Original Article

Status and development of research on clear cell carcinoma of the ovary—a visualization-based bibliometric analysis

Chao Chen^, Wei Ren, Lipeng Pei, Jingli Sun, Tianmei Bai

Department of Gynecology and Obstetrics, General Hospital of Northern Theater, Shenyang, China

Contributions: (I) Conception and design: T Bai; (II) Administrative support: L Pei; (III) Provision of study materials or patients: W Ren; (IV) Collection and assembly of data: C Chen; (V) Data analysis and interpretation: C Chen, W Ren; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tianmei Bai, BD. Department of Gynecology and Obstetrics, General Hospital of Northern Theater, No. 5 Guangrong Street, Heping District, Shenyang 110003, China. Email: baitianmeicc@163.com.

Background: Clear cell carcinoma of the ovary (CCCO) is a relatively rare type of epithelial ovarian cancer (EOC) that has unique biological characteristics and clinical features. Researchers have paid less attention to this disease than to other types of EOCs. However, in recent years, research in this area has still progressed. In this paper, a bibliometric analysis is used to integrate and analyse the literature in the field of CCCO in the past 20 years to determine research development, better understand the current status of research, and provide a reference for future study directions in this field.

Methods: With CCCO as the research subject, relevant publications indexed in the Web of Science (WOS) core dataset from September 2003 to September 2023 were retrieved. After screening the publications, we used EXCEL, VOSviewer, CiteSpace, Charticulator, Gephi, OriginPro and other tools to perform in-depth analyses of and to visualize the data.

Results: Through a comprehensive analysis of the literature in this field, we found that research on CCCO experienced a relatively rapid increase in 2006 and is now in a period of relatively high fluctuation. The quality of the literature in this field is generally high. In this field, countries in East Asia and North America play core roles, with Japan accounting for the most studies. A stable research group has been formed in this field, and extensive collaboration has occurred among the various research groups. In the past 20 years, basic research and clinical research in the field of CCCO have developed together, and a healthy development model in which basic and clinical research promote each other has formed. Research in this field has been continuously developed from a preliminary understanding of clinical features to in-depth explorations of the pathogenesis and the continuous optimization of treatment methods. The key molecular events in the pathogenesis and development of this disease and the application of novel antitumour drugs for this disease are the current research focuses and the future development direction in this field.

Conclusions: Research on CCCO has progressed significantly in the past 20 years, but there are still many important issues regarding its pathogenesis and treatment that need to be addressed, and therefore, more research in this area should be conducted in the future. The study of key molecular events and the use of novel antitumour drugs are future development directions in this field.

Keywords: Clear cell carcinoma of the ovary (CCCO); bibliometrics; ovarian endometriosis; drug resistance; novel antitumour drugs

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^ ORCID: 0009-0001-3813-8174.

Introduction

Clear cell carcinoma of the ovary (CCCO) is a type of epithelial ovarian cancer (EOC) with unique biological and clinical characteristics (1). The median age of onset is significantly younger than that of serous ovarian cancer (SOC) (2), and the incidence rates vary greatly among different races (2-4). Compared with SOC, for CCCO, there is a higher proportion of patients in the early stage at the initial diagnosis (2,3,5), and the prognosis of early CCCO is better than that of SOC (2,5-12), resulting in a better patient prognosis for CCCO than for SOC (12,13). However, the prognosis of patients with advanced or recurrent CCCO is very poor (12,14-16). From the aetiological point of view, CCCO is highly related to ovarian endometriosis (17,18), and the latter is now widely considered the direct precursor of CCCO (19,20). Because this disease is relatively rare, the research popularity of CCCO has always been lower than that of SOC. However, in recent years, research in this field has made considerable progress, and some relevant review studies have been published. However, at present, no study has used quantitative means to systematically sort out and scientifically summarize the developments in this field over a long time period.

Bibliometrics is a research method involving the quantitative analysis of literature in a specific field (21). It provides researchers with detailed metrology information on elements such as authors, keywords, journals, countries, institutions, and references. By integrating this information, researchers can better understand the intrinsic connections between the aforementioned elements, further clarify the development of a certain field, and provide guidance for subsequent research (22). Thanks to the development of computer technology and network technology, the amount of information that can be provided by bibliometrics has increased significantly, and the analysis results can be displayed more intuitively through visualization methods.

In this paper, bibliometric methods were used to analyse and summarize the development status of research on CCCO in the past 20 years.

Highlight box

Key findings

- This article uses quantitative research methods to sort out and summarize the development of the field of ovarian clear cell carcinoma over the past 20 years, identifies the main focuses of current research, and provides insights into the direction of future research in this field.

What is known and what is new?

- In the past 20 years, related scholars have conducted a lot of theoretical and practical exploration in the field of ovarian clear cell carcinoma, but there is a lack of systematic sorting and summarization of these studies.
- This paper adopts quantitative methods to systematically sort out and summarize the literature in the field of ovarian clear cell carcinoma in the past 20 years, reveals the development of the field and the current research status, and explains the future development trend of the research in this field.

What is the implication, and what should change now?

- This study provides a reference for future research in the field of ovarian clear cell carcinoma, which should focus more on the key molecular events involved in the development of ovarian clear cell carcinoma and the use of novel antitumor agents.

Methods

Data sources

As a high-quality scientific literature database widely recognized in various fields, Web of Science (WOS) has been considered the best database for bibliometric analysis (23-25). Therefore, in this study, the WOS core collection was used as the data source, and the index was specified as SCI-EXPANDED. To retrieve the literature in this field more comprehensively and accurately, after repeated testing, the final retrieval strategy was TS=("Clear cell carcinoma of the ovary" OR "Clear cell ovarian carcinoma" OR "CCCO" OR "CCOC"), and the retrieval time was set to September 1st, 2003, to September 1st, 2023. The types of documents included in the search were all documents except book chapters and preprints, and the language was set to English. A total of 352 publications (including 35 review papers and 317 original research papers) were obtained. After removing duplications and 92 publications that were inconsistent with the theme, 260 valid publications were obtained (*Table 1*).

Research tools

In this study, tools such as EXCEL (Microsoft 365 version), VOSviewer (version 1.6.19), CiteSpace (64-bit version 6.2. R4), Charticulator, Gephi (version 0.9.2), and OriginPro (version 2024) were used to analyse and visualize the literature information. In the analysis of the collaborating countries and institutions, the original information processed by VOSviewer was imported into Gephi to generate point tables and line tables, which were then

Table 1 Summary of the search strategy

Item	Specification
Date of search	October 15, 2023
Databases and other sources searched	WOS core dataset
Search terms used	Clear cell carcinoma of the ovary; Clear cell ovarian carcinoma; CCCO; CCOC
Timeframe	September 1, 2003 to September 1, 2023
Inclusion and exclusion criteria	The literature included in the search was all articles except book chapters and preprints, and the language was set to English
Selection process	The search was independently performed by the first author, and 92 publications that were duplicates and inconsistent with the topic were removed after retrieval

WOS, Web of Science; CCCO, clear cell carcinoma of the ovary; CCOC, clear cell ovarian carcinoma.

imported into the Charticulator online tool for drawing chord diagrams. When aggregating the volume of literature on malignant tumors from different countries, the data retrieved from WOS were imported into OriginPro, and 3D pie charts were plotted.

Statistical analysis

This study primarily analyses the temporal and spatial distribution of literature in the CCCO field, as well as the logical relationships and evolutionary patterns of bibliographic information. Therefore, statistical processing mainly involves descriptive statistics using absolute numbers, without conducting inter-group comparisons.

Results

Descriptive statistics and trend analysis of the publications

The 260 publications analysed in this study were authored by 1,506 researchers from 414 institutions in 37 countries, published in 104 journals and cited 4,639 publications from 980 journals.

The annual publications in this field from 2003 to 2023 are shown in *Figure 1*. The number of publications in this field maintained a slow increase during the 3-year period from 2003 to 2005 but exhibited relatively rapid growth in 2006. Then, a trend of minor fluctuations at a high level was observed, with small publication peaks occurring during the two time periods of 2014–2016 and 2020–2021.

To further analyze the intrinsic reasons for the rapid increase in the number of publications seen in 2006 and to exclude the interference of the inclusion of new journals in the database on the results, we examined the inclusion time in the WOS Core Collection of journals that published literature of CCCO field in 2006 (*Table 2*). After analyzing, we found that there were 10 pieces of literature in this field published in 2006, and the journals to which they belong were all included in SCI-EXPANDED before 2006, and the fluctuation in the number of publications in that year may not be related to the inclusion of new journals in the database. Therefore, we consider that CCCO may have begun to be gradually emphasized by academics during this period.

Author analysis

By analysing the volume of publications by a single author in a certain field, we can determine the representative authors and core research strengths in this field. In the field of bibliometrics, Price's law is often used to analyse the core authors of a particular field (26). According to Price's law, the minimum number of publications by core authors in a certain field is approximately equal to the arithmetic square root of the publication volume of the author with the highest publication volume, multiplied by 0.749. Therefore, the minimum number of publications by core authors in the field of CCCO is ~2.29. Authors who have published two or more publications are defined as core authors. VOSviewer analysis shows that there are 261 core authors in this field who have published a total of 780 publications. *Table 3* shows the publication data for the top 10 authors in this field.

Among the core authors, Kobayashi had the most publications. In the study period, he published 13 articles and received a total of 330 citations, with an approximate average of 25 citations. This author works at Nara Medical University in Japan. His research mainly focused on the

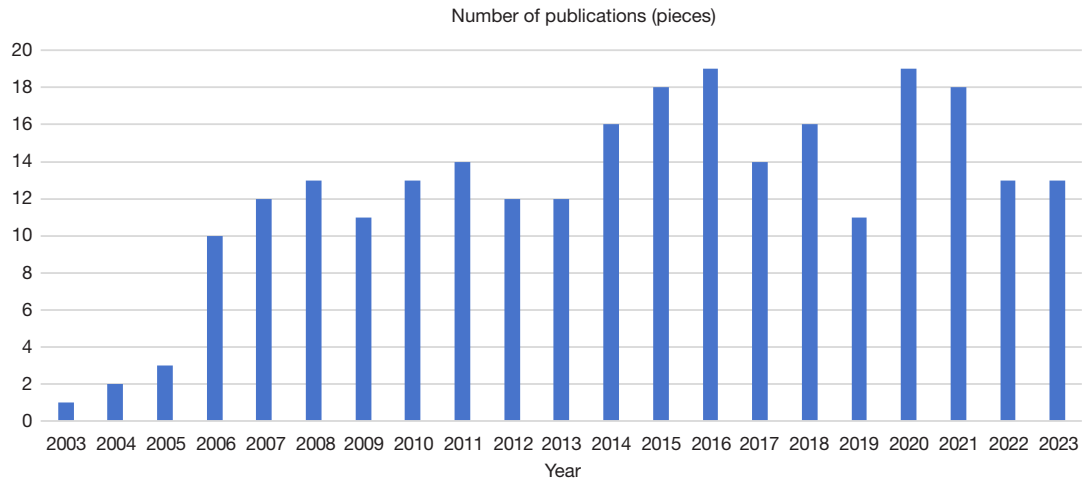

Figure 1 Volume of annual publications pertaining to research on clear cell carcinoma of the ovary from 2003 to 2023.

Table 2 Overview of the inclusion years in Web of Science for journals publishing research of clear cell carcinoma of the ovary in 2006

Lable[1]	Title	Journal	Time for journal inclusion in Science Citation Index-Expanded (year)[2]
1	Galectin-3 may contribute to CDDP resistance in clear cell carcinoma of the ovary	*Cancer Research*	2000
2	Pathogenic role of PTEN tumor suppressor gene in ovarian cancer associated to endometriosis	*Revista Medica De Chile*	2000
3	Treatment issues in clear cell carcinoma of the ovary: A different entity?	*Oncologist*	2001
4	Twist expression predicts poor clinical outcome of patients with clear cell carcinoma of the ovary	*Oncology*	2000
5	Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging	*British Journal of Cancer*	2000
6	Clinical and molecular differences between clear cell and papillary serous ovarian carcinoma	*Journal of Surgical Oncology*	2000
7	Adjuvant chemotherapy with irinotecan hydrochloride and cisplatin for clear cell carcinoma of the ovary	*Oncology Reports*	2000
8	CT findings of clear cell carcinoma of the ovary	*Journal of Computer Assisted Tomography*	2000
9	Expression of hepatocyte nuclear factor-1beta (HNF-1beta) in clear cell tumors and endometriosis of the ovary	*Modern Pathology*	2000
10	Intraoperative cytology of clear cell carcinoma of the ovary	*Cytopathology*	2000

[1], labeling is not in any order; [2], this project was queried through Web of Science, and the earliest year recorded by Web of Science for inclusion in the Science Citation Index-Expanded was 2000. CDDP, cis-diamminedichloroplatinum; PTEN, phosphatase and tensin homolog; CT, computed tomography.

pathogenesis, diagnosis and treatment of endometriosis and ovarian cancer. Mabuchi had the most citations per paper, with an average of 53 citations. This author works at the Osaka International Cancer Center, Japan, and has a close collaborative relationship with Nara Medical University. His research mainly focused on the pathogenesis and treatment

Table 3 Publications by top 10 authors in the field of clear cell carcinoma of the ovary

Ranking	Author	Number of publications (papers)	Total number of citations (times)	Average number of citations (times)
1	Kobayashi, Hiroshi	13	330	25
2	Takano, Masashi	10	314	30
3	Kigawa, Junzo	9	216	24
4	Sugiyama, Toru	9	286	32
5	Itamochi, Hiroaki	9	401	45
6	Kajiyama, Hiroaki	9	199	22
7	Kikkawa, Fumitaka	9	199	22
8	Mabuchi, Seiji	9	477	53
9	Kimura, Tadashi	9	453	50
10	Huntsman, David G	9	397	44

Table 4 Published papers by top 10 countries in the field of clear cell carcinoma of the ovary

Ranking	Country	Number of publications (papers)	Total number of citations (times)	Average number of citations (times)
1	Japan	100	2,668	27
2	United States	72	1,829	25
3	Canada	24	732	31
4	China	19	303	16
5	South Korea	12	228	19
6	Italy	11	264	24
7	Greece	9	155	17
8	UK	8	151	19
9	Australia	8	217	27
10	Spain	6	35	6

of gynaecological malignant tumours. In addition, the top nine authors in this field were all from Japan, indicating that Japan may play a core role in research in this field.

Country analysis

Through an analysis of the countries of origin of articles, we can understand the geographic distribution of research in this field and further clarify which countries or regions are in leading positions in research on CCCO. *Table 4* shows the top 10 countries by the number of publications. Japan accounts for the highest number of papers in the CCCO research field, contributing a total of 100 papers, indicating that Japan plays a core role in this field. The United States is second only to Japan, with 72 publications and an average of 25 citations per paper, indicating that studies by American scholars is also at the forefront of research on this topic worldwide. Further analysis of the top five countries by publication volume shows that three countries are located in East Asia and two countries are located in North America, indicating that research strength in this field is mainly concentrated in East Asia and North America. China accounted for 19 papers in this field, and the average citations per paper was acceptable, indicating

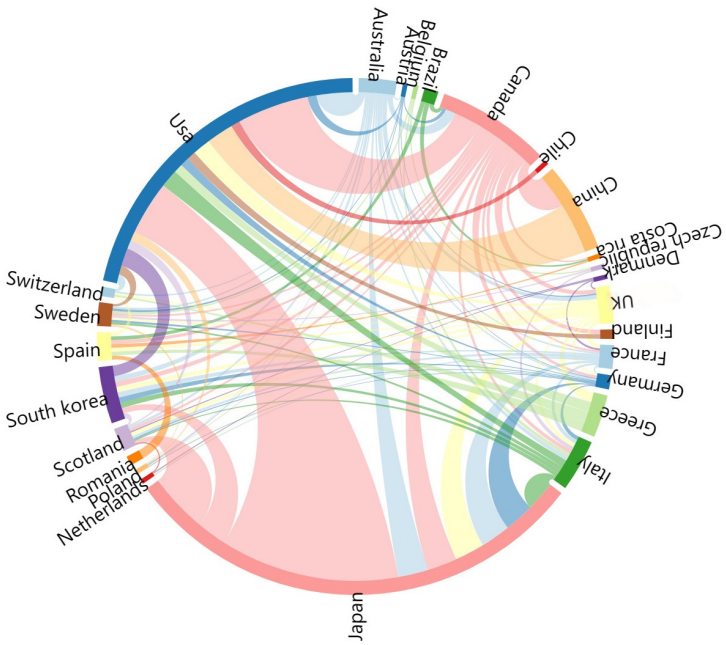

Figure 2 Collaboration among countries that published papers in the field of clear cell carcinoma of the ovary.

that the research level of Chinese scholars is also relatively advanced.

As scientific research evolves, more and more of it is done through collaboration between different countries and institutions, which can lead to greater impact and scientific value (27). *Figure 2* shows the collaboration among countries regarding research on CCCO. The results show that the countries in East Asia and North America have carried out extensive collaboration with other countries and that the collaboration among these countries is very close; there is relatively less collaboration among countries in other regions. This explains the leading positions of East Asia and North America in this field. The United States is the country with the most collaboration between Japan and Canada, and the United States and Canada have the closest collaborative relationship; Chinese scholars mainly collaborate with the United States and Canada.

To further analyse the reasons why East Asia and North America are leading in research in the field of CCCO, we compared the overall level of research in malignant tumours in each country from the perspective of publication volume. A rough search of the literature related to malignant tumors published from September 1, 2003 to September 1, 2023 was conducted in WOS using TS=("cancer" OR "malignant neoplasm" OR "malignant tumor" OR "carcinoma" OR "sarcoma") as the retrieval strategy, and a total of 772,344 relevant articles were collected. After analysis, we found that the United States is in the leading position among countries in the field of malignant tumor research with 209,200 publications, while China follows with 196,235 publications, and Japan is in the third place, but there is a large gap between its publication volume and that of the United States and China (*Figure 3*). Therefore, we consider that the higher level of CCCO research in the United States may be due to its overall research strength in the field of malignant tumors, whereas Japan's world-leading level of research in the field of CCCO may be more attributable to the higher prevalence of the disease in East Asian populations. In addition, we have seen that China, which is also a predominantly East Asian ethnic group, lags behind the United States and Japan in the field of CCCO, despite the high overall level of research on malignant tumors, indicating that Chinese scholars' attention to this field needs to be further strengthened.

Institutional analysis

By analysing the issuing institutions, we can obtain more accurate and comprehensive information on the main research strengths in this field. *Table 5* shows the top 10 institutions by publication volume. Among the top 10 institutions by the number of publications, seven are in

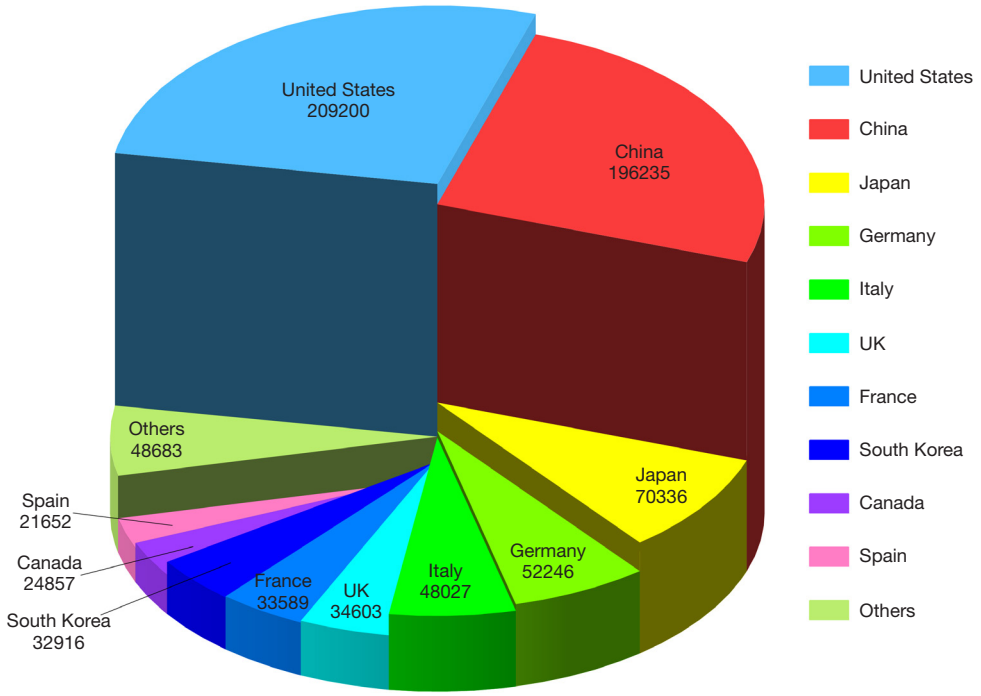

Figure 3 Publication volume in the field of malignant tumors by country.

Table 5 Publications by the top 10 research institutions in the field of clear cell carcinoma of the ovary

Ranking	Institution	Number of publications (papers)	Total number of citations (times)	Average number of citations (times)
1	Defense Medical University (Japan)	16	623	39
2	Tottori University (Japan)	15	777	52
3	Nara Medical College (Japan)	14	331	24
4	Iwate Medical University (Japan)	12	353	29
5	University of British Columbia (Canada)	12	456	38
6	Nagoya University (Japan)	12	275	30
7	Yamagata University (Japan)	12	326	27
8	Memorial Sloan-Kettering Cancer Center (USA)	11	137	13
9	Osaka University (Japan)	11	568	52
10	Mayo Clinic (USA)	9	53	6

Japan, two in from the United States, and one is from Canada. This shows that in Japan, research in this field has been extensively valued and carried out and that each research centre conducts high-level research. Further analysis revealed that in Japan, the institutions conducting research in this field were mostly universities, and in the United States, the institutions conducting research were mostly medical institutions, indicating that researchers in this field in Japan may have received more government funding. At present, no institution affiliated with China has entered the top ten, indicating that research in this field in China is still relatively scattered and that a stable research community has not yet been formed. *Figure 4* shows the collaborative relationship among research institutions.

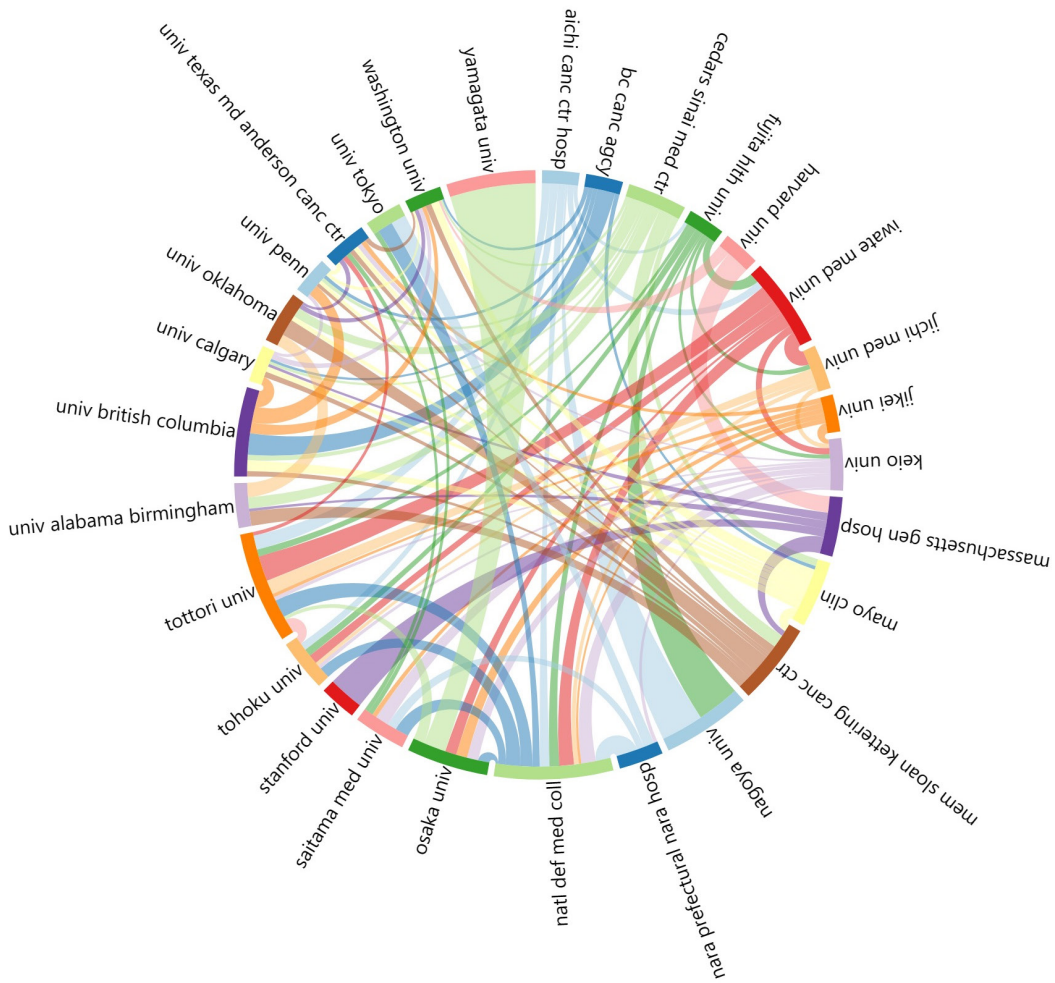

Figure 4 Collaboration among research institutions in the field of clear cell carcinoma of the ovary.

All research institutions have extensive collaborative relationships, and the research in this field has followed a development trend of interinstitutional collaboration and interoperability.

Journal analysis

Journals are important carriers of academic achievements and for the dissemination of academic thoughts. The number of papers in a particular field published in a journal and the number of citations to papers reflect to some extent the influence of the journal in the field (28). *Table 6* lists the top 10 journals by the number of publications. "*International Journal of Gynaecological Cancer*" published the largest number of articles in this field. This journal is affiliated with JCR Obstetrics and Gynecology Q1, its main focus is the detection, prevention, diagnosis and treatment of gynaecological tumours, and the publications are more biased towards clinical research. "*Gynaecologic Oncology*" received the highest average citations per paper. This journal is the official journal of the Society of Gynaecologic Oncology (SGO) and is a high-level journal in the field of gynaecological oncology, similar to "*International Journal*" in 2023. Like "*Gynaecological Cancer*", "*Gynaecological Oncology*" also emphasizes clinical and empirical research in the field of gynaecological oncology. Further analysis showed that four of the top 10 journals by the number of publications support open access and that these journals also have high average citations per paper, indicating that open access has played a clear promoting role in this field.

Journal Impact Factor (JIF) and Journal Citation Indicator (JCI) are two of the comparatively recognized indicators

Table 6 Situation of top 10 journals by the number of publications in the field of clear cell carcinoma of the ovary

Ranking	Journal	Number of publications (papers)	Total number of citations (times)	Average number of citations (times)	JIF [2022]	Rank by JIF (Category 1/rank/quartile; Category 2/rank/quartile)	JCI [2022]	Rank by JCI (Category 1/rank/quartile; Category 2/rank/quartile)
1	*International Journal of Gynecological Cancer*	39	615	16	4.8	Obstetrics and Gynecology/13/Q1; Oncology/80/Q2	1.22	Obstetrics and Gynecology/18/Q1; Oncology/59/Q1
2	*Gynecologic Oncology*	29	1,148	40	4.7	Obstetrics and Gynecology/14/Q1; Oncology/85/Q2	1.35	Obstetrics and Gynecology/12/Q1; Oncology/47/Q1
3	*Journal of Clinical Oncology*	10	58	6	45.4	Oncology/7/Q1; –	5.58	Oncology/8/Q1; –
4	*Modern Pathology*	9	192	21	7.5	Pathology/5/Q1; –	2.49	Pathology/3/Q1; –
5	*Cancer Research*	8	1	–	11.2	Oncology/26/Q1; –	1.93	Oncology/28/Q1; –
6	*Clinical Cancer Research*	7	209	30	11.5	Oncology/22/Q1; –	2.53	Oncology/15/Q1; –
7	*Laboratory Investigation (OA)*	6	0	–	5.0	Medicine Research and Experimental/51/Q1; Pathology/14/Q1	1.40	Medicine Research and Experimental/28/Q1; Pathology/11/Q1
8	*International Journal of Clinical Oncology (OA)*	5	128	26	3.3	Oncology/135/Q3; –	0.63	Oncology/169/Q3; –
9	*Journal of Pathology (OA)*	5	86	17	7.3	Oncology/45/Q1; Pathology/6/Q1	1.81	Oncology/32/Q1; Pathology/6/Q1
10	*Virchows Archiv (OA)*	5	64	13	3.5	Pathology/25/Q2; –	1.11	Pathology/24/Q2; –

JIF, Journal Impact Factor; JCI, Journal Citation Indicator; OA, open access.

for evaluating the quality and impact of journals (29), as provided by Journal Citation Reports (JCR). Of these, the JIF is mainly used to assess the frequency of citations to articles published in a journal in a given time period, whereas the JCI measures the citation performance of journals within their subject areas, and it is a standardized metric that can be used to compare journals across different subject areas. In this study, we searched the JIF and JCI of the top 10 journals in the field of CCCO, and concurrently searched for their corresponding rankings. Further analysis of *Table 6* indicates that the journals with the top 10 publication volumes in the field are essentially in the Q1 area, suggesting that the overall quality of CCCO research is relatively high.

Keyword analysis

Network analysis of keyword co-occurrence

The keywords of a paper represent the research focus of that paper. For a certain field, high-frequency keywords reflect the research hotspots in that field during a period of time (23). In 2019, Wei *et al.* (30) proposed that besides being used to analyse core authors in a field, Price's law can also be used to locate high-frequency keywords. Based on the Price's law, the threshold of high-frequency keywords in the CCCO field is four. Therefore, keywords with a number of occurrences greater than or equal to four were defined as high-frequency keywords in this field. We used VOSviewer to screen keywords and obtained a total of 39 high-frequency keywords. After removing keywords directly related to the research topic, a total of 24 keywords were included in the analysis.

Keyword co-occurrence describes the situation that two keywords appear in the same article, and the more frequently the co-occurrence appears, indicates that the keywords are more tightly linked to each other. By analyzing the co-occurrence of high-frequency keywords, it is possible to know the mainstream research direction of a

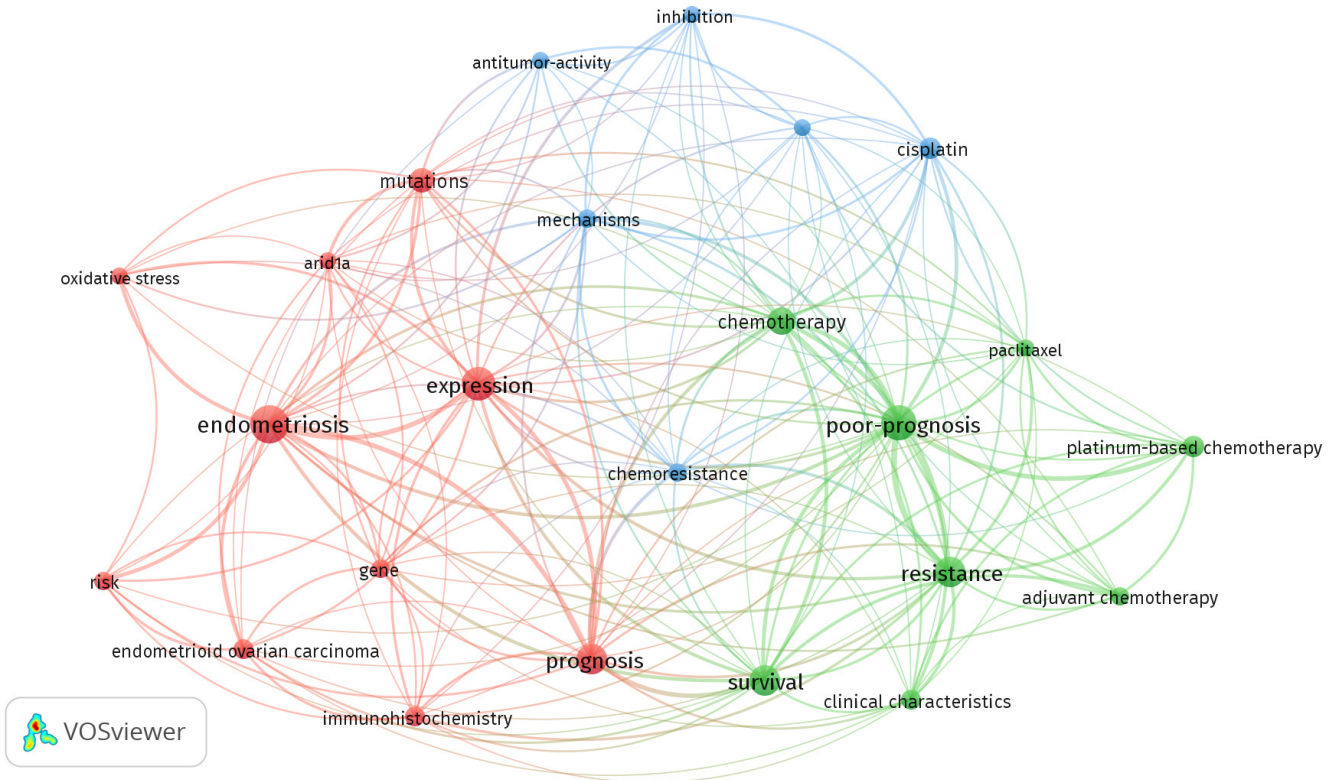

Figure 5 Clustering network of high-frequency keywords.

Table 7 Cluster analysis results for high-frequency keywords

Clustering	Keywords
Red	Endometriosis, Expression, Prognosis, Mutations, Endometrioid ovarian carcinoma, Immunohistochemistry, Gene, Risk, Oxidative stress, ARID1A
Green	Poor prognosis, Resistance, Survival, Chemotherapy, Platinum-based chemotherapy, Clinical characteristics, Adjuvant chemotherapy
Blue	Cisplatin, Chemoresistance, Mechanisms, Antitumour activity, Inhibition

ARID1A, AT-rich interaction domain 1A.

certain field (23). VOSviewer and CiteSpace are two of the most commonly utilized tools for performing bibliometric analyses, each of which takes a different methodology for analyzing data and has different advantages. VOSviewer uses a probabilistic-based data normalization method, and the keyword clustering maps drawn using VOSviewer are simple and clear (31). Therefore, when performing the analysis of keyword co-occurrence, this study used VOSviewer. *Figure 5* shows the results of the analysis of high-frequency keywords co-occurrence. In *Figure 5*, the size of the nodes represents the frequency of occurrence of the keyword, with a larger node indicating a higher frequency of occurrence of the keyword. The colours of the nodes represent different clusters of keywords. *Table 7* shows the keywords in different clusters. The connection between the nodes represents the degree of association between the keywords, and the thicker the connection, the more frequently the two keywords appear in the same document. As seen in *Figure 3*, the high-frequency keywords are clustered into three categories, and the clusters are relatively independent.

Red clustering centred around endometriosis, and the

main focus was on the pathogenesis of CCCO. Ovarian endometriosis is the direct precursor of CCCO (19,20), and the key molecular events of its malignant transformation may be AT-rich interaction domain 1A (ARID1A) mutation and the activation of the PI3K/AKT/mTOR pathway (32-37). Hepatocyte nuclear factor-1β (HNF-1β) and oxidative stress may also play important roles in the pathogenesis of this disease (38-40).

Green clustering was centred around poor prognosis, and the main focus was on the clinical features of CCCO. CCCO is highly malignant and is highly resistant to chemotherapy (41). The median age of onset is younger than that for SOC (2), and the prognosis of patients with early CCCO is better than that of patient with SOC (2,5-12); however, for advanced and recurrent CCCO, the prognosis of patients with CCCO is very poor (12,14-16).

The blue cluster centred around cisplatin, and the main focus was on the characteristics of CCCO resistance. The incidence of drug resistance in advanced CCCO is very high (42), and the response rate of recurrent CCCO to platinum is very low (43-48), which is the most substantial difference between CCCO and other types of EOC in treatment. Therefore, novel antitumour therapies, such as targeted therapy and immunotherapy, have been extensively studied for CCCO.

Keyword timeline network analysis

Keyword co-occurrence maps can be arranged in chronological order, and analyses of the chronological order of keyword occurrence can show the distribution of research hotspots in each time period, thus further identifying temporal patterns of development in a certain research field (23). CiteSpace adopts a data normalization method based on set theory to measure the similarity of data units from which the time zone view is drawn. It is more effective in showing the evolution and turnover of research hotspots in the time dimension (49). Therefore, this study used CiteSpace to perform keyword timeline analysis. The time slice length was set to two to draw a keyword timeline diagram (*Figure 6*). In *Figure 6*, the vertical axis is the time axis, and each horizontal line with a different colour represents a different cluster. Each node represents a keyword, the size of the node reflects the frequency of occurrence of the keyword, and the horizontal and vertical positions of the node represent the cluster to which it belongs and the time of occurrence, respectively. The curve in the diagram represents the co-occurrence relationship between keywords. The results indicate that basic research and clinical research in the field of CCCO have basically shown a common development trend; the two complement each other and promote each other. In the past 20 years, scholars have gradually deepened their understanding of CCCO, beginning with an initial understanding of the clinical and pathological characteristics to an understanding of treatment models and molecular mechanisms. In the timeline diagram, we noticed the appearance of keywords such as pembrolizumab and T-cell in 2023, indicating that recently, immune checkpoint inhibitors, which have achieved good efficacy in various other types of tumours, have gradually attracted the attention of CCCO researchers.

Analysis of burst words

Burst words refer to professional words whose frequency of appearance increases rapidly over a short period of time. The emergence and evolution of burst words can reflect the changes in research hotspots in a certain field (50). In this study, we used CiteSpace to perform burst word analysis. Based on the existing functions of CiteSpace, the burst words can be analysed in terms of both burst time and burst strength (51). The temporal distribution of burst words reflects, to a certain extent, the development trend of a certain field of research (52), while the burst strength usually partially reflects the degree of attention that academics pay to a research hotspot during a certain period (53). In our analysis, we set the threshold as 1.0 and ultimately obtained seven burst words (*Figure 7*). As seen in *Figure 7*, after excluding keywords closely related to themes such as "ovary cancer" and "CCCO", the burst keywords at the beginning of this century were mainly concentrated on the unique clinical pathological characteristics of CCCO, indicating that during this period, the study of CCCO was still at a preliminary stage. Recent burst keywords were "survival" and "endometrioid ovarian carcinoma". Like CCCO, endometrioid ovarian carcinoma also originates from endometriosis of the ovary. These two diseases have a high degree of homology in aetiology and pathogenesis, which indicates that the understanding of CCCO has gradually reached the mechanistic level and that more research energy has been focused on the treatment of patients with CCCO.

Literature co-citation analysis

The number of citations of publications is often used to measure the impact of a publication over a period of time (54). Through the analysis of the number of citations, the most

Figure 6 Timeline spectrum of high-frequency keywords.

Keywords	Year	Strength	Begin	End	2003–2023
Platinum based chemotherapy	2006	3.72	2006	2012	
Distinct histologic type	2003	3.43	2005	2012	
Oxidative stress	2009	3.26	2009	2014	
Ovarian carcinoma	2011	4.60	2013	2018	
Clear cell ovarian carcinoma	2014	3.75	2015	2023	
Survival	2005	3.91	2019	2023	
Endometrioid ovarian carcinoma	2012	3.16	2019	2023	

Figure 7 Burst word map.

Table 8 Top 5 publications by the number of citations

Ranking	Topic	Author	Journal	Year	Country	Number of citations (times)
1	Clinical Characteristics of Clear Cell Carcinoma of the Ovary: A Distinct Histological Type with Poor Prognosis and Resistance to Platinum-Based Chemotherapy	Toru Sugiyama	*Cancer*	2000	Japan	82
2	Clear Cell Carcinoma of the Ovary: A Distinct Histological Type with Poor Prognosis and Resistance to Platinum-Based Chemotherapy in Stage III Disease	Barbara A. Goff	*Gynaecological Oncology*	1996	USA	49
3	Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging	M. Takano	*British Journal of Cancer*	2006	Japan	37
4	ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas	Kimberly C. Wiegand	*The New England Journal of Medicine*	2010	USA	34
5	Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers	John K. Chan	*Gynaecological Oncology*	2007	USA	24

ARID1A, AT-rich interaction domain 1A.

influential information in a certain field can be obtained, and the development of a certain field can be further clarified. *Table 8* shows the top five publications in the CCCO research field by number of citations in the past 20 years. The five highly cited publications were all published in top medical journals; of the five publications, three were review papers, and two were clinical research papers. Among the reviews, two papers summarized and elaborated the special pathological manifestations and clinical characteristics of CCCO. They were published in 1996 and 2000, indicating that at the end of the last century, CCCO, a unique type of ovarian cancer, began to be recognized by academia. In addition, another review paper was published in 2010 that mainly discussed the relationship between ARID1A and endometriosis-associated ovarian cancer, indicating that at the beginning of this century, researchers gradually began to explore the molecular events involved in the development of CCCO. The two clinical research publications were both retrospective studies with large samples and focused on the prognosis of and treatment efficacy in CCCO patients. They were published in 2006 and 2007, indicating that clinical research in the CCCO field progressed at the beginning of this century. This further confirmed the conclusions from the aforementioned keyword timeline analysis. In addition, the five publications were all by Japanese or American authors, once again illustrating the leading positions of the two countries in this field.

Co-citation refers to the phenomenon that two publications are cited by a certain publication at the same time. It is generally accepted that co-cited publications have some degree of similarity in subject matter. Therefore, the number of co-citations (i.e., co-citation strength) can measure the relevance of two papers in terms of content (55), and the analysis of literature co-citations can present a better picture of the overall structure of research in a particular field (56). Same as the keyword co-occurrence analysis, this study still uses VOSviewer to perform literature co-citation analysis. *Figure 8* shows the clustering information of the publications cited more than 20 times. A total of 18 publications were included in the analysis. The red cluster mainly focused on the clinical features of, diagnosis of, and treatment methods for CCCO, and the research themes in the green cluster mostly involved the exploration of the pathogenesis of CCCO. This suggests that research in the field of CCCO can be broadly categorized into two main themes: clinical research and basic research.

Discussion

As a special type of EOC (1), CCCO accounts for approximately 10% of all ovarian cancer cases (42). In contrast to other types of EOC, the incidence of CCCO

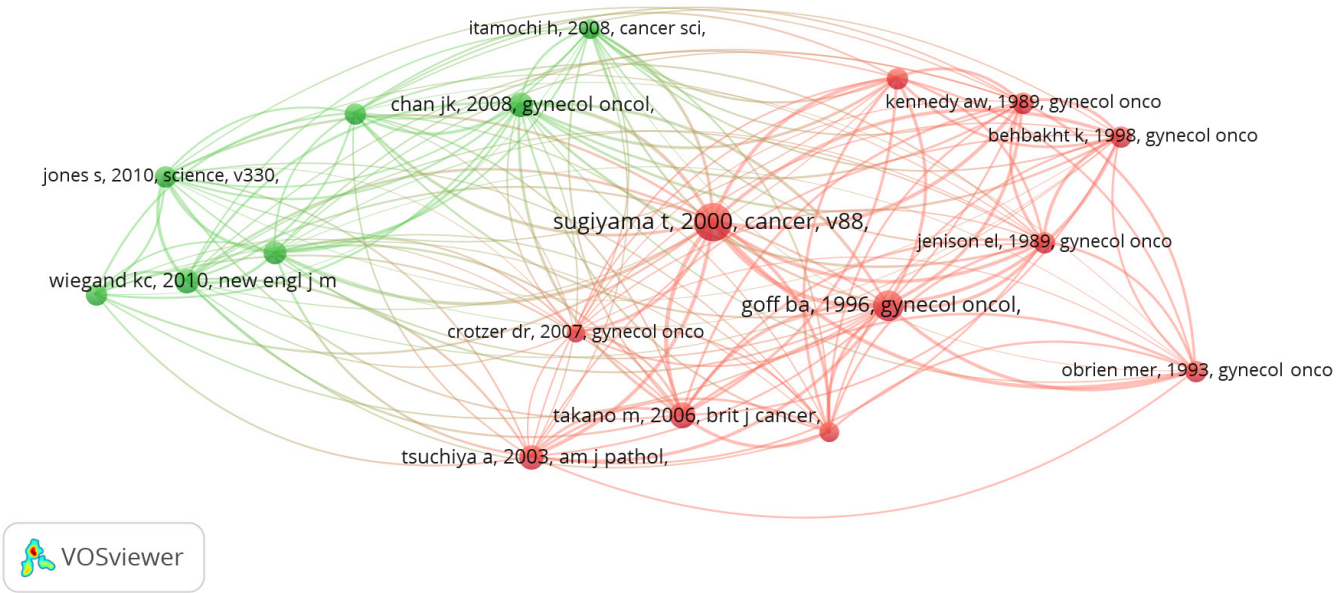

Figure 8 Document co-citation network.

is significant different among different races (2-4). The incidence of CCCO in South Korea (10.3%), Taiwan (18.6%), and Japan (15–25%) is significantly higher than that in North America and Europe (1–12%) (3,4). Among women living in the United States, the incidence of CCCO is significantly higher among Asians (11.1%) than among Whites (4.8%) and Blacks (3.1%) (2); however, the cause of this phenomenon is unclear.

Compared with that of patients with SOC, the median age of patients with CCCO is lower (55 *vs.* 64 years) (2), and the proportion of individuals with early-stage disease is higher. Among all CCCO patients, approximately 57–81% are diagnosed with stage I, and approximately 19–22% are diagnosed with stage II (2,3,5).

CCCO is highly correlated with ovarian endometriosis (17,18). Studies have shown that patients with ovarian endometriosis have a significantly increased incidence of CCCO (relative risk =12.4) (57) and that endometriosis was associated with postoperative pathological examination in approximately 51% of CCCO patients (58). Therefore, it is currently considered that ovarian endometriosis, rather than typical endometriosis, is the direct precursor of CCCO (19,20). Atypical endometriosis is considered a precancerous lesion of CCCO (57,59). In addition, in patients with endometriosis, the risk of CCCO is significantly increased when over 50 years old, which, combined with the median age of patients with CCCO (55 years), indicates that malignant transformation of ovarian endometriosis may occur more often in perimenopause (1).

The results of recent studies indicate that ARID1A mutation and the activation of the PI3K/AKT/mTOR pathway may be the key molecular events in the malignant transformation of CCCO (32-37) and that the BRCA mutation and TP53 mutation, which are common in high-grade SOC, are less common in CCCO (60,61). In addition, microarray analysis has shown that HNF-1β and oxidative stress-related genes are upregulated in CCCO (38,62). Recent studies on the pathogenesis of CCCO have focused more on the identification of subtypes. Researchers in this field have identified the subtypes of CCCO from different angles. Among them, Wang *et al.* (63) divided CCCO into two main subtypes, C-APOBEC and C-AGE, based on single nucleotide variation (SNV) characteristics, where C-APOBEC is characterized by an APOBEC mutation and C-AGE is characterized by age-associated mutations; this subtype differentiation has a relatively high degree of acceptance (64-66). In addition, Tan *et al.* (67) differentiated CCCO into an epithelial subtype and a mesenchymal subtype through cluster analysis of CCCO gene expression profiles in a public database. This subtype identification also has high clinical value.

The prognosis of early CCCO is similar to or better than that of SOC (2,5-12), while the prognosis of advanced and recurrent CCCO is significantly worse than that of

SOC (12,14-16). A variety of clinical or genetic factors can affect the prognosis of CCCO (42). A recent study showed that the prognosis of CCCO patients complicated with endometriosis is better (68); however, the results of a previous study indicated that the prognosis of CCCO patients complicated with endometriosis was not an independent factor for the improved prognosis of CCCO. Patients complicated with endometriosis tend to have earlier staging, and earlier staging can improve the prognosis of these patients (69). In addition, the C-APOBEC and epithelial subtypes often predict a better prognosis (66,67).

Similar to other types of EOC, surgery and chemotherapy are the main treatments for CCCO (1). Because the pelvic lymph node metastasis rate of stage I–II CCCO is as high as 1.2–14.4% (6,70-72) and systemic pelvic lymph node dissection is independently associated with prolonged overall survival (OS) in patients with early-stage disease (73), early-stage lymph node dissection is independently associated with prolonged OS in patients with early-stage CCCO (73). Comprehensive staging surgery should be performed for CCCO. For cytoreductive surgery in patients with advanced disease, a study showed that the prognosis of patients with residual tumour diameters >1 and <1 cm was not significantly different and that the prognosis of patients with no residual tumour was significantly better than that of patients with residual tumour (6). Therefore, for advanced CCCO, surgeons should strive to achieve R0 resection. In addition, the age of onset of CCCO is earlier, and many CCCO patients have reproductive requirements. However, it is still inconclusive whether comprehensive fertility-preserving staging surgery is suitable for CCCO patients (42,74). China's ovarian guidelines state that clear cell carcinoma is highly malignant and that the decision to preserve reproductive function should be made with caution (75).

High resistance to platinum is a clinical feature of CCCO (41). The progression-free survival of patients with advanced CCCO is significantly shorter than that of patients with SOC (12,42), and the response rate of recurrent CCCO to platinum is very low (43-48), which is also the reason for the very poor prognosis of patients with advanced and recurrent CCCO (75). Currently, paclitaxel + platinum is the first-line chemotherapy regimen for CCCO (1). Recent studies have shown that in the initial treatment of CCCO, the use of platinum-based chemotherapy alone can achieve a survival similar to that of paclitaxel plus platinum-based chemotherapy (6,73). Therefore, whether paclitaxel should be retained in the first-line chemotherapy regimen may be an issue that needs to be addressed in future clinical studies. In view of the high resistance of CCCO to platinum, it is still controversial whether postoperative adjuvant chemotherapy should be used for early CCCO (75). The current guidelines for the diagnosis and treatment of ovarian cancer in China suggest that regardless of the stage, platinum should be used after CCCO surgery. However, some studies in other countries have shown that for early CCCO patients, postoperative adjuvant chemotherapy may not bring survival benefits (76-79). Therefore, the European Society for Medical Oncology-European Society for Gynaecological Oncology (ESMO-ESGO) does not recommend adjuvant chemotherapy for stage IA–IC1 CCCO patients with complete surgical staging (80), and the guidelines of the National Comprehensive Cancer Network (NCCN) also point out that for stage IA CCCO patients, postoperative observation is another option (81).

Like other types of EOC, whole abdominal radiotherapy is not currently used as a routine treatment for CCCO. The limited study results cannot confirm that postoperative adjuvant radiotherapy yields more significant survival benefits for CCCO patients (42).

Some novel antitumour drugs, including targeted therapy drugs and immunotherapy drugs, may become breakthrough options in for the treatment of CCCO. Currently, a number of clinical trials of new antitumour drugs for the treatment of CCCO are ongoing (42). In contrast to SOC patients, CCCO patients have a low probability of having BRCA mutations (60,61). Therefore, PAPR inhibitors only play a limited role in very few patients (42). The PI3K/Akt/mTOR pathway is usually activated in CCCO (32-37); therefore, inhibitors of this pathway have received more attention. Laboratory studies have shown that the mTOR inhibitor everolimus has efficacy both *in vivo* and *in vitro*. However, mTOR inhibitors have not shown definite efficacy in clinical trials (82). In contrast, some multitarget tyrosine kinase inhibitors have been shown to impart significant survival benefits in clinical trials (83,84). In addition, immune checkpoint inhibitors have also achieved good efficacy in CCCO patients (85,86). The results of recent studies indicate that genetic changes in CCCO lead to an inhibitory immune microenvironment (87), which may be one the reasons why inhibitors perform well in CCCO (85,86). The combination of immune checkpoint inhibitors and molecular targeted drugs may become a future research hotspot in the treatment of CCCO.

This study reviewed the development of the CCCO field in the past 20 years by means of bibliometrics. In the analysis of the trends of publication numbers, we observed

that the annual number of CCCO-related publications was relatively low until 2006. However, in 2006, there was a relatively rapid increase, and after that, the annual number of publications remained at a relatively high level. This, to some extent, reflects that CCCO may have begun to receive attention from the academic community around 2006. However, we also see that overall, the volume of literature on CCCO is relatively small, and therefore, although this study excludes the interference of the inclusion of new journals in the results through analysis, it still cannot be excluded that this fluctuation in the number of publications is the result of the influence of some contingent factors. In addition, it would take some time for a study to transition from the initial proposal to the final publication, and the length of this time would be influenced by a variety of factors, which is also true for CCCO research. Therefore, our study can only provide a rough estimate of the likely period in which CCCO begins to receive attention from the academics. In the analysis of the number of publications, we also realized that research intensity in the field of CCCO has consistently been lower than that in other types of SOC. This may be related to its lower incidence rate. However, due to the large population base, the total number of patients with this disease is not insignificant. Therefore, more research input is needed in this field in the future.

In the analysis of the authors, countries, and institutions of the publications, we found that the research level of CCCO is higher in East Asia and North America, with Japan leading the research in this field and the United States following closely. After comparing the research level of CCCO with the overall research level of malignant tumours in each country, we consider that the relatively higher research level of the United States in the field of CCCO is more likely to be attributed to its overall research capability in the field of malignant tumours. While Japan's world-leading research level in the field of CCCO might be attributed more to the higher incidence of the disease in East Asian populations. This particular epidemiological phenomenon of CCCO may be an important entry point for future pathogenesis studies. Exploring the proportion of various CCCO subtypes, the incidence of known molecular events (such as ARID1A mutations), and the histologic heterogeneity of tumors, in the patients of different races may become valuable directions for future studies. In the analysis of national and institutional cooperation, we found that East Asian and North American countries have conducted extensive collaboration in this field and have formed a number of representative research groups, indicating that the research system in this field is becoming increasingly mature. However, the level of attention of this disease in other parts of the world is still low, and researchers in East Asia and North America should play leading roles in raising worldwide attention to CCCO.

In analyzing the keywords and citations, we obtained numerous meaningful findings. First, we found that research in the field of CCCO can be broadly categorized into two major themes: clinical research and basic research, and the two are generally developing in parallel. It indicating that clinical research and basic research in CCCO have promoted each other and that research in this field has basically formed a healthy development model of continuous basic and clinical transformation. Second, by analysing the evolution of keywords, we found that academics' research on CCCO has developed from a preliminary understanding to in-depth explorations, and important breakthroughs in the field of oncology also continue to drive CCCO research forward. Here, we particularly notice that professional terms such as pabolizumab, T-cells, and Akt appear simultaneously in the same cluster of the timeline spectrum of high-frequency keywords. In the preceding sections, we have discussed the great potential of immunotherapy in the field of CCCO and the key position of the PI3K/Akt/mTOR pathway in the pathogenesis and clinical application of CCCO, and the results of this analysis suggest that we should pay attention to the intrinsic connection between the PI3K/Akt/mTOR pathway and immunotherapy in the study of CCCO. Current studies have demonstrated that activation of the PI3K/Akt/mTOR pathway can induces an inhibitory immune microenvironment in a wide range of solid tumours (88), and targeting the PI3K/Akt/mTOR pathway can play a role in both direct regulation of tumor cell proliferation and apoptosis as well as the regulation of the immune microenvironment (89). Therefore, the combination strategy of immunotherapy and the targeted therapy against PI3K/Akt/mTOR may have good research prospects in the future. In addition, we found that many of the specialized terms (e.g., ARID1A, oxidative stress, etc.) that appeared frequently in the analysis were all related to "apoptosis". This may be because apoptosis of cancer cells and the removal of these apoptotic cell debris by efferocytosis are possibly essential for the effective treatment of CCCO (90). Therefore, developing new strategies for CCCO treatment from the perspective of inducing apoptosis may also be a viable approach. With the development of high-throughput sequencing technology, there has been a gradual increase in the number of recent

articles on subtype analysis, prognostic markers and therapeutic targets for CCCO. They have deepened the understanding of the disease to different degrees and provided some valuable research evidence (91-97).

This study used quantitative research tools to sort out the development of the field of CCCO by systematically summarizing the research literature in the field over a longer timeframe and provided guidelines for future directions. There is currently no study of the same type in this field. However, there are some limitations in this study. First, papers published earlier have a longer time to accumulate citation counts, and evaluating the impact of the literature through citation counts may cause a little bias, but there is a lack of methods that can absolutely and accurately assess the impact of the articles, and second, there may be the phenomenon of self-citation in the literature that is included in our study, but there is no method to identify self-citation, and self-citation may have a little interference with the study results. Additionally, the literature database selected for this article is the WOS Core Collection. While this database is widely recognized in the field of bibliometrics for the quality of its included literature and the standardization of information, we must acknowledge that the WOS Core Collection has a relatively small coverage of medical research. Consequently, our study may not have comprehensively covered all relevant research within the CCCO field. This limitation implies that, although our analysis provides an important perspective on research trends within this field, there may still be some literature not encompassed by our study. Our future research will consider integrating a broader range of data sources, including other major academic databases such as Scopus and PubMed, to more comprehensively capture the research dynamics in the CCCO field.

Conclusions

In conclusion, research on CCCO, a special type of EOC, has developed significantly in the past 20 years, but there are still many urgent issues that need to be addressed with regard to its pathogenesis and treatment. Although the overall incidence of the disease is low, CCCO still affects a large number of people. In the future, more research efforts are needed in this field, and more extensive collaboration is needed worldwide. The exploration of the genomic variations and pathogenic molecular events unique to CCCO, the search for more accurate and valuable classification methods, the investigation of the preservation of reproductive function, and the exploration and optimization of immune-target combination treatment strategies are directions of future CCCO research.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2351/coif). The authors have no conflicts of interest to declare.

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

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