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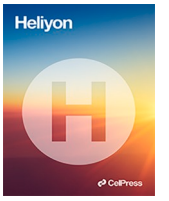

Knowledge mapping of early-onset colorectal cancer from 2000 to 2022: A bibliometric analysis

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ABSTRACT

The incidence of early-onset colorectal cancer (EO-CRC), diagnosed in patients younger than 50 years, has increased in incidence alarmingly over the past few decades, while overall incidence and mortality of colorectal cancer are stabilizing or declining in many high-income countries. These unfavorable changes have raised significant concerns and led to extensive research, resulting in a surge in studies on EO-CRC. Our aim was to obtain a more comprehensive understanding of the current state of this field and to identify prospective research directions by performing a bibliometric analysis of EO-CRC. A total of 1952 papers on EO-CRC published from 2000 to 2022 were identified after a thorough search of the Web of Science Core Collection. The United States dominated this field, with Harvard University contributing the greatest number of papers, while the journal *Familial Cancer* (n = 52) published the most articles. Cooperation network analysis revealed close internal cooperation among countries, institutions and authors. Based on reference and keyword analysis, high-frequency keywords showed several popular research directions, including epidemiology (incidence, young patients, age of onset, etc.), risk factors (obesity, family history, lynch syndrome, etc.) and molecular characterization (germline mutation, genome wide association, MLH1, etc.). Overall, our research provides an overview of the current status in this field, which we hope will give researchers a comprehensive perspective on the present trends within this domain.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide [1–3]. While the overall incidence and mortality rates of CRC are stabilizing or declining in many high-income countries due to advances in screening, surveillance, and treatment [4], an alarming rise in the number of occurrences of early-onset colorectal cancer (EO-CRC),

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defined as diagnosis in patients younger than 50 years of age, has occurred worldwide over the past few decades [3,5,6]. It's predicted that by 2030, 10–12% of colon cancers and 25% of rectal cancers will be diagnosed in patients under 50 years old [4,7]. The reasons for this trend remain unclear, although genetic predisposition, environmental and lifestyle factors may all play a role [8,9]. Moreover, early-onset patients were more likely to present with later stages than those aged 50 or older [10]. As this growing health problem affects young individuals significantly [8,11], research on EO-CRC is also increasing. However, these studies have yet to be evaluated systematically, it's necessary to make a complete analysis of the literature, which can provide suggestions and inspirations to researchers in this field.

Bibliometrics is an interdisciplinary science that analyzes documents statistically in a particular research domain, using mathematical and statistical methodologies to reveal cutting-edge knowledge development and research trends [12–14]. Commonly used bibliometric analysis software, such as CiteSpace and VOSviewer, facilitates this process [15,16]. Hence, with the help of these programs, we systematically analyzed the research on EO-CRC from the perspective of publications, countries, institutions, journals, authors and keywords. We hope that our study can help researchers to better understand the current research hotspots and development trends in this field, thereby contributing to the advancement of EO-CRC.

2. Materials and methods

2.1. Data collection

Literature search was conducted on January 9, 2023, and all documents were obtained from the Web of Science Core Collection (WoSCC) using Clarivate Analytics [17,18]. The search formula was [TS = ("Rectal Neoplasm*" OR "Rectal Tumor*" OR "Rectal Cancer*" OR "Rectal Carcinoma*" OR "Rectum Neoplasm*" OR "Rectum Cancer*" OR "Carcinoma of Rectum" OR "Tumor of Rectum" OR "Colonic Neoplasm*" OR "Colonic Tumor*" OR "Colonic Cancer*" OR "Colonic Carcinoma*" OR "Colon Neoplasm*" OR "Colon Tumor*" OR "Colon Cancer*" OR "Carcinoma of the Colon" OR "Colorectal Neoplasm*" OR "Colorectal Tumor*" OR "Colorectal Cancer*" OR "Colorectal Carcinoma*") AND TS = ("Early Onset" OR "Young Onset" OR "Early-Age Onset" OR "Young Adult*" OR "Age of Onset")] AND [Language = (English)]. The publication year was limited to 2000–2022, and only articles and reviews were included; other types of publications were excluded. Articles meeting these criteria were downloaded as "Full Record and Cited References" and "Plain Text". To enable the CiteSpace program to read them, the files were renamed as "download *.txt" for further analysis. The detailed search strategy is depicted in Fig. 1.

2.2. Data analysis

CiteSpace (version 6.1. R6), VOSviewer (version 1.6.18) and Microsoft Excel 2019 were used to analyze and visualize the selected literature. CtieSpace is a JAVA-based bibliometric and visual analysis software developed by Chaomei Chen, which allows for

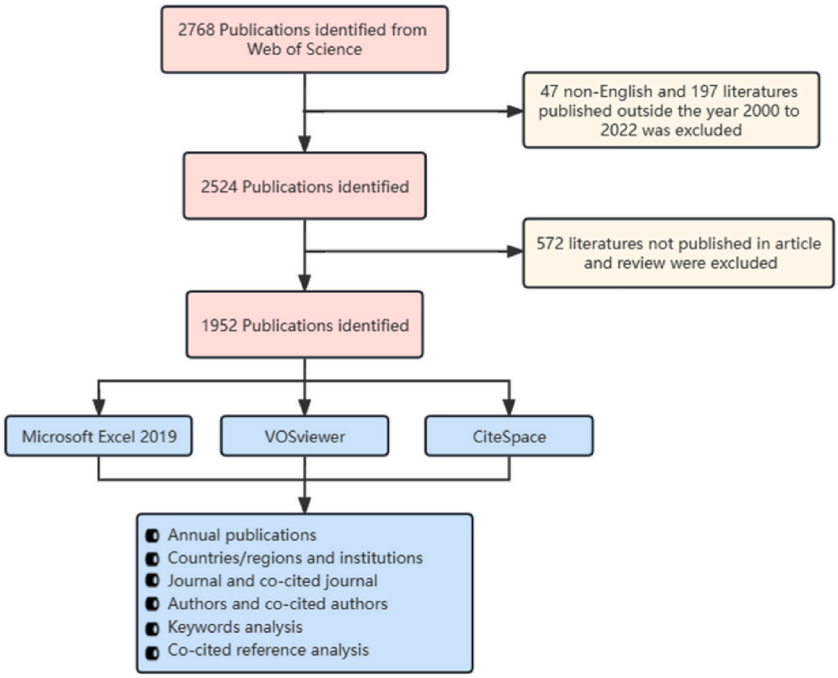


Fig. 1. Flow diagram of data collection and study design.

exploration of research trends in a certain area and extraction of keywords and references with high citation bursts [15,19]. We used CiteSpace to analyze the dual-map of journals, keyword bursts, reference timeline and citation bursts. The settings were as follows: time span (2000–2022), years per slice (1), selection criteria (g-index k = 25 or Top N% = 2), link retaining factor (LRF = 3), e for top N (e = 1.0), look back years (LBY = 5), links (strength: cosine, scope: within slices), cluster labels were extracted by the log-likelihood ratio (LLR) algorithm, and others remained default. The dual-map overlay of journals indicates how the journals' topics were distributed. On the map, the citing journals appear on the left, and the cited on the right, with corresponding labels signifying their respective fields of study. The colored lines illustrate the citation paths from left to right. Timeline view is a kind of visual analysis which combines time slicing and clustering algorithms. In order to show the trend and interconnectedness of study subjects through time, as well as the distribution of topics in this field, cluster labels are arranged according to whether they occur early or late after clustering. Different colors of nodes on the same line in the timeline view signify different years, the nodes on the right reflect more recent references, whereas those on the left represent older references. A straight line at the same horizontal position indicates the set to which all cluster references belong, with the cluster label at the line's rightmost end. "Burst" refer to sudden and steep increases in the frequency of certain keywords. The burst map portrays a light blue line corresponding to the 2000–2022 time period, a dark blue line indicating the initial appearance of a given keyword, and a red line signifying its subsequent burst. The higher the burst strength, the higher the frequency of that keyword/reference in the observed period. Additionally, "centrality" measures the percentage of shortest paths in the network to which a given node belongs. It quantifies the importance of the node's position in a network. The higher the centrality, the greater the influence.

VOSviewer is another bibliometric software that excels at creating and visualizing knowledge maps, effectively illustrating different types of cluster, overlay, and density [16,20]. In this study, VOSviewer was employed to analysis country/institution/journal/author/keyword. The resulting visualizations showcase nodes representing a variety of items, including countries, institutions, journals, and more. The size of the nodes reflects the frequency of occurrence, while node color indicates different clusters or years. Lines between nodes symbolize cooperation or co-citation relationships among these items. Microsoft Excel 2019 was used to analyze the annual publications. Additionally, the impact factor (IF) and Journal citation reports (JCR) division of journals were obtained from the Web of Science on January 10, 2023.

3. Results

3.1. The annual growth trend of publications

A total of 1952 papers on EO-CRC were published from 2000 to 2022, including 1716 articles and 236 reviews. Their annual distribution trends are shown in Fig. 2. Only 28 papers were reported in 2000; however, this number increased to 212 in 2021 and 214 in 2022. Due to the delay of WoSCC indexed articles, the number of publications in 2022 is still rising as of the retrieval date. Over the past 23 years, an average of 85 publications per year have been released, with an average growth rate of 9.25%.

3.2. Countries/regions and institutions

A total of 1952 papers were from 89 different countries/regions and 2829 institutions (Table 1). Fig. 3A shows that the USA published the most articles (n = 798), followed by China (n = 208) and the UK (n = 153). The top ten countries are predominantly developed country (n = 9). Fig. 3B visually represents cooperative relationships among countries with publication outputs that meet or exceed 10. It is noteworthy that a number of countries display particularly robust collaborative efforts.

The top 10 institutions are located in 3 countries, including USA, Australia, Netherlands. Harvard University boasts the highest number of relevant publications (n = 68), followed by Mayo Clinic (n = 49) and UT MD Anderson Cancer Center (n = 42). Remarkably, all seven of the top-ranking institutions are located in the USA. Fig. 3C presents a visualization of institutions with at least 20 articles, revealing the presence of four distinct clusters denoted by various colors (Fig. 3C). Cluster 1 (red) is the largest, followed by clusters 2 (green), 3 (blue), and 4 (yellow). Notably, the cooperation between Harvard University, Brigham and Women's Hospital, Dana-Farber

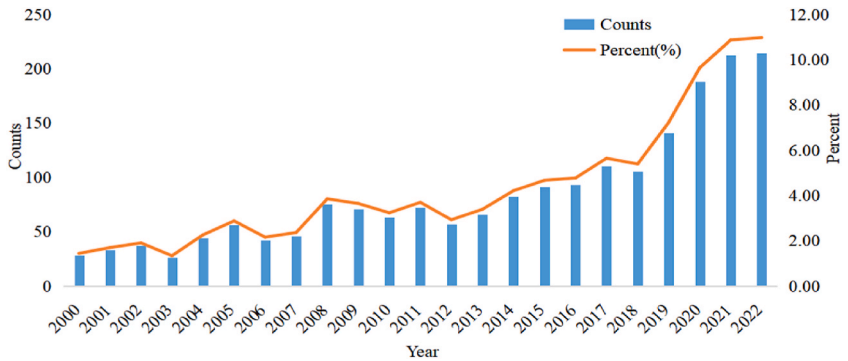


Fig. 2. The trend of publication outputs about EO-CRC.

Table 1
The top 10 countries/regions and institutions involved in EO-CRC.

Rank	Country	Counts	Citations	Organization	Counts	Citations
1	USA	798	35,286	Harvard University	68	2008
2	China	208	4019	Mayo clinic	49	2619
3	UK	153	6219	UT MD Anderson Cancer Center	42	2981
4	Germany	134	4328	Dana-Farber Cancer Institute	41	1321
5	Canada	130	6285	Memorial Sloan-Kettering Cancer Center	40	1876
6	Australia	122	3632	Brigham and Women's Hospital	39	1364
7	Italy	116	2799	Massachusetts General Hospital	39	887
8	Netherlands	109	7604	The University of Melbourne	39	1293
9	Spain	96	3159	Leiden University	37	1728
10	Japan	94	2508	National Cancer Institute	32	4371

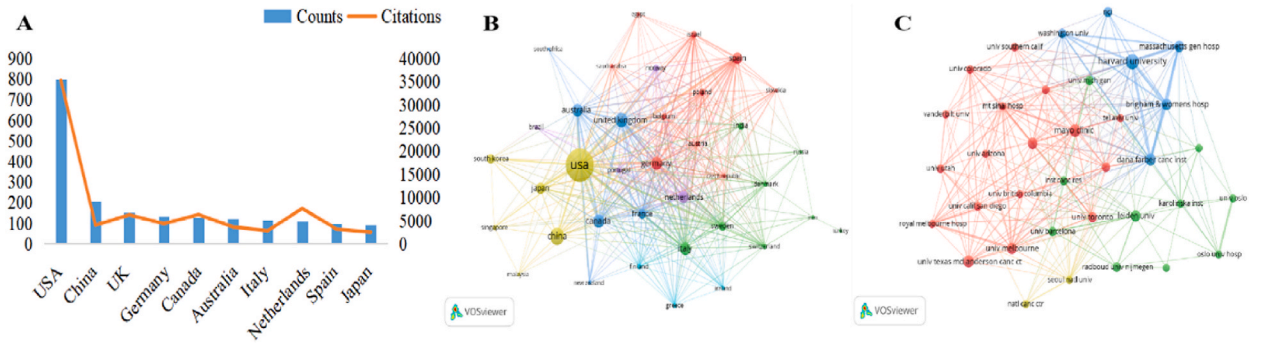


Fig. 3. Analysis of countries/regions and institutions engaged in researches related to EO-CRC. A: The top 10 most productive countries/regions. B: A network map showing countries/regions involved in the research on EO-CRC. C: A network map showing institutions involved in the research on EO-CRC.

Cancer Institute and Massachusetts General Hospital is very strong. In addition to intra-cluster collaborations, active cooperative relationships are also evident among each cluster.

3.3. Journal and co-cited journal

A total of 614 academic journals have published articles relating to EO-CRC. The top ten journals are detailed in Table 2, with *Gastroenterology* boasting the highest IF of 33.883, followed by *International Journal of Cancer* with an IF of 7.316. Fig. 4 shows a collaborative network of journals with publications greater than or equal to 10. Notably, there were positive citation relationships between different journals. As for co-cited journals, *Gastroenterology* (3422) has the highest citations, followed by *Cancer Research* (2,691) and *Journal of Clinical Oncology* (2290). All of the top 10 co-cited journals have been cited more than 1300 times. Nine of the top 10 journals with co-cited times were located in the Q1 JCR region. Three of these journals boast an IF over 50, while seven maintain an IF exceeding 10.

Fig. 5 presents a dual-map overlay of journals, revealing the distribution of respective topics. Notably, three distinct citation paths

Table 2
Top 10 journals and co-cited journals related to EO-CRC.

Rank	Journal	Counts	JCR	IF (2021)	Co-Cited Journal	Cited Counts	JCR	IF (2021)
1	Familial Cancer	52	Q3/Q4	2.446	Gastroenterology	3422	Q1	33.883
2	International Journal of Cancer	43	Q1	7.316	Cancer Research	2691	Q1	13.312
3	Cancers	42	Q1	6.575	Journal of Clinical Oncology	2290	Q1	50.739
4	Gastroenterology	34	Q1	33.883	International Journal of Cancer	1931	Q1	7.316
5	World Journal of Gastroenterology	31	Q2	5.374	New England Journal of Medicine	1891	Q1	176.082
6	Cancer	30	Q1	6.921	Gut	1712	Q1	31.795
7	Cancer Epidemiology Biomarkers & Prevention	28	Q3/Q2	4.090	Nature Genetics	1541	Q1	41.376
8	PloS One	28	Q2	3.752	Cancer	1472	Q1	6.921
9	Diseases of the Colon & Rectum	27	Q1/Q2	4.657	Cancer Epidemiology Biomarkers & Prevention	1346	Q3/Q2	4.090
10	Frontiers in Oncology	26	Q2	5.738	Nature	1315	Q1	69.504

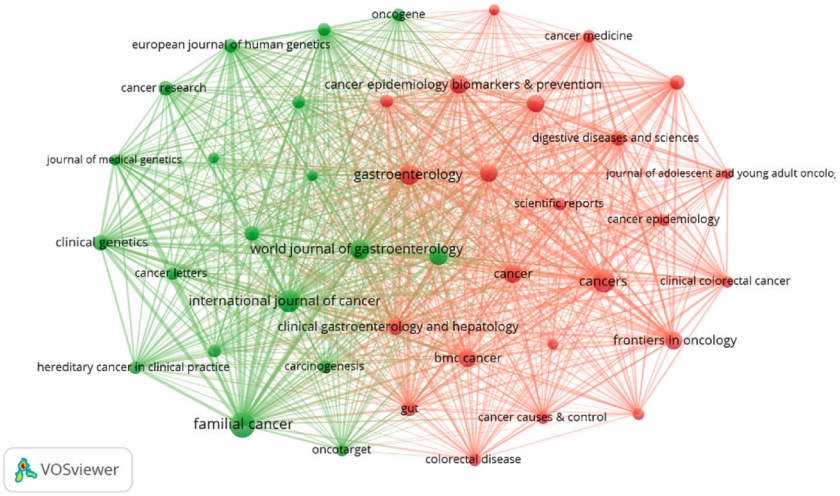


Fig. 4. A network map showing academic journals publishing research on EO-CRC.

can be identified. The first, designated by an orange line, indicates that studies sourced from Molecular/Biology/Genetics journals were frequently cited in studies published in Molecular/Biology/Immunology journals. Two green paths suggest that studies sourced from both Molecular/Biology/Genetics journals and Health/Nursing/Medicine journals were frequently cited from publications in Medicine/Medical/Clinical journals.

3.4. Authors and co-cited authors

A total of 11,732 authors have contributed to the field of EO-CRC, with 120 authors publishing six or more papers. The top 10 authors in this field are detailed in Table 3, with each author having published over fifteen papers. Perea J has the most related papers (n = 19), followed by Valle L (n = 17), Wu K (n = 16), among others. As is shown in Fig. 6A, an author visualization map featuring eight colors representing eight clusters is presented. Notably, collaborations exist both within individual clusters and between different clusters.

As for co-citation authors, Siegel RL from American Cancer Society ranked first (n = 877) and all top 10 co-citation authors are cited more than 170 times. Fig. 6B presents a co-citation network map featuring three distinct clusters represented by Siegel RL, Lynch HT, and Carethers JM, respectively. It is noteworthy that there are active collaborative relationships within and between individual clusters.

3.5. Analysis of keywords

Table 4 details the top 20 high-frequency keywords used in EO-CRC research. All of these keywords appeared more than 30 times,

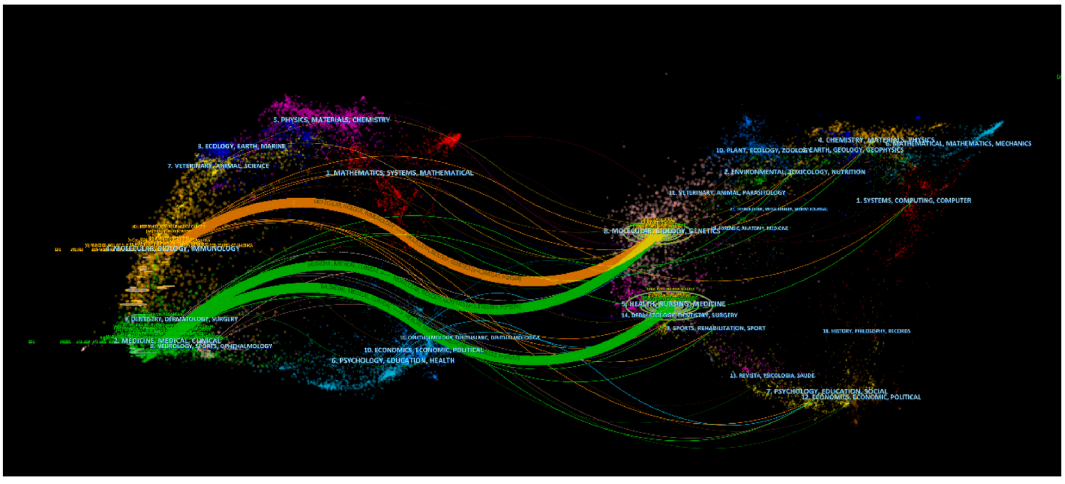


Fig. 5. A dual-map overlay of journals related to research on EO-CRC.

Table 3
The top 10 authors and co-cited authors of EO-CRC research.

Rank	Author	Counts	Citations	Co-Cited Author	Cited Counts
1	Perea J	19	371	Siegel RL	877
2	Valle L	17	342	Lynch HT	629
3	Capella G	16	159	Vasen HF	584
4	Ogino S	16	648	O'Connell JB	287
5	Song M	16	487	Boland CR	243
6	Wu K	16	695	Bailey CE	228
7	Giovannucci EL	15	569	Heather H	191
8	Goel A	15	393	Aaltonen LA	190
9	Lubinski J	15	301	Rex DK	180
10	Urioste M	15	290	Aaltonen LA	173

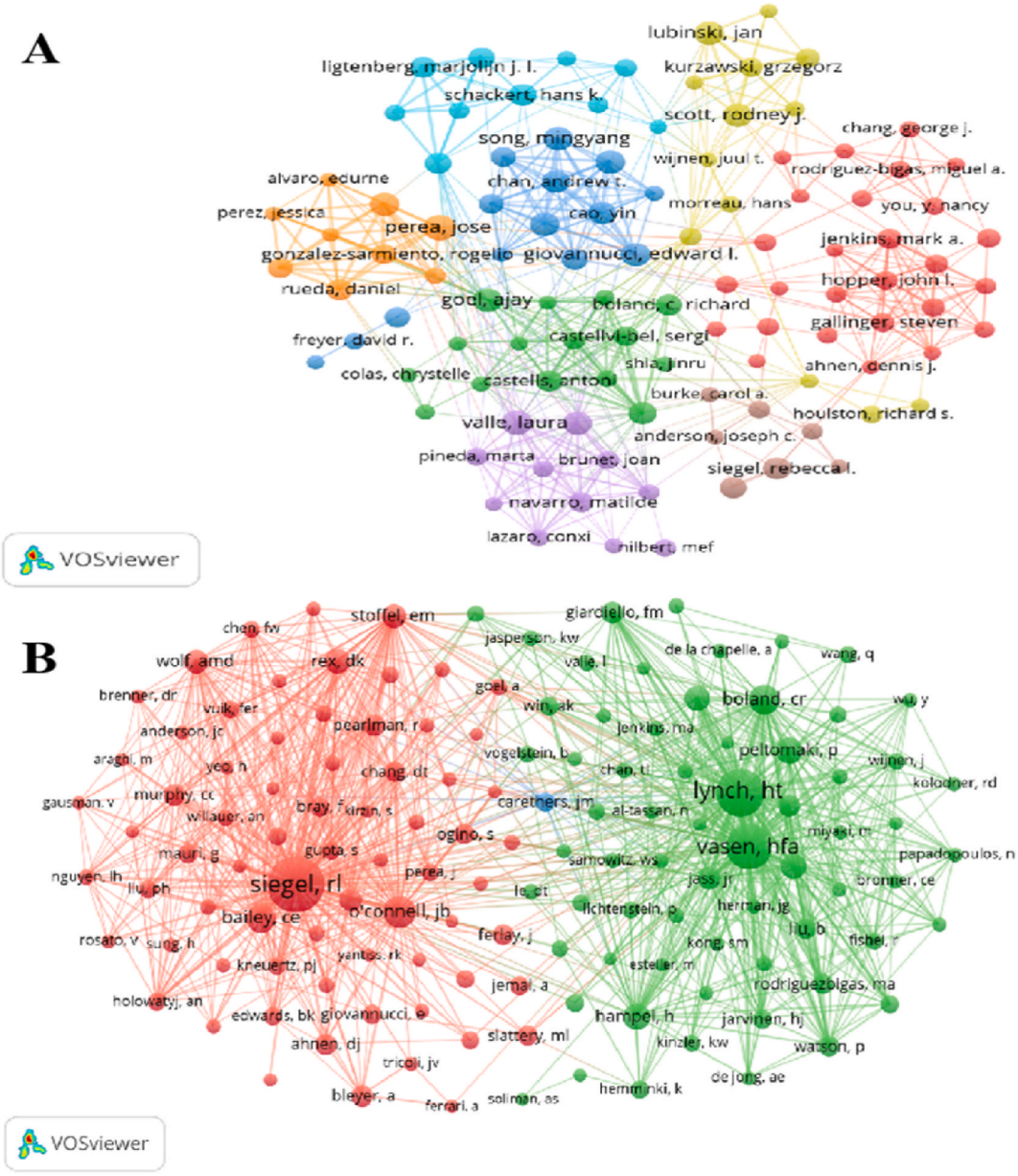


Fig. 6. Analysis of authors engaged in researches related to EO-CRC. A: A network map showing authors involved in the research on EO-CRC. B: A network map showing co-cited authors involved in the research on EO-CRC.

among them, "Young Adult", "Lynch Syndrome" and "HNPCC" appeared more than 100 times. Fig. 7A shows the results of keywords cluster analysis, resulting in eight distinct clusters representing eight research directions. Red clusters represent keywords such as Early-Onset, Young Adults, Epidemiology, Incidence, Mortality, Survival, among others. Green clusters denote HNPCC, Lynch Syndrome, Microsatellite Instability, Mismatch Repair, MLH1, MSH2, among others. Dark blue clusters comprise Risk Factors, Diet, Obesity, and other related keywords. Yellow clusters are represented by APC, Adenoma, Familial Adenomatous Polyposis, and so on. Purple clusters highlight Family History, Cancer Predisposition, Brac1, and similar themes. Light blue clusters consist of 5-FU, Capecitabine, chemotherapy, and related terms. Orange clusters consist of KRAS, MSI, DNA methylation, and similar topics. Finally, brown clusters cover Ulcerative Colitis, Crohn's Disease, inflammatory bowel disease and surgery. Fig. 7B presents an overlay map of the high-frequency keywords ($n \geq 10$). As we can see, risk factors, next generation sequencing and biomarkers are emerging fields that were depicted in yellow hues. Fig. 7C highlights the top 25 keywords with the strongest citation bursts. HNPCC showed the highest burst strength with 45.17, beginning in 2000 and continuing through 2013. Keywords featuring citation bursts after 2016 also demonstrated high strength, including "United States" (2016–2022, strength 10.94), "Obesity'' (2019–2022, strength 11.01), and "Prevalence'' (2018–2022, strength 14.03). Notably, these keywords continue to attract attention up to the present day.

3.6. Co-cited reference and reference burst

Table 5 summarizes the top 15 co-cited references. These 15 references were cited least more than 60 times, among which the top 4 references were cited more than 100 times. Moreover, all of these references were from JCR Q1, with the paper entitled "Colorectal Cancer Incidence Patterns in the United States, 1974–2013" published by Siegel RL attracting the most co-citations ($n = 162$). It is also worth noting that one-third of the TOP15 references were published by Siegel RL.

Fig. 8A shows a timeline display of co-cited references. The closest clusters on the timeline were "Lynch Syndrome", followed by "HNPCC", "Microsatellite Instability" and "Young Patients". Fig. 8B presents the top 15 references with the strongest citation bursts, the paper entitled "Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010" published by Bailey CE had the most strength (2015–2020, strength 42.39). Moreover, recent high-citation references include "Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society" (2019–2022, strength 19), "Early-onset colorectal cancer in young individuals" (2020–2022, strength 18.91), "Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women" (2020–2022, strength 17.29) and "Clinical and molecular characterization of early-onset colorectal cancer" (2020–2022, strength 16.49). The bursts strength of these 15 references range from 14.91 to 42.39, with endurance strength spanning three to six years.

4. Discussion

4.1. General information

The present study provides an enhanced understanding of research domains pertaining to EO-CRC, offering researchers and physicians a comprehensive overview of the field and potential areas for future research. In order to achieve this goal, a comprehensive literature search was conducted on this topic until December 2022 in the Web of Science Core Collection, resulting in the retrieval of 1952 bibliographic records, which were then subjected to bibliometric analysis.

Publications on EO-CRC have exhibited a notable upward trend, particularly since 2018. This indicates that the investigation of EO-CRC is a burgeoning area of interest. This phenomenon may be attributed to American Cancer Society's decision in 2018 to lower the recommended age for cancer screening from 50 to 45, considering the evolving incidence of EO-CRC in recent years [21].

Globally, the incidence of CRC occurring at younger ages has attracted increased attention from the academic community [22]. In this bibliometric analysis, research outputs on the EO-CRC have been published in multiple countries, with USA being the most productive country, followed by the China, UK and Germany. It is worth noting that among the top ten countries with the highest number of published papers, China stands out as the only developing country. This phenomenon can be elucidated by China's socio-economic development and the resulting lifestyle changes, which may partly account for the growing burden of EO-CRC [23,24]. The adoption of a Westernized diet and a decrease in physical activity contribute to the prevalence of obesity and overweight, which

Table 4
The top 20 keywords related to EO-CRC.

Rank	Keyword	Counts	Rank	Keyword	Counts
1	Colorectal cancer	505	11	Screening	58
2	Young adults	184	12	Risk factors	57
3	Lynch syndrome	147	13	Survival	54
4	Early-onset colorectal cancer	141	14	Rectal cancer	42
5	hnpcc	113	15	Germline mutation	39
6	Colon cancer	101	16	Incidence	38
7	Microsatellite instability	84	17	Cancer predisposition	35
8	Cancer	79	18	Early-onset	35
9	Mismatch repair	66	19	Colonoscopy	33
10	Epidemiology	60	20	mlh1	32

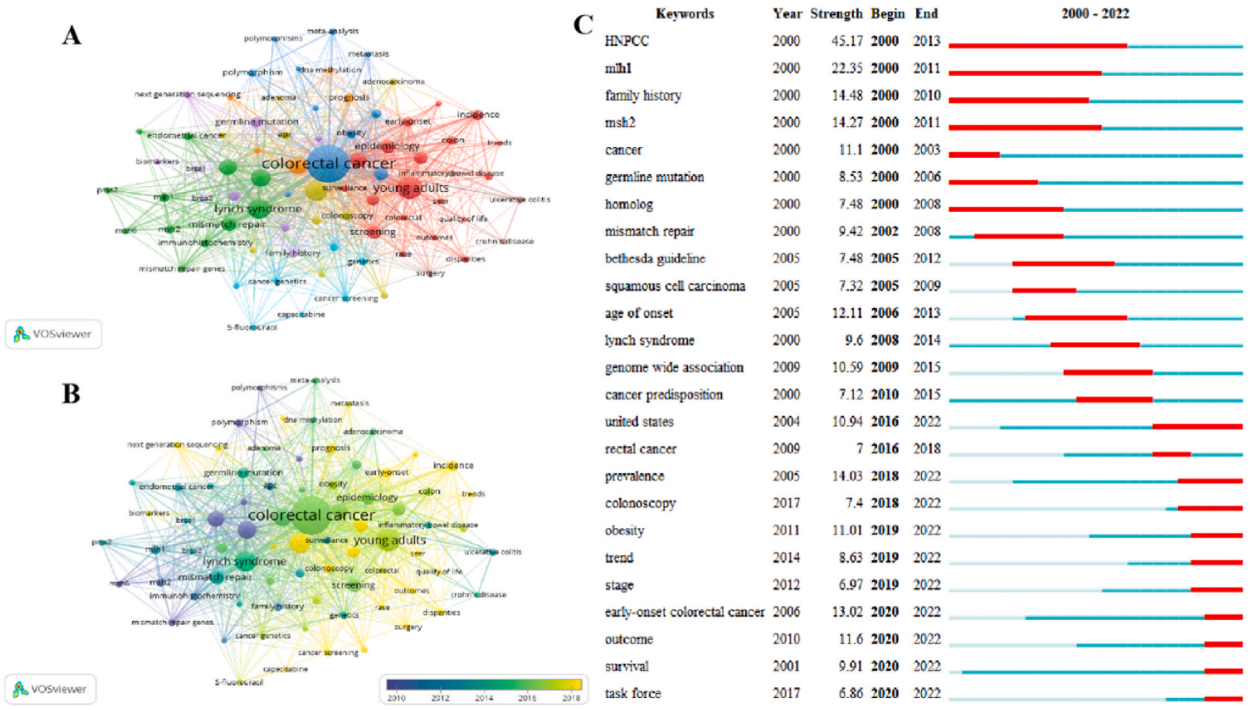


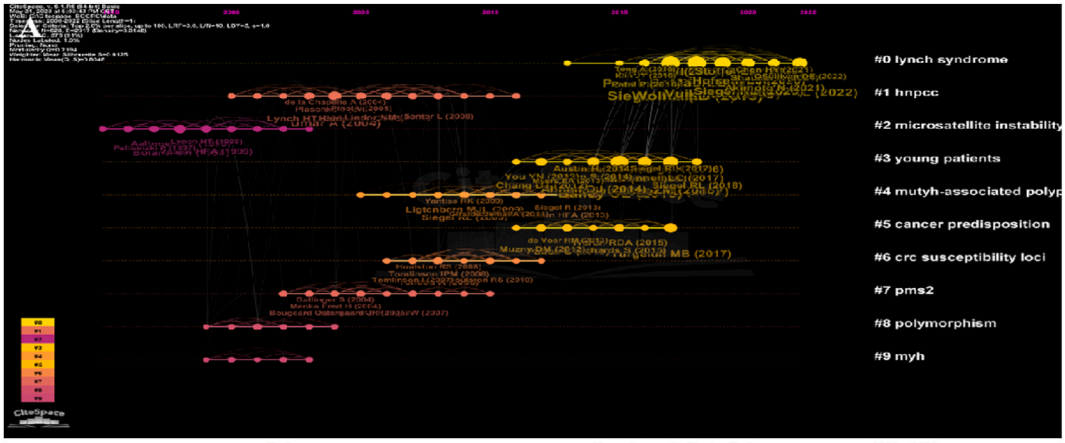
Fig. 7. Analysis of keywords involved in researches related to EO-CRC. A: The co-occurrence network and clusters of keywords related to EO-CRC. B: The overlay map of keywords related to EO-CRC. C: Top 25 Keywords with the Strongest Citation Bursts involved in EO-CRC.

Table 5
TOP15 co-cited reference related to EO-CRC.

Rank	First Author	Year	Title	Journal	Counts	Centrality
1	Siegel RL	2017	Colorectal Cancer Incidence Patterns in the United States, 1974–2013	J Natl Cancer Inst	162	0.02
2	Wolf AMD	2018	Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society	CA Cancer J Clin	151	0.04
3	Pearlman R	2017	Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer	JAMA Oncol	125	0.04
4	Bailey CE	2015	Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010	JAMA Surg	117	0.13
5	Bray F	2018	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	CA Cancer J Clin	99	0
6	Mauri G	2019	Early-onset colorectal cancer in young individuals	Mol Oncol	95	0
7	Vuik FE	2019	Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years	Gut	95	0.01
8	Siegel RL	2019	Global patterns and trends in colorectal cancer incidence in young adults	Gut	91	0
9	Liu PH	2019	Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women	JAMA Oncol	87	0.03
10	Willauer AN	2019	Clinical and molecular characterization of early-onset colorectal cancer	Cancer	83	0.03
11	Siegel RL	2022	Cancer statistics, 2022	CA Cancer J Clin	82	0.01
12	Siegel RL	2017	Colorectal cancer statistics, 2017	CA Cancer J Clin	76	0.01
13	Stoffel EM	2018	Germline Genetic Features of Young Individuals With Colorectal Cancer	Gastroenterology	72	0.02
14	Siegel RL	2020	Cancer statistics, 2020.	CA Cancer J Clin	63	0
15	Abdelsattar ZM	2016	Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening.	Cancer	61	0.15

may partly account for the growing burden of EO-CRC globally [24,25].

Many academic institutions have published a large number of articles on EO-CRC, mirroring the contributions of countries on relevant publications. Harvard University, Mayo Clinic, UT MD Anderson Cancer Center, Dana-Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, Brigham and Women's Hospital, Massachusetts General Hospital and National Cancer Institute, all situated within the United States, comprised 80% of the top ten institutions. Notably, Harvard University occupies the foremost position among them. As one of the preeminent institutions for medical education and research, Harvard University commands an esteemed position in the field of medicine and exerts significant influence and leadership on a global scale. The university actively collaborates with numerous international institutions, facilitating multinational research initiatives that make substantial



B

References	Year	Strength	Begin	End	2000 - 2022
Boland CR, 1998, CANCER RES, V58, P5248	1998	20.78	2000	2003	
Aaltonen LA, 1998, NEW ENGL J MED, V338, P1481, DOI 10.1056/NEJM199805213382101, DOI	1998	14.91	2000	2003	
Vasen HFA, 1999, GASTROENTEROLOGY, V116, P1453, DOI 10.1016/S0016-5085(99)70510-X, DOI	1999	16.49	2001	2004	
Lynch HT, 2003, NEW ENGL J MED, V348, P919, DOI 10.1056/NEJMra012242, DOI	2003	16.27	2004	2008	
Umar A, 2004, J NATL CANCER I, V96, P261, DOI 10.1093/jnci/djh034, DOI	2004	30.76	2005	2009	
Siegel RL, 2009, CANCER EPIDEM BIOMAR, V18, P1695, DOI 10.1158/1055-9965.EPI-09-0186, DOI	2009	15.89	2011	2014	
Chang DT, 2012, MODERN PATHOL, V25, P1128, DOI 10.1038/modpathol.2012.61, DOI	2012	17.45	2014	2017	
Bailey CE, 2015, JAMA SURG, V150, P17, DOI 10.1001/jamasurg.2014.1756, DOI	2015	42.39	2015	2020	
Ahnen DJ, 2014, MAYO CLIN PROC, V89, P216, DOI 10.1015/j.mayocp.2013.09.006, DOI	2014	27.06	2015	2019	
Palles C, 2013, NAT GENET, V45, P136, DOI 10.1038/ng.2503, DOI	2013	15.27	2015	2018	
Mork ME, 2015, J CLIN ONCOL, V33, P3544, DOI 10.1200/JCO.2015.61.4503, DOI	2015	16.52	2016	2020	
Wolf AMD, 2018, CA-CANCER J CLIN, V68, P250, DOI 10.3322/caac.21457, DOI	2018	19	2019	2022	
Mauri G, 2019, MOL ONCOL, V13, P109, DOI 10.1002/1878-0261.12417, DOI	2019	18.91	2020	2022	
Liu PH, 2019, JAMA ONCOL, V5, P37, DOI 10.1001/jamaoncol.2018.4280, DOI	2019	17.29	2020	2022	
Willauer AN, 2019, CANCER-AM CANCER SOC, V125, P2002, DOI 10.1002/cncr.31994, DOI	2019	16.49	2020	2022	

Fig. 8. Analysis of references involved in researches related to EO-CRC. A: The timeline view of references. B: The top 15 references with the strongest citation bursts involved in EO-CRC.

contributions to the advancement of global medical progress. Our findings reveal a closely interconnected network of collaboration between Harvard University and various institutions, particularly involving Dana-Farber Cancer Institute, Brigham and Women's Hospital and Massachusetts General Hospital, given their affiliations as teaching hospitals of Harvard University. Moreover as depicted in Fig. 3C, the cooperation within and between clusters exhibits notable strength, which not only enhances the quantity and quality of publications but also propels the relentless progress of the field.

Journal analysis can help scholars select appropriate journals for their research outputs. Within this study, *Familial Cancer*, *International Journal of Cancer*, *Cancers*, *Gastroenterology* and *World Journal of Gastroenterology* were the most productive journals on the EO-CRC field. Furthermore, co-citation analysis revealed that among the top 10 journals ranked by co-cited counts, nine were classified within the Q1 JCR region, with seven having an impact factor exceeding 10. These findings imply a strong interest from prestigious journals in EO-CRC-related research, offering valuable guidance to future researchers in selecting appropriate journals for the submission of their EO-CRC-related manuscripts.

Scholars from the United States and Europe exert preeminent influence in the domain of EO-CRC. All of the top 10 authors and co-cited authors are from USA and Europe. It is noteworthy that Siegel RL (877 co-citations), a cancer epidemiologist affiliated with American Cancer Society, has exerted a substantial influence through her remarkable publication impact and invaluable contributions to the field of EO-CRC. In 2008, Siegel RL observed the rising occurrence of CRC among individuals under the age of 50, subsequently publishing her seminal research in 2009, titled "Increase in incidence of colorectal cancer among young men and women in the United States" [26]. This pioneering study serves as a vital reminder for heightened vigilance toward early-onset colorectal cancer, particularly in light of the overall decline in colorectal cancer incidence.

4.2. Research hotspots

Keywords function as indicators of prominent research areas and trends within a specific domain. Fig. 7 presents the results of keywords analysis, including keyword co-occurrence (Fig. 7A), keyword overlay (Fig. 7B) and keyword burst (Fig. 7C). These keywords represent the research hotspots in the field of EO-CRC. Prominent keywords include incidence, young patients, age of onset, obesity, family history, lynch syndrome, germline mutation, genome wide association, MLH1, and more. These keywords enable us to synthesize the comprehensive landscape of the EO-CRC field, leading to the inference that the primary research focuses on epidemiology, risk factors, and molecular characterization. Moreover, the same conclusion can also be obtained from the co-citation and

reference burst analysis. As depicted in the results section, the top 15 co-cited references related to EO-CRC primarily concentrate on epidemiology and clinical and molecular characterization of EO-CRC. The most frequently cited reference in recent years is "Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010" [27], consistently highlighting the aspect of incidence. We therefore conclude that epidemiology, risk factors and molecular characterization appear to be the primary focus of research in this field.

4.2.1. Epidemiology

Compared with the early 2000s, the median age at CRC diagnosis has decreased from 72 to 66 years due to a rise in EO-CRC cases and a parallel decline in later-onset cases [28]. The rising incidence of EO-CRC underscores the growing importance of research in this field, but it is crucial to investigate the reasons behind this trend. Our bibliometric analysis reveals that increased exposure to risk factors, particularly those associated with a Westernized diet, is the primary cause for this rise. Moreover, genetic factors also play a significant role in the development of EO-CRC. However, the exact causes for the rise in incidence remain unclear due to limited large-scale prospective studies. Therefore, future research must conduct comprehensive prospective studies to illuminate the underlying reasons for the escalating prevalence of EO-CRC.

4.2.2. Risk factors

Obesity, which is postulated as a risk factor for EO-CRC [29], is also a keyword that has exploded in recent years. As is widely known, the occurrence of EO-CRC is influenced by external environmental and genetic factors. Over the past few decades, there have been significant changes in environmental and lifestyle factors compared with hereditary determinants [30], including increased consumption of red and processed meats [31], refined grains, and processed sugar [32]. These dietary factors are presumed contributors to the rising rates of obesity and its adverse health effects, including colorectal cancer occurring at younger ages [30,33]. Moreover, Harvard University, a prominent institution in this field, has conducted several prospective cohort studies to analyze risk factors associated with EO-CRC, including obesity. The results indicate that dietary and lifestyle interventions potential may be effective for CRC prevention among younger individuals, which is meaningful for primary prevention measure against cancer [34–36].

Inherited factors also play a pivotal role in EO-CRC alongside environmental aspects. HNPCC occupies first place in our timeline and keywords burst analysis. Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is one of the most common types of hereditary colorectal cancer and accounts for 4%–13.5% of patients with EO-CRC [37]. Patients with Lynch syndrome are 2–3 times more susceptible to developing EO-CRC, and the probability of hereditary colorectal cancer increases with an earlier onset age [38]. Furthermore, Bethesda Guidelines also emerged in our keywords burst. It was developed in 1996 by the National Cancer Institute International Workshop on HNPCC and revised in 2002 to better understand the role of genetics in its pathology, including identification criteria for detecting microsatellite instability (MSI) [39,40]. These guidelines have also raised awareness of the disease. However, with the rapid development of molecular biology and genetic diagnosis, it has gradually been realized that the screening methods mentioned above have a certain rate of missed diagnosis. Therefore, the National Comprehensive Cancer Network guidelines recommend MSI and mismatch repair (MMR) screening for all newly diagnosed colorectal cancer patients since 2015 [41]. This approach not only helps with genetic screening but also guides medication selection and prognosis evaluation.

4.2.3. Molecular characteristics

Exploring the molecular characteristics of EO-CRC is advantageous for identifying potential causes and guiding the development of targeted treatment. Multigene testing has revolutionized the clinical approach to testing affected patients at risk and their families. Compared to traditional detection methods, Next-Generation Sequencing (NGS) can analyze a set of genes simultaneously with greater efficiency [41]. Enhancing the application of NGS technology in detecting molecular markers and genetic evaluation is crucial not only for clinicians in clinical practice but also for future research. With the advancement of genetic testing technology [22], more pathogenic variants beyond germline variants linked to typical hereditary colorectal cancer syndromes (such as MSI-High) have been discovered in EO-CRC [37,42–44]. Half of these mutations involve high or moderate penetrance genes that are not commonly associated with CRC, such as TP53, BRCA1, BRCA2, CHEK2 and ATM [45–48]. Nonetheless, it is important to recognize that many developing countries face significant obstacles in implementing multigene testing due to limited resources. In these countries, traditional methods like immunohistochemistry (IHC) are still widely used for detecting MSI, despite having a limited role in diagnosis and prognosis assessment compared to multigene testing. From the perspectives of disease diagnosis, treatment, and prognosis assessment, we recommend that regions with sufficient resources perform multigene testing on high-risk populations, which is consistent with the emergence of the keyword "Next-Generation Sequencing" in our recent keyword analysis results.

Despite significant progress in the molecular characterization of EO-CRC, numerous questions remain to be resolved. Studies involving relatively small sample sizes leave uncertainty regarding whether these unusual makers cause EO-CRC or are coincidental findings [49]. Furthermore, the etiologic and treatment implications of many EO-CRC mutation markers are yet to be fully understood. Therefore, further work is necessary to clarify molecular landscape in EO-CRC.

5. Conclusion

To our knowledge, this is the first comprehensive and quantitative bibliometric analysis of research on EO-CRC. Our findings indicate that current research related to EO-CRC mainly focuses on epidemiology, risk factors and molecular characterization, with high-income countries, particularly the United States, leading the way in this field. As the incidence of EO-CRC continues to rise, clarifying its etiology, risk factors, and clinical and molecular characterization remains an urgent challenge to be solved. This is also the

primary research direction in the future. We hope that our study will give researchers a comprehensive landscape of the field to grasp current overall trends precisely.

However, our study does have some limitations. Firstly, we only retrieved data from WOSCC, which may have results in overlooking other noteworthy publications. Nevertheless, we are confident that our findings can effectively display the overall status and trends of this discipline as WOSCC is widely recognized as the most reputable database for bibliometric analysis [17,18]. Secondly, our search was limited to research written in English, potentially causing a linguistic bias and missing out on non-English publications. Finally, owing to the delay in citations, researches published in recent time may not have received the attention they deserve and need to be updated timely.

Author contribution statement

Mengmeng Zhang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Shentao Zhu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lili Chen; Yue Wu; Yingquan Ye; Gaoxiang Wang; Zhongxuan Gui: Contributed reagents, materials, analysis tools or data.

Congjun Zhang; Mei Zhang: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, 2022, CA A Cancer J. Clin. 72 (1) (2022) 7–33, https://doi.org/10.3322/caac.21708.
[2] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.
[3] F.A. Sinicrope, Increasing incidence of early-onset colorectal cancer, N. Engl. J. Med. 386 (16) (2022) 1547–1558, https://doi.org/10.1056/NEJMra2200869.
[4] M. Araghi, I. Soerjomataram, A. Bardot, J. Ferlay, C.J. Cabasag, D.S. Morrison, et al., Changes in colorectal cancer incidence in seven high-income countries: a population-based study, Lancet Gastroenterol. Hepatol. 4 (7) (2019) 511–518, https://doi.org/10.1016/S2468-1253(19)30147-5.
[5] R.L. Siegel, L.A. Torre, I. Soerjomataram, R.B. Hayes, F. Bray, T.K. Weber, et al., Global patterns and trends in colorectal cancer incidence in young adults, Gut 68 (12) (2019) 2179–2185, https://doi.org/10.1136/gutjnl-2019-319511.
[6] F. Vuik, S. Nieuwenburg, M. Bardou, I. Lansdorp-Vogelaar, M. Dinis-Ribeiro, M.J. Bento, et al., Increasing incidence of colorectal cancer in young adults in europe over the last 25 years, Gut 68 (10) (2019) 1820–1826, https://doi.org/10.1136/gutjnl-2018-317592.
[7] A. Zaborowski, A. Abdile, M. Adamina, F. Aigner, L. D'Allens, C. Allmer, et al., Characteristics of early-onset vs late-onset colorectal cancer a review, Jama Surg 156 (9) (2021) 865–874, https://doi.org/10.1001/jamasurg.2021.2380.
[8] D.E. O'Sullivan, R.L. Sutherland, S. Town, K. Chow, J. Fan, N. Forbes, et al., Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis, Clin. Gastroenterol. Hepatol. 20 (6) (2022) 1229, https://doi.org/10.1016/j.cgh.2021.01.037.
[9] R.N. Lui, K. Tsoi, J. Ho, C.M. Lo, F. Chan, M.H. Kyaw, et al., Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1,922,167 cases, Cancer Epidemiol. Biomarkers Prev. 28 (8) (2019) 1275–1282, https://doi.org/10.1158/1055-9965.EPI-18-1111.
[10] A.N. Willauer, Y. Liu, A.A.L. Pereira, M. Lam, J.S. Morris, K.P.S. Raghav, et al., Clinical and molecular characterization of early-onset colorectal cancer, Cancer 125 (12) (2019) 2002–2010, https://doi.org/10.1002/cncr.31994.
[11] G. Mauri, A. Sartore-Bianchi, A.G. Russo, S. Marsoni, A. Bardelli, S. Siena, Early-onset colorectal cancer in young individuals, Mol. Oncol. 13 (2) (2019) 109–131, https://doi.org/10.1002/1878-0261.12417.
[12] C.M. Chen, M. Song, Visualizing a field of research: a methodology of systematic scientometric reviews, PLoS One 14 (10) (2019), e0223994, https://doi.org/10.1371/journal.pone.0223994.
[13] I.D. Cooper, Bibliometrics basics, J. Med. Libr. Assoc. 103 (4) (2015) 217–218, https://doi.org/10.3163/1536-5050.103.4.013.
[14] J.S. Brandt, O. Hadaya, M. Schuster, T. Rosen, M.V. Sauer, C.V. Ananth, A bibliometric analysis of top-cited journal articles in obstetrics and gynecology, JAMA Netw. Open 2 (12) (2019), e1918007, https://doi.org/10.1001/jamanetworkopen.2019.18007.
[15] M.B. Synnestvedt, C. Chen, J.H. Holmes, Citespace ii: visualization and knowledge discovery in bibliographic databases, AMIA Annu. Symp. Proc. 2005 (2005) 724–728.
[16] N.J. van Eck, L. Waltman, Citation-based clustering of publications using citnetexplorer and vosviewer, Scientometrics 111 (2) (2017) 1053–1070, https://doi.org/10.1007/s11192-017-2300-7.
[17] S.T. Jiang, Y.G. Liu, L. Zhang, X.T. Sang, Y.Y. Xu, X. Lu, Immune-related adverse events: a bibliometric analysis, Front. Immunol. 13 (2022), 1096806, https://doi.org/10.3389/fimmu.2022.1096806.
[18] A. Yeung, Comparison between scopus, web of science, pubmed and publishers for mislabelled review papers, Curr. Sci. 116 (11) (2019) 1909, https://doi.org/10.18520/cs/v116/i11/1909-1914.
[19] C. Chen, Searching for intellectual turning points: progressive knowledge domain visualization, Proc. Natl. Acad. Sci. U.S.A. 101 (Suppl 1) (2004) 5303–5310, https://doi.org/10.1073/pnas.0307513100.
[20] N.J. van Eck, L. Waltman, Software survey: vosviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2010) 523–538, https://doi.org/10.1007/s11192-009-0146-3.
[21] A. Wolf, E. Fontham, T.R. Church, C.R. Flowers, C.E. Guerra, S.J. Lamonte, et al., Colorectal cancer screening for average-risk adults: 2018 guideline update from the american cancer society, Ca-Cancer, J. Clin. 68 (4) (2018) 250–281, https://doi.org/10.3322/caac.21457.
[22] S.G. Patel, J.J. Karlitz, T. Yen, C.H. Lieu, C.R. Boland, The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection, Lancet Gastroenterol. Hepatol. 7 (3) (2022) 262–274, https://doi.org/10.1016/S2468-1253(21)00426-X.
[23] X. Chen, J. Giles, Y. Yao, W. Yip, Q. Meng, L. Berkman, et al., The path to healthy ageing in China: a peking university-lancet commission, Lancet 400 (10367) (2022) 1967–2006, https://doi.org/10.1016/S0140-6736(22)01546-X.

[24] X.Q. Lao, W.J. Ma, T. Sobko, Y.H. Zhang, Y.J. Xu, X.J. Xu, et al., Dramatic escalation in metabolic syndrome and cardiovascular risk in a Chinese population experiencing rapid economic development, BMC Publ. Health 14 (2014) 983, https://doi.org/10.1186/1471-2458-14-983.
[25] S.W. Ng, E.C. Norton, B.M. Popkin, Why have physical activity levels declined among Chinese adults? Findings from the 1991-2006 China health and nutrition surveys, Soc. Sci. Med. 68 (7) (2009) 1305–1314, https://doi.org/10.1016/j.socscimed.2009.01.035.
[26] R.L. Siegel, A. Jemal, E.M. Ward, Increase in incidence of colorectal cancer among young men and women in the United States, Cancer Epidemiol, Biomarkers Prev. 18 (6) (2009) 1695–1698, https://doi.org/10.1158/1055-9965.EPI-09-0186.
[27] C.E. Bailey, C.Y. Hu, Y.N. You, B.K. Bednarski, M.A. Rodriguez-Bigas, J.M. Skibber, et al., Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010, Jama Surg. 150 (1) (2015) 17–22, https://doi.org/10.1001/jamasurg.2014.1756.
[28] R.L. Siegel, K.D. Miller, S.A. Goding, S.A. Fedewa, L.F. Butterly, J.C. Anderson, et al., Colorectal cancer statistics, 2020, CA A Cancer J. Clin. 70 (3) (2020) 145–164, https://doi.org/10.3322/caac.21601.
[29] R.S. Mehta, M. Song, R. Nishihara, D.A. Drew, K. Wu, Z.R. Qian, et al., Dietary patterns and risk of colorectal cancer: analysis by tumor location and molecular subtypes, Gastroenterology 152 (8) (2017) 1944–1953, https://doi.org/10.1053/j.gastro.2017.02.015.
[30] H. Li, D. Boakye, X. Chen, L. Jansen, J. Chang-Claude, M. Hoffmeister, et al., Associations of body mass index at different ages with early-onset colorectal cancer, Gastroenterology 162 (4) (2022) 1088–1097, https://doi.org/10.1053/j.gastro.2021.12.239.
[31] D.S. Chan, R. Lau, D. Aune, R. Vieira, D.C. Greenwood, E. Kampman, et al., Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies, PLoS One 6 (6) (2011), e20456, https://doi.org/10.1371/journal.pone.0020456.
[32] L. Schwingshackl, C. Schwedhelm, G. Hoffmann, S. Knuppel, P.A. Laure, K. Iqbal, et al., Food groups and risk of colorectal cancer, Int. J. Cancer 142 (9) (2018) 1748–1758, https://doi.org/10.1002/ijc.31198.
[33] A. Hruby, F.B. Hu, The epidemiology of obesity: a big picture, Pharmacoeconomics 33 (7) (2015) 673–689, https://doi.org/10.1007/s40273-014-0243-x.
[34] Y. Yue, J. Hur, Y. Cao, F.K. Tabung, M. Wang, K. Wu, et al., Prospective evaluation of dietary and lifestyle pattern indices with risk of colorectal cancer in a cohort of younger women, Ann. Oncol. 32 (6) (2021) 778–786, https://doi.org/10.1016/j.annonc.2021.03.200.
[35] H.K. Joh, D.H. Lee, J. Hur, K. Nimptsch, Y. Chang, H. Joung, et al., Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors, Gastroenterology 161 (1) (2021) 128–142, https://doi.org/10.1053/j.gastro.2021.03.028.
[36] P.H. Liu, K. Wu, K. Ng, A.G. Zauber, L.H. Nguyen, M. Song, et al., Association of obesity with risk of early-onset colorectal cancer among women, JAMA Oncol. 5 (1) (2019) 37–44, https://doi.org/10.1001/jamaoncol.2018.4280.
[37] R. Pearlman, W.L. Frankel, B. Swanson, W. Zhao, A. Yilmaz, K. Miller, et al., Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer, JAMA Oncol. 3 (4) (2017) 464–471, https://doi.org/10.1001/jamaoncol.2016.5194.
[38] C. Eng, A.A. Jacome, R. Agarwal, M.H. Hayat, M.X. Byndloss, A.N. Holowatyj, et al., A comprehensive framework for early-onset colorectal cancer research, Lancet Oncol. 23 (3) (2022) e116–e128, https://doi.org/10.1016/S1470-2045(21)00588-X.
[39] M.A. Rodriguez-Bigas, C.R. Boland, S.R. Hamilton, D.E. Henson, J.R. Jass, P.M. Khan, et al., A national cancer institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and bethesda guidelines, Jnci-J. Natl. Cancer Inst. 89 (23) (1997) 1758–1762, https://doi.org/10.1093/jnci/89.23.1758.
[40] A. Umar, C.R. Boland, J.P. Terdiman, S. Syngal, A. de la Chapelle, J. Ruschoff, et al., Revised bethesda guidelines for hereditary nonpolyposis colorectal cancer (lynch syndrome) and microsatellite instability, Jnci-J. Natl. Cancer Inst. 96 (4) (2004) 261–268, https://doi.org/10.1093/jnci/djh034.
[41] J.M. Weiss, S. Gupta, C.A. Burke, L. Axell, L.M. Chen, D.C. Chung, et al., NCCN Guidelines® insights: genetic/familial high-risk assessment: colorectal, version 1.2021, J. Natl. Compr. Cancer Netw. 19 (10) (2021) 1122–1132, https://doi.org/10.1164/jnccn.2021.0048.
[42] J.T. Liang, K.C. Huang, A.L. Cheng, Y.M. Jeng, M.S. Wu, S.M. Wang, Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age, Br. J. Surg. 90 (2) (2003) 205–214, https://doi.org/10.1002/bjs.4015.
[43] E.M. Stoffel, E. Koeppe, J. Everett, P. Ulintz, M. Kiel, J. Osborne, et al., Germline genetic features of young individuals with colorectal cancer, Gastroenterology 154 (4) (2018) 897–905, https://doi.org/10.1053/j.gastro.2017.11.004.
[44] M.E. Mork, Y.N. You, J. Ying, S.A. Bannon, P.M. Lynch, M.A. Rodriguez-Bigas, et al., High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer, J. Clin. Oncol. 33 (31) (2015) 3544–3549, https://doi.org/10.1200/JCO.2015.61.4503.
[45] M.B. Yurgelun, M.H. Kulke, C.S. Fuchs, B.A. Allen, H. Uno, J.L. Hornick, et al., Cancer susceptibility gene mutations in individuals with colorectal cancer, J. Clin. Oncol. 35 (10) (2017) 1086–1095, https://doi.org/10.1200/JCO.2016.71.0012.
[46] M.B. Yurgelun, B. Allen, R.R. Kaldate, K.R. Bowles, T. Judkins, P. Kaushik, et al., Identification of a variety of mutations in cancer predisposition genes in patients with suspected lynch syndrome, Gastroenterology 149 (3) (2015) 604–613, https://doi.org/10.1053/j.gastro.2015.05.006.
[47] D. Cragun, C. Radford, J.S. Dolinsky, M. Caldwell, E. Chao, T. Pal, Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a us laboratory, Clin. Genet. 86 (6) (2014) 510–520, https://doi.org/10.1111/cge.12359.
[48] M.B. Yurgelun, S. Masciari, V.A. Joshi, R.C. Mercado, N.M. Lindor, S. Gallinger, et al., Germline tp53 mutations in patients with early-onset colorectal cancer in the colon cancer family registry, JAMA Oncol. 1 (2) (2015) 214–221, https://doi.org/10.1001/jamaoncol.2015.0197.
[49] A.N. Burnett-Hartman, J.K. Lee, J. Demb, S. Gupta, An update on the epidemiology, molecular characterization, diagnosis, and screening strategies for early-onset colorectal cancer, Gastroenterology 160 (4) (2021) 1041–1049, https://doi.org/10.1053/j.gastro.2020.12.068.