundation laid by predecessors, which may drive progression and achieve breakthroughs in

Table 3 The 15 most productive institutions regarding olaparib and pancreatic cancer research

Rank	Institution	Country	Counts	TLCS	TGCS
1	Memorial Sloan-Kettering Cancer Center	United States	14	147	1667
2	AstraZeneca	United Kingdom	13	208	2755
3	University of Michigan	United States	10	36	752
4	Harvard Medical School	United States	7	15	173
5	University of Bologna	Italy	7	6	92
6	University of Pennsylvania	United States	7	62	1254
7	Dana-Farber Cancer Institute	United States	6	21	633
8	Beaujon Hospital	France	6	121	931
9	Tel Aviv University	Israel	6	110	907
10	University of Oxford	United Kingdom	6	18	192
11	University of Texas, MD Anderson Cancer Center	United States	6	27	859
12	Vall d'Hebron University Hospital	Spain	6	130	1163
13	Sheba Medical Center	Israel	5	70	1220
14	University College London	United Kingdom	5	127	1150
15	University of Glasgow	United Kingdom	5	7	105

TLCS: Total local citation score; TGCS: Total global citation score.

Table 4 The top 10 journals publishing research on olaparib and pancreatic cancer

Rank	Journal	Counts	IF 2021	TLCS	TGCS
1	*Cancers*	13	6.575	0	94
2	*Clinical Cancer Research*	7	13.801	16	169
3	*International Journal of Molecular Sciences*	5	6.208	0	14
4	*Annals of Oncology*	4	51.769	43	566
5	*European Journal of Medicinal Chemistry*	4	7.088	8	139
6	*Journal of Clinical Oncology*	4	50.717	74	1293
7	*BMC Cancer*	3	4.638	0	13
8	*British Journal of Cancer*	3	9.075	6	99
9	*Cancer Biology & Therapy*	3	4.875	0	6
10	*Cancer Research*	3	13.312	11	75

TLCS: Total local citation score; TGCS: Total global citation score.

scientific research. In this study, we analyzed the top 10 most co-cited studies on olaparib in pancreatic cancer, the results of which are listed in Table 5. The article with the most co-citations, titled "Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer", was written by Golan *et al*[11] and published in *The New England Journal of Medicine* in 2019 (103 citations). This article is the result of a clinical trial and revealed that PFS was longer with maintenance olaparib compared to the placebo in patients with *gBRCAmt* and metastatic pancreatic cancer[11]. This reference holds paramount significance within the field for several reasons. First, this study provides substantial evidence of the clinical efficacy of olaparib in a distinct cohort of patients afflicted by pancreatic cancer-particularly those harboring germline *BRCA* mutations. This discovery has profound implications for personalized medicine, emphasizing the pivotal role of genetic testing in tailoring treatments for individual patients. Furthermore, the study's rigorous design, exemplified by its randomized controlled trial framework, fortifies the credibility of the findings and the therapeutic advantages of olaparib. Consequently, this has had a discernible impact on regulatory determinations, as evidenced by the FDA endorsement of olaparib for this specific indication. The journals *Nature*, the *Journal of Clinical Oncology*, *The New England Journal of Medicine*, and *Cancer Research* have tremendous scientific influence on scholars and academics in this

Table 5 The top 10 cocited references related to olaparib and pancreatic cancer

Rank	Ref.	Title	Citations	Journal
1	Golan *et al*[11], 2019	Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic cancer	103	*The New England Journal of Medicine*
2	Kaufman *et al*[35], 2015	Olaparib monotherapy in patients with advanced cancer and a germline *BRCA1/2* mutation	56	*Journal of Clinical Oncology*
3	Farmer *et al*[36], 2005	Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy	52	*Nature*
4	Robson *et al*[10], 2017	Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation	46	*The New England Journal of Medicine*
5	Bryant *et al*[37], 2005	Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase	44	*Nature*
6	Murai *et al*[38], 2012	Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors	40	*Cancer Research*
7	Waddell *et al*[39], 2015	Whole genomes redefine the mutational landscape of pancreatic cancer	39	*Nature*
8	Fong *et al*[40], 2009	Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers	37	*The New England Journal of Medicine*
9	Moore *et al*[21], 2018	Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer	37	*The New England Journal of Medicine*
10	Conroy *et al*[4], 2011	FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer	36	*The New England Journal of Medicine*

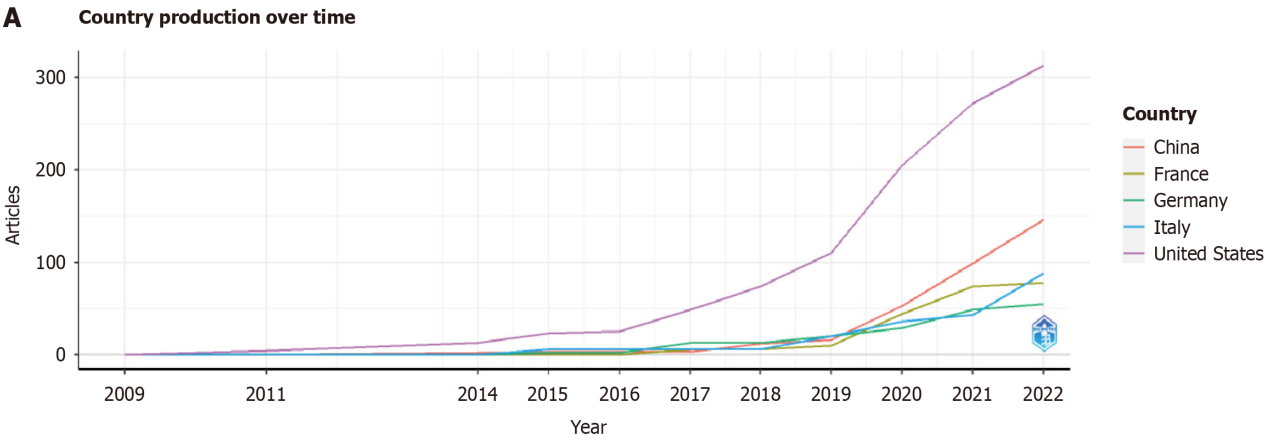
field, and all highly cocited papers are published in these high-quality journals. These references have significantly influenced subsequent research by establishing a standard for the design and implementation of clinical trials, emphasizing the importance of biomarker-driven therapies and providing directions for developing novel treatment approaches. They have also influenced clinical guidelines and recommendations for managing pancreatic cancer. Additionally, these findings have inspired further investigations into the synergistic effects of olaparib in combination with other therapies, the discovery of additional predictive biomarkers, and the examination of olaparib's potential application in earlier stages of the disease.

Keyword analysis

VOSviewer was used to present the map of the co-occurrence of keywords. Eight hundred and sixty-eight keywords were extracted, 89 of which appeared > 5 times and 44 appeared > 10 times. As shown in Figure 7A, the density map revealed high-frequency keywords, which occurred more than 10 times, indicating the hotspots and research trends in the field of olaparib in pancreatic cancer. The color represents the number of keyword occurrences. Among them, the top 5 keywords in terms of occurrence were "olaparib", "PARP inhibitors", "gemcitabinel", "survival", and "brcachemotherapy". These keywords highlight the central themes of the research, with "olaparib" and "PARP inhibitors" emphasizing the drug and its mechanism of action, "gemcitabine" representing standard chemotherapy, "survival" indicating the clinical outcomes of interest, and "*BRCA* chemotherapy" pointing toward the importance of genetic markers in treatment selection.

CiteSpace was used to perform cluster analysis and visualize the timeline map and keyword burst diagram. First, the modularity Q value was 0.7119, and the weighted mean silhouette S value was 0.8902, demonstrating the excellence of the cluster analysis. A total of 12 clusters with the highest K values were obtained (Figure 7B), which included "chemotherapy", "DNA repair", *etc.* We then performed cluster analysis graphically in the timeline view. As shown in Figure 7C, research on the DNA damage response, PARP inhibitors, *BRCA* mutations, precision medicine, and phase III trials has recently become a concern of researchers, who are predicting research frontiers and concerns. These topics collectively suggest the research frontiers and concerns in the field, with a particular emphasis on the integration of targeted therapies and personalized medicine in pancreatic cancer treatment.

Finally, keyword analysis with strong burst strength was performed to reflect recent emerging trends (Figure 7D). We found that "ADP ribose polymerase", "synthetic lethality", and "inhibitors" were related to drug mechanisms, whereas "*BRCA2* mutation", "combination", "chemotherapy", and "cisplatin" were related to clinical therapy. In particular, the citation burst time of the keyword "therapy" (2020-2022) has continued to 2021, which is still ongoing, suggesting that articles on olaparib in clinical research have attracted the attention of researchers. These findings suggest that future research will likely concentrate on optimizing the use of olaparib in combination with other agents, refining treatment strategies on the basis of genetic markers, and further elucidating the molecular mechanisms underlying the drug's efficacy.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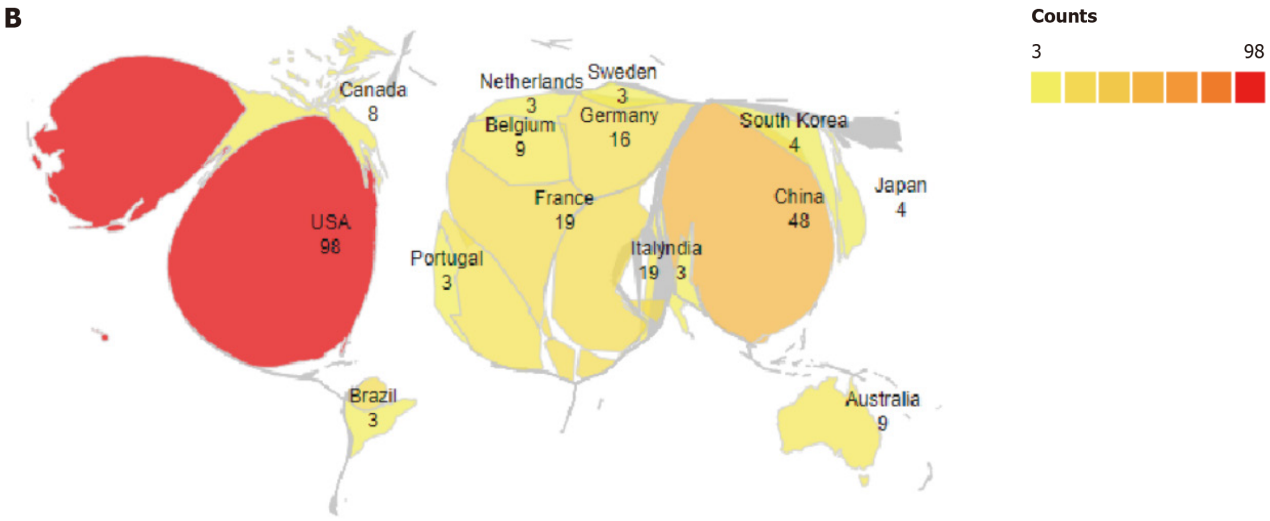
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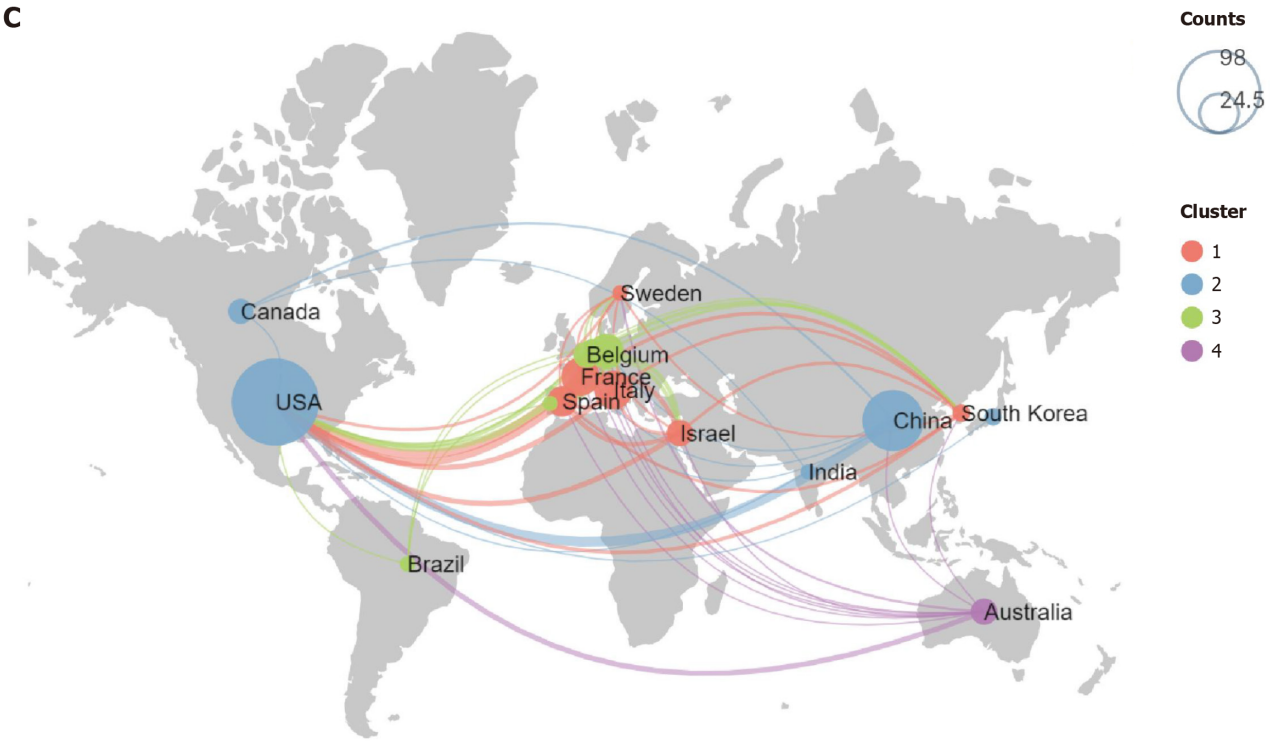
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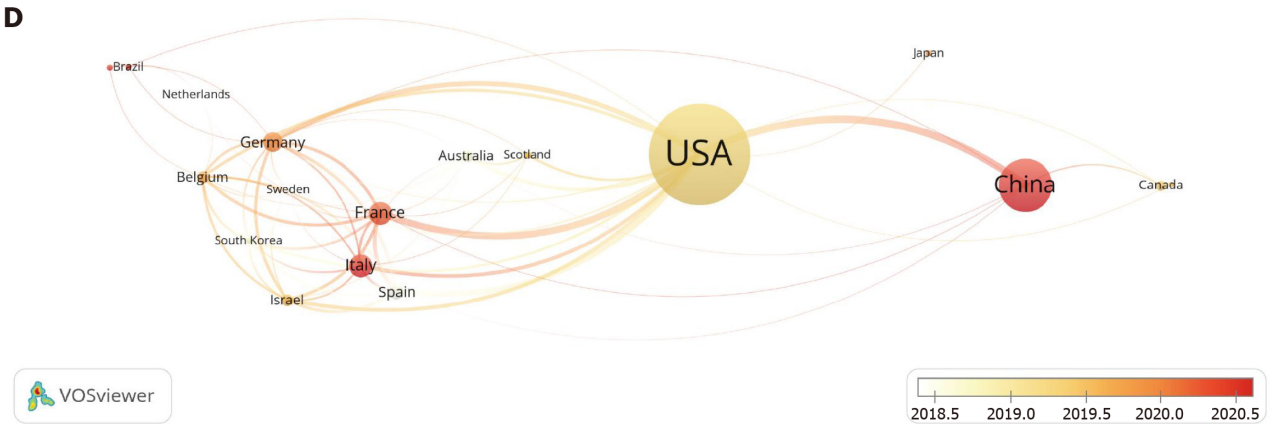

Figure 3 Analysis of countries/regions. A: Countries' production throughout the year; B: Deformed geographical distribution map of global productivity related to olaparib in pancreatic cancer. The area and color represent the number of publications; C: Geographical distribution map and collaboration map of publications related to olaparib in pancreatic cancer. Node size and color represent the number of publications; D: Global collaboration and time evolution of countries/regions in this field. The colors of the nodes represent the average number of publications annually.

DISCUSSION

In our study, we analyzed the main overview and development trends of olaparib and pancreatic cancer. Since the usage of olaparib in cancer patients with *BRCA* mutations, annual production and citations have increased. The United States is the most productive country, and the top 12 of the 30 most productive institutions are located in the United States. The most influential scholar is O'Reilly EM. She is the lead specialist in pancreatic cancer, specializing in the tumor microenvironment of pancreatic cancer and integrating immunotherapy into the treatment of pancreatic cancer[16-18]. Her latest study involved categorizing gATMmt, sATMmt, and zygosity and their roles in HRD. She discovered that ATM variants in pancreatic cancer represent a distinct biological feature with better overall survival (OS) but are not relevant to the HRD signature[19]. The most productive institution is the Memorial Sloan-Kettering Cancer Center (14 published articles), which is among the top 6 most productive institutions. The latest publication concerning OS results from a phase III study of active maintenance therapy with olaparib *vs* placebo in *gBRCAmt* metastatic pancreatic cancer patients was named the Pancreatic Cancer Olaparib Ongoing (POLO) trial[20].

Our analysis shows that the keywords from 2009 to 2022 were "olaparib", "parp inhibitor", "gemcitabine", "breast cancer", "ovarian cancer", "adenocarcinoma", "platinum", "brachemotherapy", and "maintenance therapy" (Figure 7A). Maintenance therapy means reaching the goal of extending PFS and OS without compromising a patient's quality of life. The idea of maintenance therapy was new to pancreatic cancer, but it has already been applied in ovarian cancers and many other cancers with significant benefits[21,22]. The POLO trial was conducted to evaluate the efficacy of olaparib as a maintenance treatment for metastatic pancreatic cancer patients with germline *BRCA* mutations that had not progressed during previous platinum-based first-line chemotherapy[11]. The results certainly support that olaparib as maintenance therapy benefits pancreatic cancer patients with no refractory previous platinum-based chemotherapy, as it prolongs the disease progression rate in 2 years from 9.6% to 22.1% compared with that in the placebo group. Notably, olaparib as a maintenance therapy has few adverse effects, suggesting that pancreatic cancer patients have maintained their quality of life. From 2014 to 2016, the keywords started with the biological function of *BRCA* genes in clinical trials, from "DNA damage", "apoptosis" and "DNA repair" to "veliparib", "gemcitabine", "multicenter" and "AZD2281". From 2017 to 2022, the keywords changed to "aphidicolin glycinate", "bard1 expression", "atm protein", "secondary mutation rad51", "frfg1", and "checkpoint" (Figure 7B). This finding indicates that research in this field has changed from single-regimen treatment to combination therapy. In preclinical studies, an antiangiogenic phenomenon has been reported in *PARPi*- and *PARP-1*-knockout mice[23]. Downregulation of *RAD51*, another homologous recombination gene, was observed to be downregulated in the setting of hypoxia and was associated with increased PARPi sensitivity[24]. A randomized phase II study of a combination of cediranib (FGFR1 inhibitor) and olaparib *vs* olaparib monotherapy for women with recurrent platinum-sensitive ovarian cancer revealed improvement in mPFS[25]. The mPFS increased from 9.0 months to 17.7 months with the addition of cediranib. Surprisingly, patients with *gBRCAwt*/u status also benefitted from the addition of cediranib with prolonged mPFS compared with olaparib monotherapy. Lai *et al*[26] reported that FGFR1 inhibitor-resistant pancreatic cancer cells are sensitive to the *FGFR1* inhibitor-- PD173074 after olaparib treatment, indicating that *FGFR1*/PARP can mediate synthetic lethality *in vitro*. However, in a clinical study including 19 patients with metastatic *gBRCAmt* pancreatic cancer, no objective response (OR) was observed after oral treatment with cediranib or olaparib 2 times daily[27]. The median OS was 3.4 months, which suggested that the combination of cediranib and olaparib does not result in clinically effective outcomes in patients with metastatic *gBRCAmt* pancreatic cancer.

For immunotherapy, one potential synergy between PARP inhibitors and immune checkpoint inhibitors, namely PARP inhibitors, is mediated through interferon-independent mechanisms such as PD-L1 upregulation[28,29]. With this underlying mechanism, the use of CTLA-4 and PARP inhibitors in *BRCA1*-deficient tumors produces significant preclinical responses. Long-term inhibition of PARP enzymes results in persistent DNA damage, altering the epigenetics of tumor cells and making them more readily recognized and eliminated by T cells and NK cells, ultimately resulting in

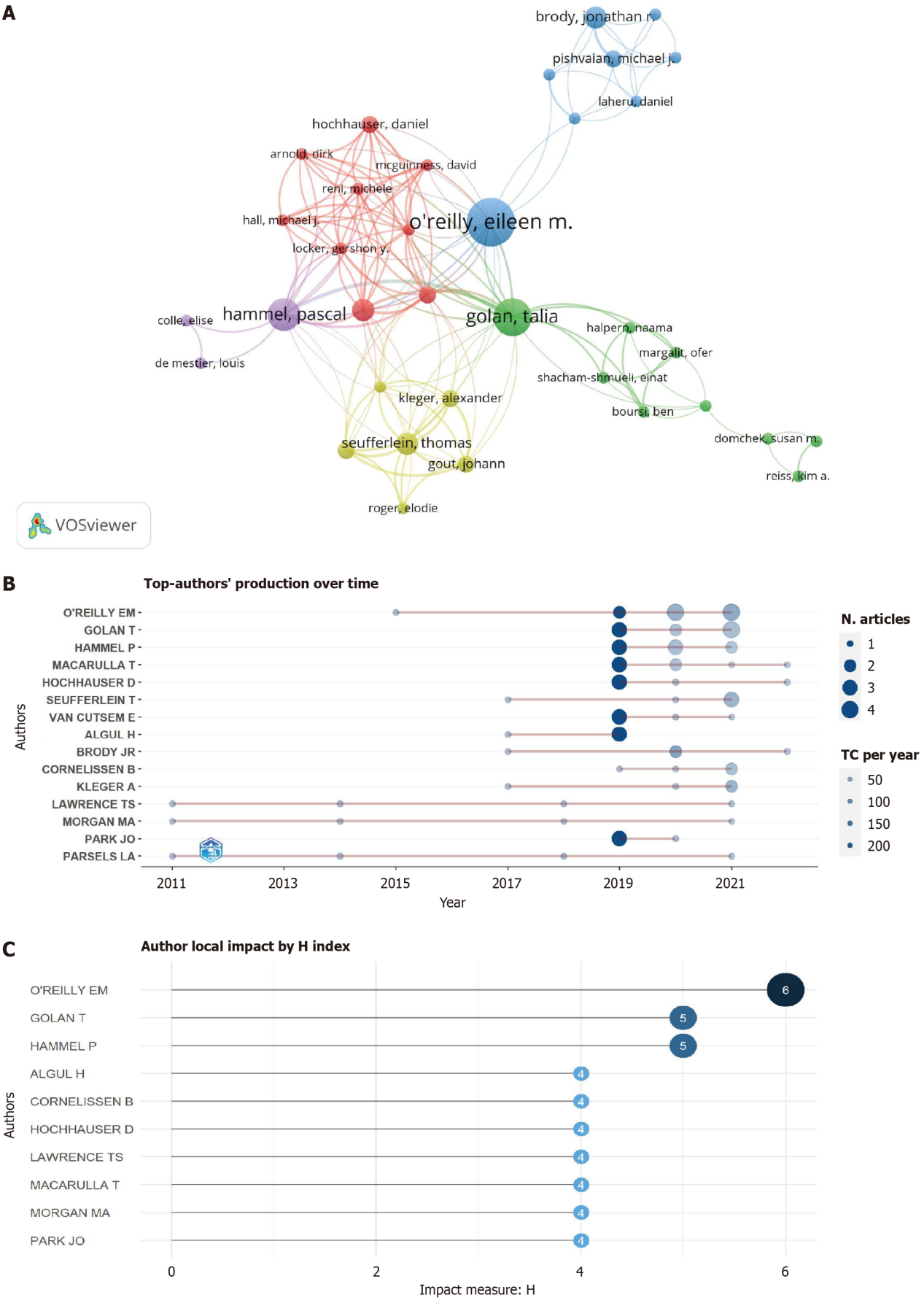

Figure 4 Illustrations of the collaborative network in olaparib and pancreatic cancer. A: Cooperative network and cluster analysis of authors. The thickness of the line indicates the strength of cooperation; B: The top 15 authors' production over time; C: Author local impact according to the H index.

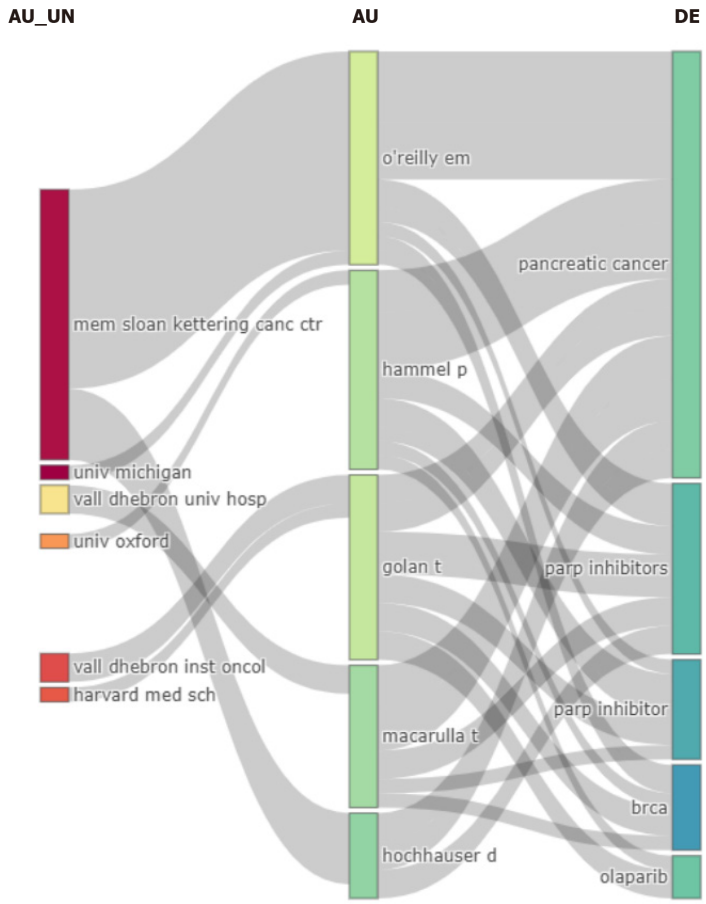

Figure 5 Relationships among institutions, authors, and keywords. Three-field plot of institutions, authors, and keywords related to olaparib in pancreatic cancer.

increased intrinsic immunogenicity of tumor cells[30-32]. Combination therapy with anti-PD-1 (pembrolizumab) and a PARP inhibitor (niraparib) is more effective than therapy with wild-type *BRCA1/2* in *BRCA*-mutated ovarian and triple-negative breast cancer (TNBC) tumors in the TOPACIO trial[33]. Among all 60 patients, the OR rate (ORR) was 25%, the disease control rate (DCR) was 68%, and nearly one-third of patients with platinum-resistant ovarian cancer achieved a response. The ORR and DCR were elevated to 45% and 73%, respectively, in *BRCAmt* tumors. However, as pancreatic cancer has a low response rate to checkpoint inhibitors, investigations have been launched to identify opportunities to increase immunotherapy efficacy *via* combination approaches. The currently ongoing phase Ib/II study named PARPVAX is designed for patients with locally advanced/metastatic pancreatic cancer who do not progress after platinum-based first-line chemotherapy. Eligible patients were included in the niraparib with nivolumab (anti-PD-1) group or the niraparib with ipilimumab group. The primary outcome measure was the 6-month PFS in 2 arms (NCT03404960). Our analysis revealed that combination therapy is a trend in the field of olaparib and pancreatic cancer, and the results of the combination of immunotherapies and PARP inhibitors are promising.

As can be seen from Figure 7D, clinical medication dominates the top 11 most-cited keywords, such as "combination", "chemotherapy", "clinical trial", and "cisplatin", "synthetic lethality". In recent years, more PARP inhibitors have sprung up gradually. The inhibition and trapping of PARP1 alone would be enough to achieve antitumor ability, while selectively inhibiting PARP2 could improve targeted killing of tumor cells with DNA repair deficiency and protect normal cells more effectively. Unlike first-generation PARPi, the newly invented drug AZD5305 minimizes hematological side effects and kills tumor cells with DNA repair deficiency more precisely[34]. This trend means that an increasing number of PARP inhibitors will appear, and an increasing number of combination therapies will be united.

CONCLUSION

By analyzing publication and citation numbers, productive countries, influential authors and institutions, mainstream journals, representative works, co-occurrence keywords, and frontier hotspots over the past 23 years, we can identify both historical and future research trends in olaparib use for pancreatic cancer. The results section highlights the leading roles played by institutions from China and the USA, with other countries and institutions showing steady participation. Global cooperation is becoming increasingly high and productive over time. The team led by O'Reilly EM has contributed the most to this field, with the Memorial Sloan-Kettering Cancer Center having the highest output of articles. The Journal

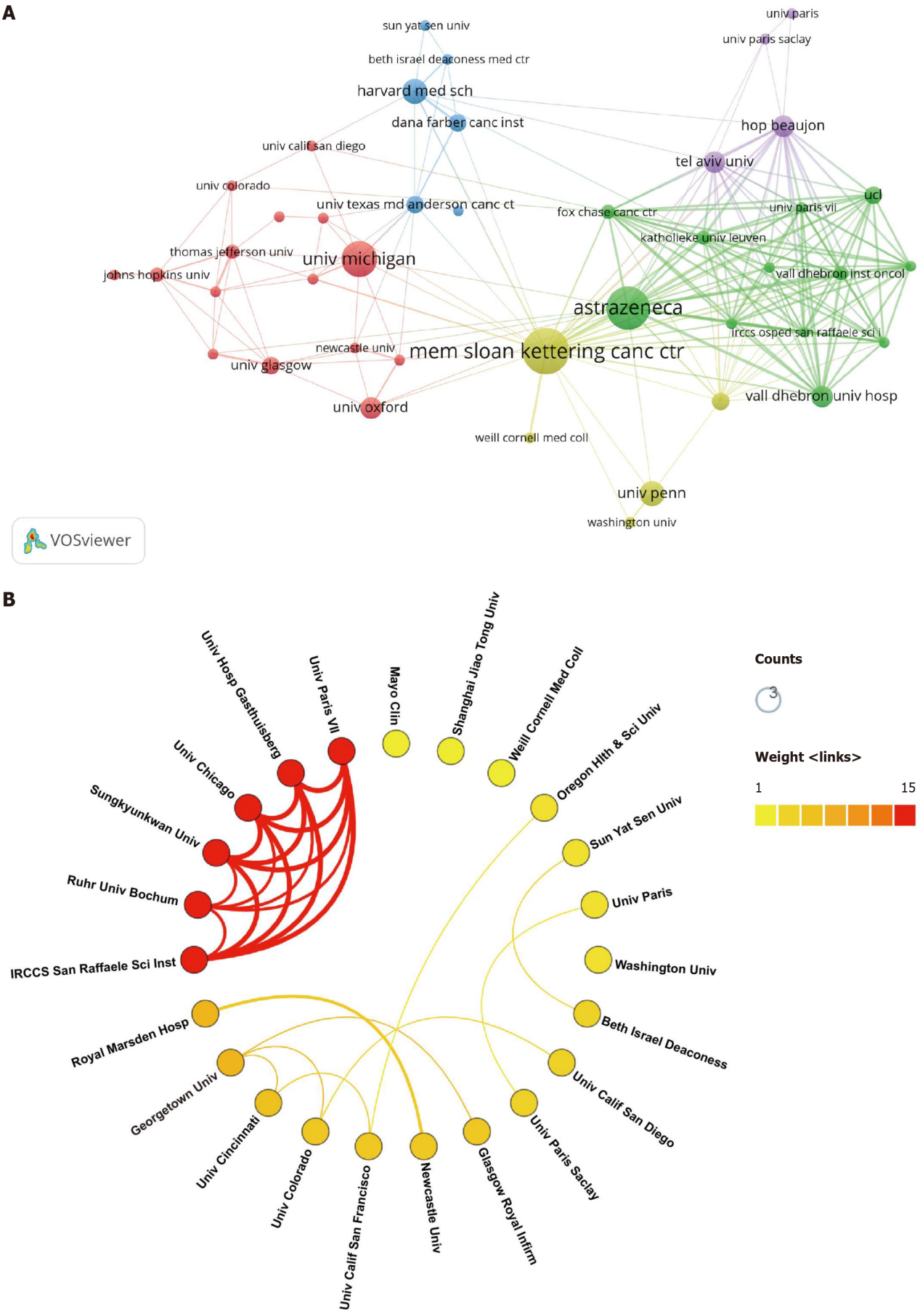

Figure 6 Illustrations of cluster analysis of cooperation among institutions and collaboration networks. A: Visual cluster analysis of cooperation among institutions *via* VOSviewer; B: Cross-institution collaboration network. The color indicates the strength of cooperation between institutions.

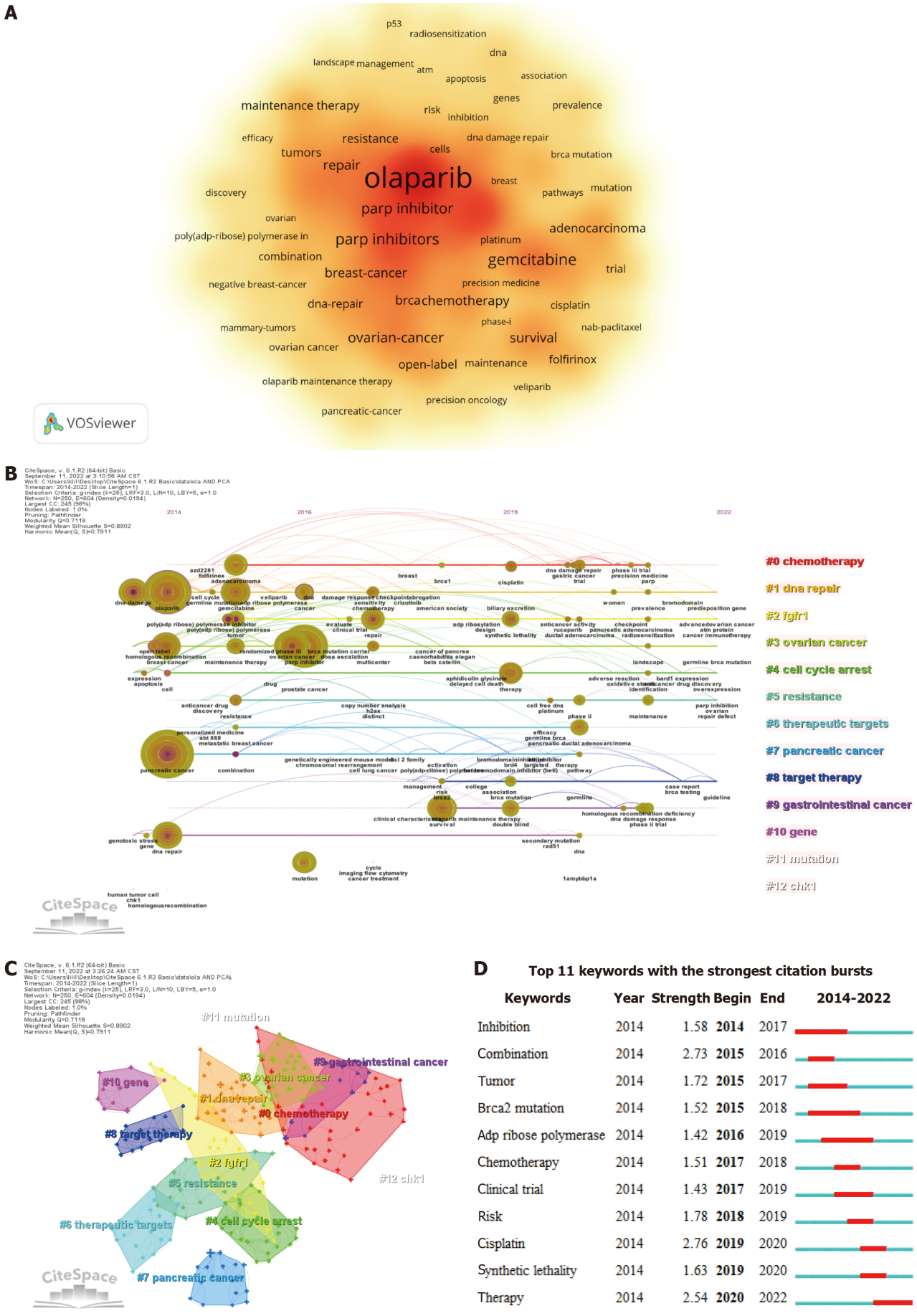

Figure 7 The top 12 clustering terms of olaparib and pancreatic cancer and the keyword trends. A: Density map of the co-occurrence analysis of

keywords. The word size, circle size, and opacity of color are positively related to frequency; B: Cluster analysis of keywords; C: Keyword timeline map of 12 clusters; D: The top 11 keywords with the strongest bursts.

of Clinical Oncology was the most highly cited journal. Keyword trends suggest the emergence of more articles on PARP inhibitors, and combination therapy is becoming a therapeutic trend. In light of practical implications, the emerging trend of a combination therapy underscores the necessity for clinicians to investigate the viability of incorporating olaparib in conjunction with other pharmaceutical agents, such as gemcitabine, to improve the prognosis of individuals afflicted with pancreatic cancer. Furthermore, the discernment of these patterns underscores the importance of personalized medicine, wherein genetic screening for *BRCA* mutations and other pertinent biomarkers can inform the identification of suitable therapeutic interventions.

FOOTNOTES

Author contributions: Feng X and Jiang KX were responsible for conceptualization; Chai YH and Pan Y were responsible for methodology; Jiang KX and Feng X were responsible for investigation; Pan Y, Feng X and Chai YH were responsible for visualization; Chen WC, Jiang WB and Feng X were responsible for supervision; Feng X and Chen WC were responsible for writing – original draft; Pan Y, Feng X and Jiang WB were responsible for writing – review & editing. Feng X and Chai YH are listed as co-first authors for their contributions to both the research and the manuscript. They share responsibility as well as accountability for the work delivered and the research that has been conducted, including substantial contributions to the conception or design of the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be 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. Chen WC and Pan Y are listed as co-corresponding authors for their contributions to this manuscript. They have read and agreed to the published version of the manuscript, ensuring that all aspects of the work are accurately represented and that all conditions for authorship are met.

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Country of origin: China

ORCID number: Xu Feng 0000-0002-4445-8174; Yi-Han Chai 0000-0001-6392-6001; Wen-Bin Jiang 0000-0002-4588-9670; Yu Pan 0000-0003-2810-842X.

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