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Analysis

Fumarate hydratase in cancer research: scientific trends and findings over 22 years

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Abstract

Objective Fumarate hydratase (FH) is a key enzyme in the Krebs cycle and cellular energy metabolism, playing a crucial role in tumorigenesis. It is considered a prognostic, diagnostic, and therapeutic target for many types of cancer. Therefore, FH is a popular scientific subject in cancer research. The current study aimed to identify cancer research in the WoS database and examine studies conducted on FH molecules using bibliometric indicators.

Methods The keywords "fumarate hydratase" OR fumarase" AND "cancer OR tumor OR neoplasm" were used to search the WoS database. This search was performed using abstracts, titles, and keywords. The "Article" and "Review" options were used to access the data of papers published between 2002 and March 2024.

Results A total of 840 publications (616 articles and 224 reviews) were published by the end of March 2024. Research output on FH and cancer has significantly increased recently, with the highest number of publications in 2020 (n = 69, 8.214%). The most commonly used language was English (n = 823, 97.976%), and the USA led in productivity, contributing 306 studies (36.429%). The University of Helsinki is the most productive affiliation with 138 published articles. The researcher who conducted most studies (n = 58, 6.904%) was also the most-cited author, with 1562 citations. In the current bibliometric study, "hereditary leiomyomatosis", "mutations", and "renal-cell cancer" were frequently included in publications.

Conclusion This bibliometric study provides a quantitative overview of FH research in oncology and presents the most recent FH status in cancer research.

Keywords Fumarate hydratase · Cancer · WoS · Bibliometric analysis

1 Introduction

Cancer is a complex and widespread disease that poses a significant threat to human health [1]. It is characterized by uncontrolled cell growth and proliferation, and results from the interaction of genetic, environmental, nutritional, and lifestyle factors [2, 3]. The ability to escape regulatory mechanisms governing normal cellular growth, cell division, and cell death leads to the formation of malignant tumors and the potential to metastasize to distant parts of the body [4, 5].

In recent years, the complex relationship between energy metabolism and cancer has been the focus of oncological research, and new insights into the basic mechanisms of carcinogenesis have been revealed. Metabolic alterations due to dysregulation of the cycle between cellular energy production and utilization constitute one of the most critical

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aspects of cancer development and progression [6]. Regulation of this cascade at the molecular level is largely based on a complex network of enzymes that catalyze fundamental biochemical reactions in cells. Enzymes such as hexokinase, phosphofructokinase, and pyruvate kinase are involved in the regulation of the glycolytic pathway, whereas citrate synthase, isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) are essential for the maintenance of the tricarboxylic acid (TCA) cycle under physiological conditions. While energy metabolism has traditionally served as a means for cells to maintain vital processes, such as growth and proliferation, abnormalities in these metabolic pathways have been implicated in the pathogenesis of many malignancies [7, 8]. Therefore, alterations in energy metabolism are recognized as the hallmarks of cancer. This makes the enzymes involved in these metabolic pathways important targets for cancer research. Understanding the complex roles of these enzymes in energy metabolism is crucial for uncovering the molecular basis of cancer and developing targeted therapeutic strategies [9].

FH, also known as fumarase, is an essential enzyme involved in the tricarboxylic acid (TCA) or Krebs cycle. It plays a pivotal role in cellular energy production and metabolism by catalyzing the reversible hydration/dehydration of fumarate to malate. Dysfunction or deficiency of fumarate hydratase has been associated with various medical conditions, including hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome [10, 11]. Additionally, fumarate plays a key role in cell transformation [12]. Although fumarate accumulation can alter cellular signaling, the mechanism by which it provides cancer cells with a growth advantage remains unclear [11, 13].

Cellular energy metabolism is one of the most important processes in cancer development [14]. FH also plays an essential role in the cellular energy metabolism. Therefore, they are thought to play an important role in cancer biology. Differences in the expression levels of enzymes involved in energy metabolism, such as FH, IDH, and SDH, and mutations in these genes are reported to be involved in the molecular pathogenesis of malignant and benign tumors [15]. In recent decades, many studies on energy metabolism and cancer have yielded results that support this hypothesis.

Cellular energy metabolism is currently one of the most popular fields of study in medical research. The increasing number of studies in which enzymes involved in energy metabolism and conditions such as loss of activity, expression changes, and genetic mutations in the genes encoding these enzymes are associated with cancer pathology highlights the importance of this subject. FH is one of the markers studied and is one of the Krebs cycle enzymes required for cellular respiration. The link between FH and HLRCC makes FH a potential diagnostic, prognostic, and therapeutic target for studies on various other cancer types. Understanding the complex mechanism between fumarate hydratase and cancer holds promise for advancing our knowledge of tumorigenesis and for developing new strategies for cancer diagnosis and treatment. Identifying the scientific status of fumarate hydratase in cancer research through a bibliometric analysis will shed light on future studies in this field.

Currently, bibliometric analyses can be performed in different databases. In this study, the Web of Science (WoS) database was used, along with a bibliometric analysis of articles published on FH in cancer research from 2002 until the end of March 2024. This report contains original and up-to-date information on the subject. To date, there has been no bibliometric research on FH.

2 Materials and methods

Keywords (TS = "fumarate hydratase" OR fumarase) AND (TS = cancer OR tumor OR neoplasm) were searched in all WoS database indices. In this research, the "TOPIC" option was used to search abstracts, titles, and keywords. “Article” and “review” publications in the database were included in the study. The remaining publications were excluded from the study. As a result of the search of the WoS database, 840 publications (616 articles, 224 reviews) were accessed. These publications represent articles related to FH in cancer research between 2002 and the end of March, 2024. The data obtained from the analysis were evaluated in terms of the publication year and number, number of citations, authors, countries, publication language, funding agencies, publishers, and keywords. Excel, Biblioshiny, and R (version 4.3.3) programs were used for bibliometric analysis of the data obtained from the database. The bibliometrix package of the R software program (http://www.bibliometrix.org) was used. In addition, the Medical Subject Headings (MeSH) used in the indexing of medical and biological articles were utilized to determine the suitability of keywords.

The first study on this subject was published in 1991. However, only one article was published between 1991 and 1999. All the other articles were published in 2002 or later. For the data obtained to reflect the study trends, analyses within the scope of the study were carried out using the data collected between 2002 and the end of March 2024, since only 2 studies were conducted before 2002. Notably, there has been an increase in the number of studies conducted over the last 10 years.

The limitations of this study include the fact that publications cannot be accessed with the keywords used, are accepted for publication but not yet published, and are not scanned in the WoS database. In addition, regional publication disparities and the exclusion of pre-2002 studies in the WoS database are among the limitations of the study. Ethical committee approval was not required for this study.

3 Results

As a result of the research conducted to access the data of research and review articles, 840 studies were conducted between 2002 and the end of March 2024. From 1991, when the first study was published until 2002, only one study was conducted in 1999. Furthermore, more than one article on the subject of our study was published every year between 2002 and 2024. While there has been an increase in the number of studies in the last decade compared to previous years, the highest number of articles was published in 2020 (n = 69, 8.214%) (Table 1). Studies carried out in the last decade constitute approximately 70% of all studies.

When the number of citations was analyzed, the highest annual average number of citations was 2002 (n = 19.1). This was followed by 2005, with an annual average of 14.35 citations. Notably, in 2002, this citation average was reached for only three articles (Table 1).

The American Journal of Surgical Pathology (n = 27, 3.214%) was the journal in which the most studies on cancer and FH were published (Fig. 1). This group was followed by Familial Cancer (n = 18, 2.143%) and Clinical Cancer Research (n = 13, 1.548%) groups.

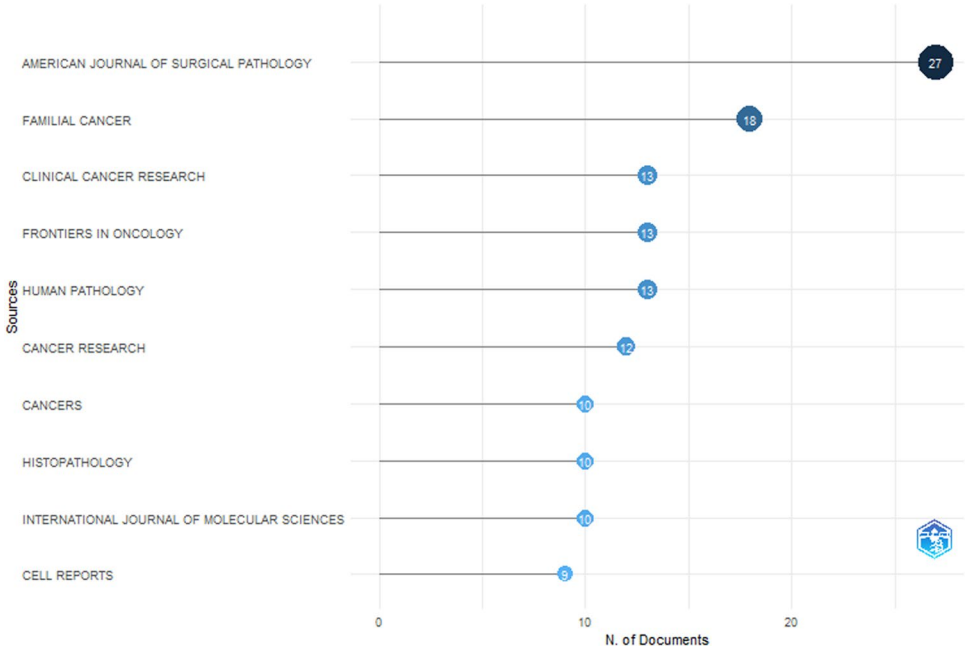
The researcher who conducted most studies on the subject was W.M. Linehan (n = 58, 6.904%) (Fig. 2). W.M. Linehan was also the most-cited author, with 1562 citations. He was followed by P.J. Pollard, the second most cited author, with 1076 citations (Table 2). The highest WoS h index values also belong to the same authors, Linehan (h index: 130) and Pollard (h index: 23).

Table 1 Number of publications, total citations, and average citations by year

Year	Number of publications	Total citation	Mean citation per year	Citable years
2002	3	439.33	19.1	23
2003	11	156.73	7.12	22
2004	7	79.14	3.77	21
2005	14	286.93	14.35	20
2006	25	85.64	4.51	19
2007	22	106.05	5.89	18
2008	23	51.52	3.03	17
2009	22	70	4.38	16
2010	25	60.64	4.04	15
2011	30	88.73	6.34	14
2012	35	118.83	9.14	13
2013	40	61.12	5.09	12
2014	50	62.46	5.68	11
2015	36	60.64	6.06	10
2016	48	81.42	9.05	9
2017	54	29.41	3.68	8
2018	57	24.84	3.55	7
2019	49	59.24	9.87	6
2020	69	21.9	4.38	5
2021	67	20.18	5.04	4
2022	65	5.23	1.74	3
2023	65	2.89	1.45	2
2024*	23	0.22	0.22	1

*Until the end of March

Fig. 1 Most relevant sources



When the countries of the corresponding authors were analyzed, it was found that most studies were produced in the United States of America (USA) (n = 306, 36.429%). The USA was followed by China (n = 108), the UK (n = 81), Finland (n = 33), and France (n = 31). In addition, although there are publications produced in collaboration between different countries (MCP: multiple-country publications), it was determined that more of the articles were produced in a single center (SCP: single-country publications) (Fig. 3).

The most-cited papers are listed in the table below (Table 3). In addition, the most relevant and cited authors, W.M. Linehan and P.J. Pollard, are also included in this list. This is remarkable in terms of the productivity and contribution of the authors to the subject.

There are many affiliations from different countries where the relationship between FH and cancer has been investigated. The University of Helsinki is the most productive affiliation with 138 published articles (Table 4).

Fig. 2 Most relevant authors

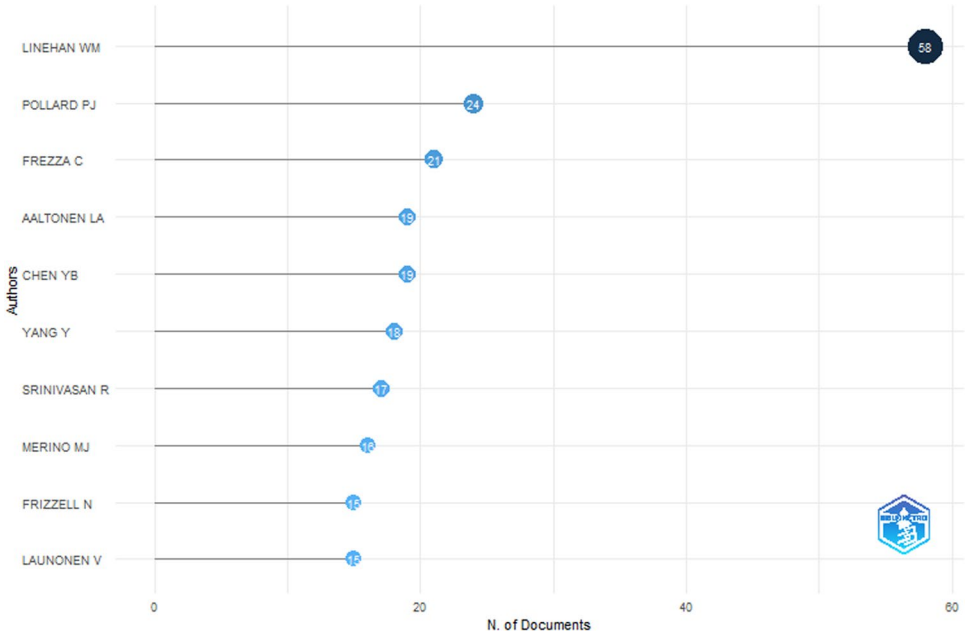


Table 2 Ten most cited authors and citation numbers

Author	Citation count
Linehan WM	1562
Pollard PJ	1076
Zbar B	738
Tomlinson IPM	731
Neckers L	655
Merino M	578
Frizzell N	553
Aaltonen LA	512
Launonen V	510
Olpin S	492

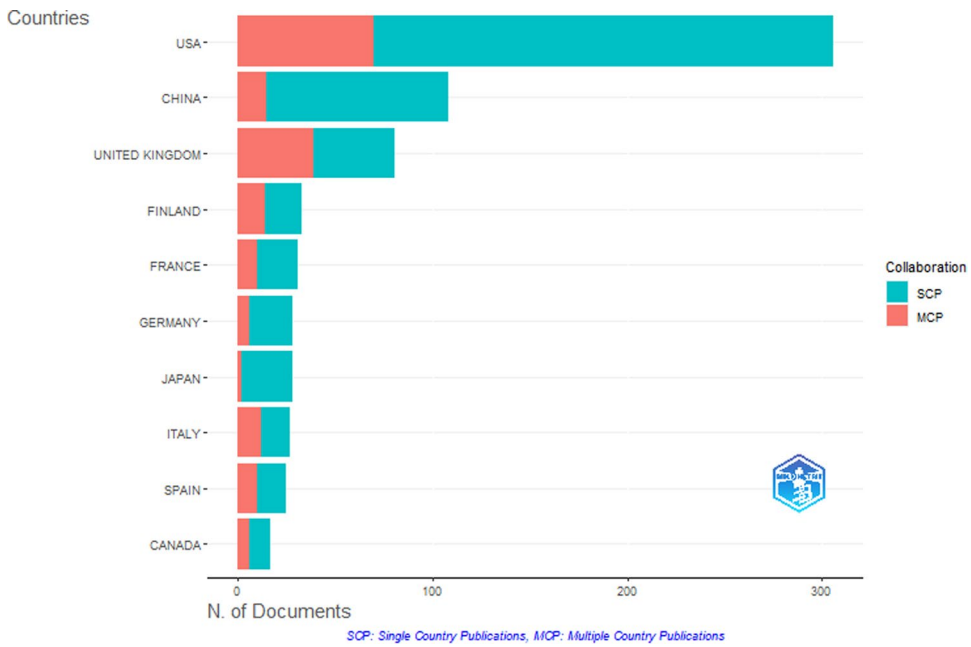


Fig. 3 Corresponding author's countries

Table 3 The most cited papers

Paper	DOI	Total citations
Selak MA, 2005, Cancer Cell	https://doi.org/10.1016/j.ccr.2004.11.022	1532
Tomlinson IPM, 2002, Nature Genet	https://doi.org/10.1038/ng849	1128
Mullen AR, 2012, Nature	https://doi.org/10.1038/nature10642	954
Gao M, 2019, Mol Cell	https://doi.org/10.1016/j.molcel.2018.10.042	948
Linehan WM, 2016, N Engl J Med	https://doi.org/10.1056/NEJMoa1505917	867
Xiao M, 2012, Genes Dev	https://doi.org/10.1101/gad.191056.112	757
Isaacs JS, 2005, Cancer Cell	https://doi.org/10.1016/j.ccr.2005.06.017	723
Pollard PJ, 2005, Hum Mol Genet	https://doi.org/10.1093/hmg/ddi227	681
Brandon M, 2006, Oncogene	https://doi.org/10.1038/sj.onc.1209607	629
Deberardinis RJ, 2012, Cell	https://doi.org/10.1016/j.cell.2012.02.032	582

Keyword co-occurrence analysis was performed to examine the frequency of keywords in articles obtained from the WoS database (Fig. 4). This analysis revealed keywords that were more densely related to each other. Thus, we aimed to determine the current situation and provide researchers with more detailed information on the subject. The word cloud plot revealed that in addition to the keywords we used, the terms "hereditary leiomyomatosis",

Table 4 The most relevant affiliations

Affiliation	Articles
University of Helsinki	138
Center for Cancer Research (NCI)	99
University of Cambridge	88
Memorial Sloan Kettering Cancer Center	71
Fudan University	51
University of Oxford	50
Sichuan University	45
University of Michigan	44
Charles University Prague	42
Shanghai Jiao Tong University	42

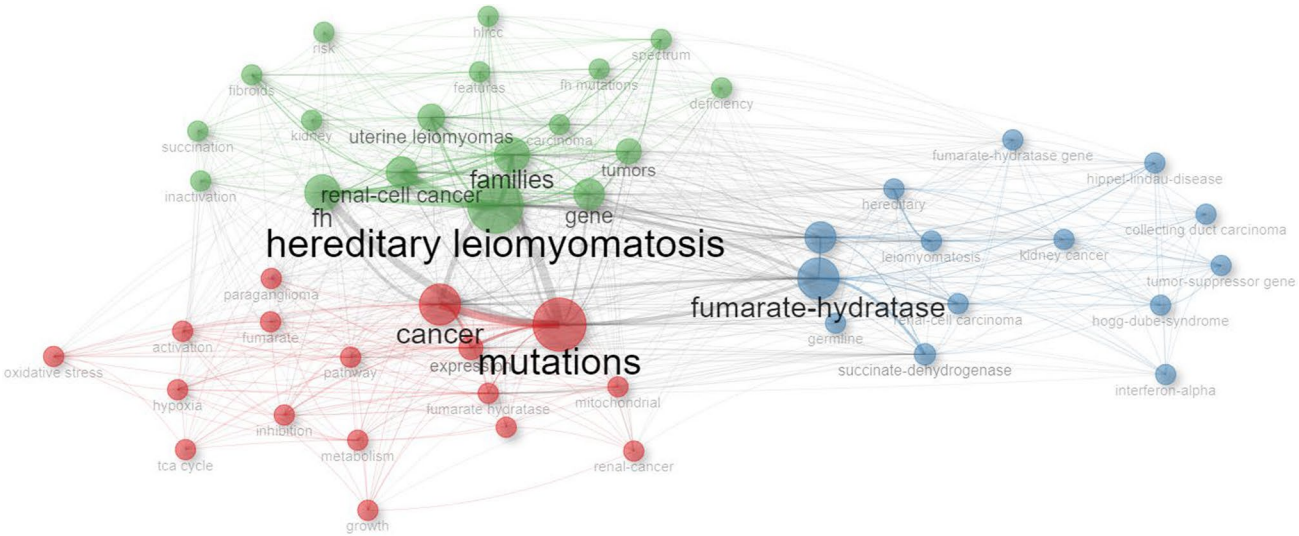


Fig. 4 Co-occurrence network of keywords

"mutations, and "renal-cell cancer" were very common, and the Krebs cycle enzyme, "succinate dehydrogenase", was another frequently found keyword (Fig. 5). SDH, similar to FH, is an important enzyme in energy metabolism and has been frequently studied in cancer research.

The results of our analyses showed that cancer research on FH is largely based on hereditary leiomyomatosis. Understanding the results of studies on this issue is important for revealing the relationship between FH and other cancer types.

The United States Department of Health and Human Services National Institutes of Health (NIH, USA) was the most supportive funding agency, with 168 studies. The publishers with the most articles were Elsevier (n = 184, 21.9%), Springer Nature (n = 133, 15.84%) and Wiley (n = 100, 11.9%). Finally, when the publication languages of the articles obtained from the WoS database were analyzed, five French, five German, four Spanish, two Polish, and one Hungarian articles were found, and all of the remaining articles were published in English.

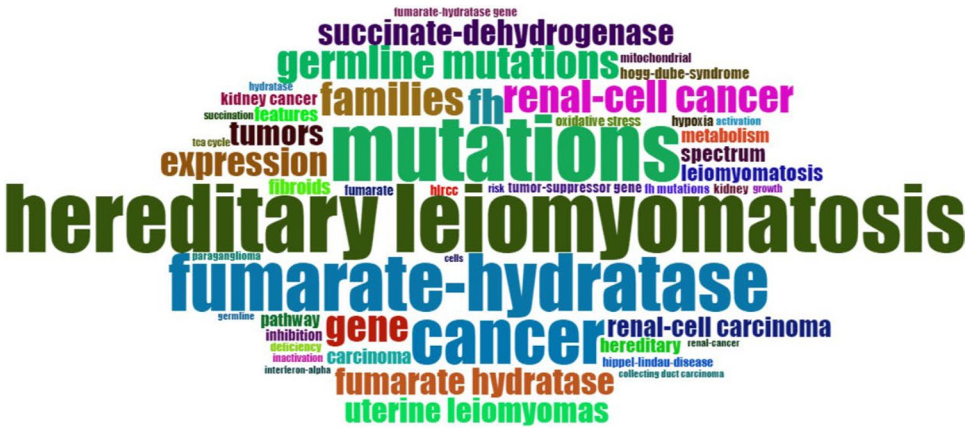


Fig. 5 Word Cloud plot of keywords from FH and cancer publications

4 Discussion

Bibliometric analysis is the evaluation of many parameters, such as publication trends, relevant authors and institutions, examination of citation networks, and the impact of research outputs using statistical and mathematical methods to evaluate various aspects of scientific literature [16]. It is used to explore and analyze large amounts of scientific data. This method utilizes data from the academic literature to reveal the current situation and predictions regarding the dynamics of scientific communication, dissemination of knowledge, and impact of research within and between disciplines. Bibliometric analyses have become crucial for academic institutions, funding agencies, publishers, and researchers to evaluate academic processes and shape strategic decision-making [16, 17]. It is increasingly being used to assess trends and progress in various research areas [18]. One important consideration in bibliometric analyses of our study is the potential bias introduced by limiting the dataset to publications indexed in the WoS database. While WoS is a widely recognized and comprehensive database for tracking scientific literature, it does not include all relevant studies, particularly those published in regional journals, books, or non-indexed conference proceedings. This means that our study has limitations, although it almost completely reflects the current situation in the relationship between FH and cancer research.

Cancer cells exhibit alterations in many cellular processes including energy metabolism. Dysregulation of cellular energetics is a hallmark of cancer [19]. Genetic and epigenetic alterations in Krebs cycle enzymes favor the ability of cancer cells to abandon oxidative phosphorylation and consequently produce many oncometabolites. Mutations in the genes encoding fumarate hydratase, isocitrate dehydrogenase, succinate dehydrogenase, aconitase, and citrate synthase enzymes have been observed in many cancer types [20]. FH is an important Krebs cycle enzyme that has been investigated in cancer in terms of its role in cellular energy metabolism. FH has been found to be mutated in cancers. Some of these mutations can be evaluated as diagnostic, prognostic, and therapeutic parameters for different cancer types. Results supporting this idea have been reported in many studies [8].

The first study of FH and cancer in the WoS database was published in 1991. However, no other study was conducted until 2002, except for one study in 1999. After 2002, the number of studies increased and more than one article was published every year. These data also reflect the general status of energy metabolism studies in cancer and Krebs cycle. Although energy metabolism in cancer was first studied by Otto Warburg in the 1920s, it has been intensively studied since the early 2000s. The data obtained revealed that the research processes were carried out similarly in FH.

Cancer research plays an important role in medicine. In recent years, many studies have been published on the relationship between Krebs cycle enzymes and cancer. In our preliminary analyses of FH, we observed that most studies were related to cancer. Therefore, we performed a comprehensive bibliometric analysis to determine the role of FH in cancer research. In this way, we have presented the current situation in all aspects of the literature in a way that other researchers can benefit from. The results show that the majority of FH-related cancer research has been carried out in patients with hereditary leiomyomatosis. We were able to clearly identify this in WordCloud and co-occurrence analyses. Moreover, in the analyses where the keywords "succinate dehydrogenase" and "mutation" were also prominent, we concluded that FH plays a role in cancer development as a result of inherited mutations and is involved in cancer research, together with other Krebs cycle enzymes.

We found that the studies conducted in the last decade covered a large proportion of the publications on the relevant subject. This shows the scientific value of publications on the relationship between FH and cancer, its potential contribution to clinical practice, and the possibility of further studies in the coming years as a current topic.

5 Conclusion

For many years, extensive research has been conducted to understand the molecular mechanisms of cancer development and progression. These studies have revealed factors such as genetic and biochemical alterations, abnormal signaling pathways, and microenvironmental factors underlying cancer biology. Despite significant advances in cancer research, there is an increasing need to elucidate the complex molecular and cellular processes underlying cancer, identify new diagnostic and therapeutic targets, and improve the quality of life of patients. This will only be possible with further scientific research. In the present study, we report the current status of an important enzyme, FH, in cancer research and demonstrate its potential. Our results will contribute to cancer research, particularly those related to energy metabolism enzymes.

In this study, we conducted a comprehensive bibliometric analysis of FH in cancer research. Our findings underscore the growing scientific interest in FH and its implications in hereditary leiomyomatosis and other malignancies. The observed research trends provide valuable insights into the direction of FH-related studies and suggest potential areas for further research. Future research could benefit from integrating bibliometric analyses with experimental and clinical studies to identify emerging research gaps, prioritize key areas of study, and enhance translational applications. By mapping the evolving landscape of FH research, our study contributes to shaping future research directions and promoting a more targeted approach to understanding the role of metabolic enzymes in cancer.

Author contributions C.Y. design, data analysis, wrote the main manuscript text. S.E.A. Data analysis All authors reviewed the manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Ethical committee approval was not required for this study. No writing assistance was used in the production of this manuscript.

Competing interests The authors declare no competing interests.

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