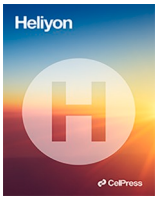
Heliyon 10 (2024) e35686

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Research trend of lung cancer epigenetics research: Bibliometric and visual analysis of top-100 cited documents

Wangzhouyang Lou, Yunsheng Li *

Chun'an County First People's Hospital, Hangzhou, 311700, People's Republic of China

ARTICLE INFO

Keywords:
Lung cancer
Epigenetics
DNA methylation
Non-coding RNA
Bibliometric analysis

ABSTRACT

Background: Lung cancer is a highly prevalent cancer on a global scale and its oncogenic process is driven by the accumulation of multiple pathological events. Epigenetics has gained significant recognition in recent years as a crucial contributor to the development of lung cancer. Epigenetics include processes such as DNA methylation, histone modification, chromatin remodeling, and RNA modification. These pathways lead to enduring alterations in genetic phenotypes, which are crucial in the advancement and growth of lung cancer. However, the specific mechanisms and roles of epigenetics in lung cancer still need to be further elucidated.

Methods: We obtained publications from the Web of Science databases and applied a rigorous search method to filter them. Ultimately, we gathered high-quality publications that had received the highest 100 number of citations. The data were processed and visualized by various bibliometric tools.

Results: The 100 papers had varying numbers of citations, with the lowest being 491 and the most being 6316. On average, each work received 1119 citations. A total of 1056 co-authors were involved in publishing these papers in 59 journals from 185 institutions in 27 countries. The majority of high-caliber research in the subject of lung cancer epigenetics is conducted in advanced countries, with the United States taking the lead in terms of both the quantity of articles produced and their academic influence. The study of DNA methylation has been a longstanding research priority in the discipline. With the development of next-generation sequencing technology in recent years, research related to non-coding RNA has become a research hotspot. Future research directions may focus more on exploring the mechanisms of action of messenger RNA and circular RNA and developing targeted treatment strategies based on non-coding RNA drugs.

Conclusion: We analyzed 100 top lung cancer and epigenetics documents through various bibliometric analysis tools. This study provides a concise overview of the findings from prior research, anticipates future research directions, and offers potential avenues for additional investigation.

1. Introduction

Lung cancer is currently a widespread and growing disease on a global scale [1]. Based on pathologic classification, Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are two of the most prominent, with NSCLC accounting for the vast majority of all lung cancer cases [2]. The majority of individuals with lung cancer are often identified at an advanced stage and have a bleak

* Corresponding author.
E-mail address: yunsheng820121@163.com (Y. Li).

https://doi.org/10.1016/j.heliyon.2024.e35686
Received 15 September 2023; Received in revised form 1 August 2024; Accepted 1 August 2024

prognosis. Despite the rapid advances in medical technology, there is still no satisfactory treatment. Early-stage lung cancer patients can receive surgical treatment, while radiation therapy, chemotherapy and immunotherapy are mainly used for advanced patients and are mostly palliative in nature [3]. The final result of lung cancer is contingent upon timely identification, prompt diagnosis, and expeditious treatment. Insufficient early detection of lung cancer results in a low survival rate for patients, with 86 % of them dying within 5 years after diagnosis [4]. Therefore, continuing to explore the mechanisms of occurrence and development on the basis of previous studies is an endeavor for a long time to come.

Lung cancer is multifactorial, multigenic, and multistage. These events include, but are not limited to, DNA damage, mutation of oncogenes and inactivation of oncogenes. These abnormal factors caused abnormal proliferation of lung epithelial cells, which gradually evolved into precancerous lesions and then progressed to primary cancer. Finally, cancer cells form metastatic lung tumors through metastasis, which further affects the health and survival of patients [5]. The abnormality of the genome may come from gene mutation, homozygous gene deletion, gene amplification and translocation or epigenetic silence. These genomic changes not only affect the function of cells at the molecular level but also directly affect the normal operation of the cell pathway, which further drives precancerous cells to evolve in the direction of tumour development [6]. Thanks to the persistent efforts of academics throughout the world, several oncogenes and tumor suppressor genes have been identified. Moreover, there has been a notable progress in the therapeutic strategy for lung cancer by employing immunotherapy [7]. However, the challenge remains that the genome picture of individual lung cancer is not static but presents spatial and temporal diversity. In the process of cancer development, the genomic instability within the tumour leads to the continuous evolution of tumour cell clones with different genomic profiles and molecular characteristics. Epigenetic modifications significantly influence the behavior and features of tumor cells in this process [8].

Epigenetics pertains to the inheritance of gene expression or cellular traits resulting from modifications in genetic pathways that are independent of changes in gene sequences [9]. Epigenetic changes regulate genetic changes by directly changing the structure of chromatin or indirectly creating protein binding sites for chromatin [10]. More efforts have been made by previous scholars to study epigenetic mechanisms in lung cancer [11]. The early events of lung cancer include the inactivation of tumour suppressor genes caused by hypermethylation of p16INK4a, RASSF1a, APC, and other promoters [12]. Promoter hypomethylation or methylation deletion is more common in progressive and advanced lung cancer [13]. Markedly abnormal histone acetylation levels are also a distinctive feature in lung cancer tissues [14,15]. Furthermore, researchers have discovered that non-coding RNA fulfills many functions. The levels of some non-coding RNAs, such as microRNAs, are markedly increased in lung cancer tissues [16]; Research indicates that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and long-stranded non-coding RNA (HOTAIR), along with other long non-coding RNAs (lncRNAs), have a role in the regulation of proteins and structures inside lung cancer tissues [17]; Many microRNA and DNA methylation interactions have even been found [18,19]. A comprehensive examination of the epigenetic pathways underlying lung cancer is crucial for the advancement of early diagnostic and prognostic evaluation tools, as well as the development of targeted pharmaceuticals. In recent years, the number of related studies has increased dramatically, reflecting the importance and research enthusiasm of this field. However, in the face of the massive influx of research results, there is an urgent need for a systematic and scientific approach to assess the key advances of these studies and summarize their emerging trends in lung cancer pathogenesis and therapeutic strategies.

In 1969, Alan Pritchard, a distinguished intelligence scientist, initially proposed the notion of bibliometrics, which he described as the utilization of mathematical and statistical techniques to assess and examine published research in a particular topic [20]. Bibliometric analysis helps to assess the quality and impact of research more objectively, and by quantitatively analyzing existing research, it is possible to predict future research prospects and directions [21,22]. In bibliometrics research, citation analysis is the most widely used method [23]. The Web of Science (WOS) Core Collection (WOSCC) is the predominant database utilized for bibliometric analysis due to its extensive collection of published research of diverse quality. We conducted a rigorous analysis of 100 prominent publications using visualization methods to provide a concise overview of the present state of research and identify potential future avenues.

2. Methods

2.1. Data sources and search strategies

The documents of this study come from the WOSCC database, and we chose the WOSCC database for the following reasons. First, because it is the most commonly used database in bibliometrics, the citation report provided by the WOSCC database in the retrieval process can verify the accuracy of the econometric analysis results. The literature information obtained by the WOSCC database can be analyzed directly through the current mainstream metrology tools, eliminating the potential data loss problem. The data utilized in this study were acquired from the Science Citation Index Expanded (SCIE), ensuring the high caliber of journals and publications [24]. Time span for inclusion of articles is January 1, 1998 to March 1, 2023. The manuscript types are research article and review, and the language is English. The search strategy is: TS=("pancoast syndrome" "lung tumour*" OR OR "lung squamous cell carcinoma" OR "pulmonary neoplasm*" OR "lung adenocarcinoma" OR "adenocarcinoma of lung" OR "NSCLC" OR "none small cell lung cancer" OR "non-small cell lung cancer" OR″non-small cell lung carcinoma" OR "non-small lung cancer" OR "large cell lung cancer" OR "small-cell lung cancer" OR "SCLC" OR "small-cell lung carcinoma" OR "bronchial neoplasm*" OR "lung cancer*" OR "lung neoplasm*") AND TS=(epigenetic OR "DNA methylation" OR "chromatin remodeling" OR "genomic imprinting" OR OR "histone glycosylation" "histone acetylation" OR "histone modification" OR "histone phosphorylation" OR "ubiquitination of histone" OR "histone methylation" OR "RNA methylation" OR "lncRNA" OR "antisense RNA" OR "microRNA" OR "miRNA" OR "pri-miRNAs" OR "tiny RNA" OR "RNA modification" OR "non-coding RNA" OR "RNA hydroxymethylation" OR "riboswitch" OR "RNA acetylation"). We went through all the search results

one by one, sorted the articles according to how many times they were cited, eliminated irrelevant literature, and finally identified the top 100 high-quality studies, and gave the final results to all the authors to view obtained.

2.2. Data collection

To avoid data bias, we downloaded and validated the raw data from WOSCC on the same day and performed subsequent data processing analysis. They were extracted from plain text files with "fully documented and cited references". According to the instructions for use, the data information was imported into the "Bibliometric Package 4.0.2″ of the R software (version 4.2.3) for storage, and key information such as title, country, institution, journal, keywords, authors, and were imported into Microsoft Office Excel (version 2019).

2.3. Bibliometric analysis

Bibliometrics software can be used for data processing and visualization. EXCEL is utilized for tallying the quantity and occurrence of citations in papers, as well as creating histograms for published documents and their frequencies; VOSviewer (version1.6.19) and Citespace (version6.2.R2) are two other mainstream tools in the field of bibliometrics, which are used for subsequent visual analysis. VOSViewer software is used to draw visualization networks and related density visualization diagrams of keywords, countries, organizations, and co-citations; Citesspace software is used to search for outbreak keywords, construct keyword visualization time charts, draw journal superposition maps, and R is used to draw national cooperation and distribution maps. In the visualization network created using VOSviewer and Citespace software, The size of a node has a direct relationship with the number of occurrences, while the connections between nodes indicate cooperation or linkage between them.

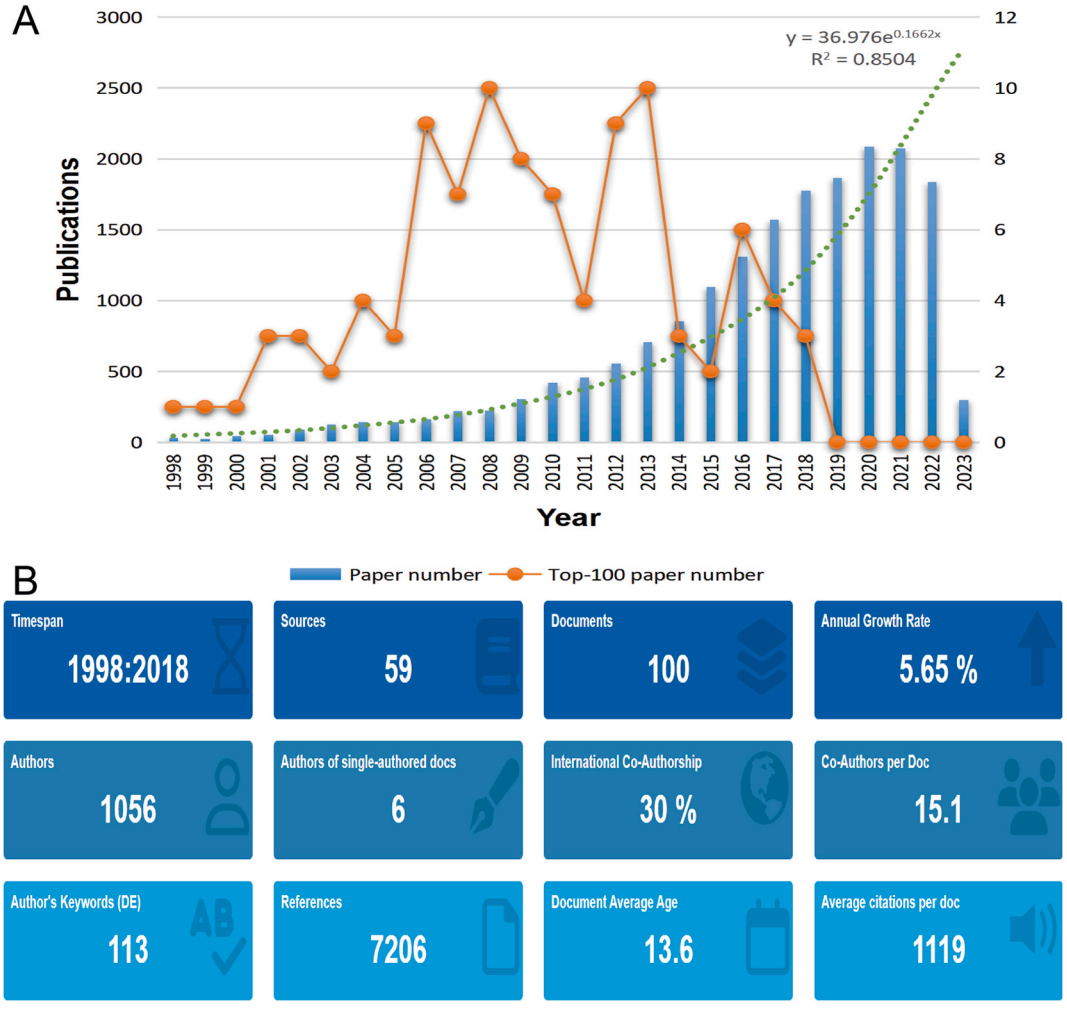


Fig. 1. Analysis of published papers. (**A**) Trends in lung cancer and epigenetic research and year distribution of the 100 most cited papers. (**B**) General information on the 100 most cited papers related to lung cancer and epigenetics.

3. Result

3.1. An overview of publications

Through the retrieval strategy mentioned in the methods section, we retrieved 18480 published articles (Fig. 1A). Subsequently, a more rigorous selection process was used to these articles, resulting in the identification of the top 100 articles based on their citation count. The average number of citations for these articles was 1119, with a range spanning from 491 to 6316. The publications most commonly referenced were published between 2005 and 2014, with the highest number of citations occurring from 2008 to 2013. This suggests that considerable advancements have been achieved in the study of epigenetics in relation to lung cancer during this time frame. The top 100 articles are from 1056 co-authors in 185 institutions in 27 countries and published in 59 journals. These articles cited 7206 articles in 1030 journals (Fig. 1B). Table 1 is a compilation of the 10 articles that have received the highest number of citations. The three most cited articles are "MicroRNA signatures in human cancers", published by Calin, GA, in the journal *Nat Rev Cancer* in 2006, "Oncomirs-microRNAs with a role in cancer" by Esquela-Kerscher, A in *Nat Rev Cancer* in 2006, and "MicroRNA therapeutics: towards a new era for the management of cancer and other diseases" by Rupaimoole, R in *Nat Rev Drug Discov* in 2017.

3.2. Visual analysis of keyword

The article's keywords indicate the primary components of a study, and by creating a co-occurrence map of these terms, one can depict the research focal points and current trends in the area. By extracting the keywords that appear three or more times in the article, we get 88 keywords for visual analysis. As can be seen from Fig. 2A and B, the larger the circle where the keyword is located represents a higher frequency and is more suggestive of the main research themes in the field. This suggests that among the top 100 publications included in this study, the five most frequently used keywords are "lung cancer", "expression", "cell lung cancer", "downregulation", and "gene expression". In Fig. 2B, the colour changes from dark blue to bright yellow over time. The keywords "metastasis", "epithelial-mesenchymal transition", "tumour suppressor", and "mir-200 family" appeared later, which shows that new research directions have emerged in this field recently. As shown in Fig. 2C, nine clusters were separated, with topics including "human lung cancer", "early diagnosis", "DNA methylation marker", "tumour suppressor".

Topic trends can be indicative of research trends over a long period of time. Fig. 3 shows the top thematic terms in terms of frequency. The blue line indicates the average duration of occurrence and larger circles represent a higher number of occurrences. It can be found that the longest duration is DNA methylation, while most of the other thematic trends have a duration of about 5 years.

3.3. Analysis of journals

Nat Rev Cancer had the highest overall number of citations and the highest average number of citations per publication, followed by *Cancer Res and Nature*(Table 2). We draw the cited map of journals through the VOS viewer, set the citation number of 20 as the minimum threshold, and 75 journals appear for analysis, as shown in Fig. 4A. Citation analysis can also analyze the relationship between published and cited journals. We used the superposition diagram of periodicals to analyze the relationship between citing journals and cited journals (Fig. 4B). Journals on the left represent exerting a citation, journals on the right represent being cited, and connecting lines indicate citation relationships between journals. The figure shows that articles whose disciplines are biology, molecular science, and immunology mainly cite articles from the disciplines of molecular science, biology, and genetics.

3.4. Analysis of co-citation references

When one published article references another published piece, a co-citation connection is formed and the two articles are connected. There is a direct relationship between the number of co-citations and the impact. Similarly, we employed VOSviewer to create a co-citation map of the literature. The criterion for the number of citations was established at 10. A total of fifty-one journals were

Table 1
The top 10 most cited papers related to lung cancer and epigenetics.

Ranking	Title	Journal	Publishing year	Citations
1	MicroRNA signatures in human cancers	Nat Rev Cancer	2006	6319
2	Oncomirs - microRNAs with a role in cancer	Nat Rev Cancer	2006	5840
3	MicroRNA therapeutics: towards a new era for the management of cancer and other diseases	Nat Rev Drug Discov	2017	2852
4	Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases	Cell Res	2008	2836
5	RAS is regulated by the let-7 MicroRNA family	Cell	2005	2834
6	Comprehensive genomic characterization of squamous cell lung cancers	Nature	2012	2642
7	Unique microRNA molecular profiles in lung cancer diagnosis and prognosis	Cancer Cell	2006	2498
8	Causes and consequences of microRNA dysregulation in cancer	Nat Rev Genet	2009	2433
9	Comprehensive molecular profiling of lung adenocarcinoma	Nature	2014	2078
10	microRNAs as oncogenes and tumour suppressors	Dev Biol	2007	2055

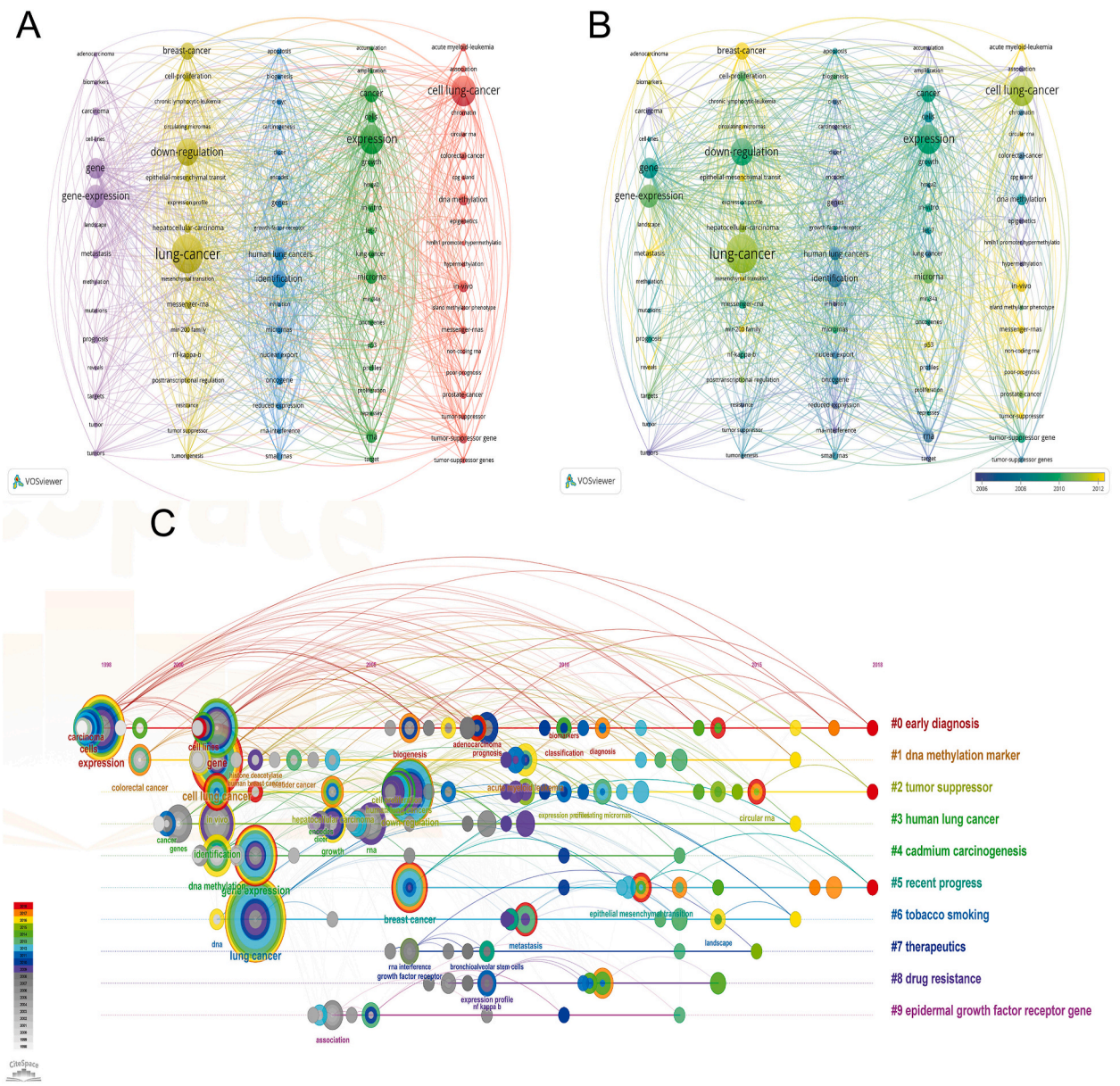


Fig. 2. Keywords related to lung cancer and epigenetics. (**A**) Mapping of the keywords that occurred at least 3 times. (**B**) Visualization of keyword that occurred at least 3 times overlays drawn by the VOSviewer. (**C**) Timeline graph of keywords related to lung cancer and epigenetic research between 1998 and 2018.

included for co-citation analysis. Fig. 5A displays the co-citation network of references. Each circle symbolizes a document, with the magnitude of the circle representing the quantity of citations it has garnered. The densely populated regions in Fig. 5B provide a more pronounced visual representation of the sources with greater citation rates.

3.5. Analysis of countries

The 100 most influential studies on lung cancer and epigenetics are spread across 27 different nations(Fig. 6A). The countries of all authors appearing in the articles were taken into account, with the United States having the highest number of participating papers [78]. It was followed by nine articles from China and eight from Italy. Fig. 6B and C shows a visual network of international cooperation. International cooperation plays an important role in advancing research. Most of the partnerships revolve around developed countries, most notably the United States, while those between other countries are relatively weak, indicating the dominance of the United States in international cooperation in this area.

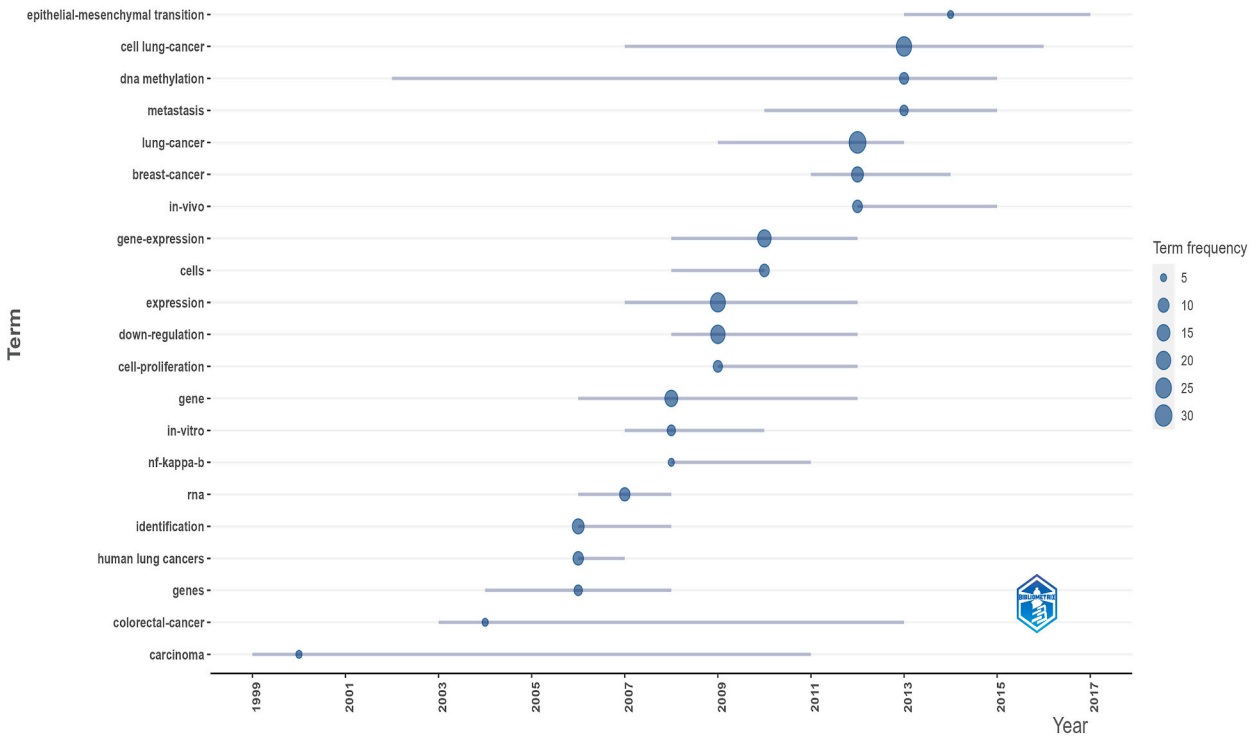


Fig. 3. Trends in research topics over time.

Table 2
The top 10 journals with the most Citations among the 100 most cited papers.

Ranking	Journals	Citations	Documents	Average Citation/ Publication
1	NATURE REVIEWS CANCER	18432	8	2304
2	CANCER RESEARCH	14066	13	1082
3	NATURE	5600	3	1866.7
4	NATURE REVIEWS DRUG DISCOVERY	5579	4	1394.75
5	CELL	4961	3	1653.7
6	NATURE GENETICS	4802	5	960.4
7	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	3940	5	788
8	CANCER CELL	3166	2	1583
9	NATURE REVIEWS GENETICS	3119	2	1559.5
10	CELL RESEARCH	2833	1	2833

3.6. Analysis of organizations

A total of 185 authors' organizations participated in the publication of the article, Fig. 7A shows the ten organizations with the highest number of participating contributions out of 100 high-quality papers. Among them, HARVARD UNIV ranks first in the number of published studies and most cited, followed by OHIO STATE UNIV and UNIV TEXAS MD ANDERSON CANC CTR. Almost all of the most relevant institutions are from the United States. Fig. 7B shows the partnerships between the various organizations. We set the minimum number of collaborations between organizations to 2 to observe the connections between organizations. It can be seen that OHIO STATE UNIV, HARVARD UNIV, and YALE UNIV are at the center of the institutional collaboration network.

3.7. Analysis of authors

Through data collation, 488 authors contributed to the article, and the top 10 authors with the most relevance are shown in Fig. 8A. Croce, CM is the most relevant authors, followed by Getz, G. and Meyerson, M. The threshold for the number of collaborations between authors is set to 2, and Fig. 8 illustrates some of the inter-author links with collaborative relationships. Croce, CM, Calin, GA, and Slack, F have a very close relationship.

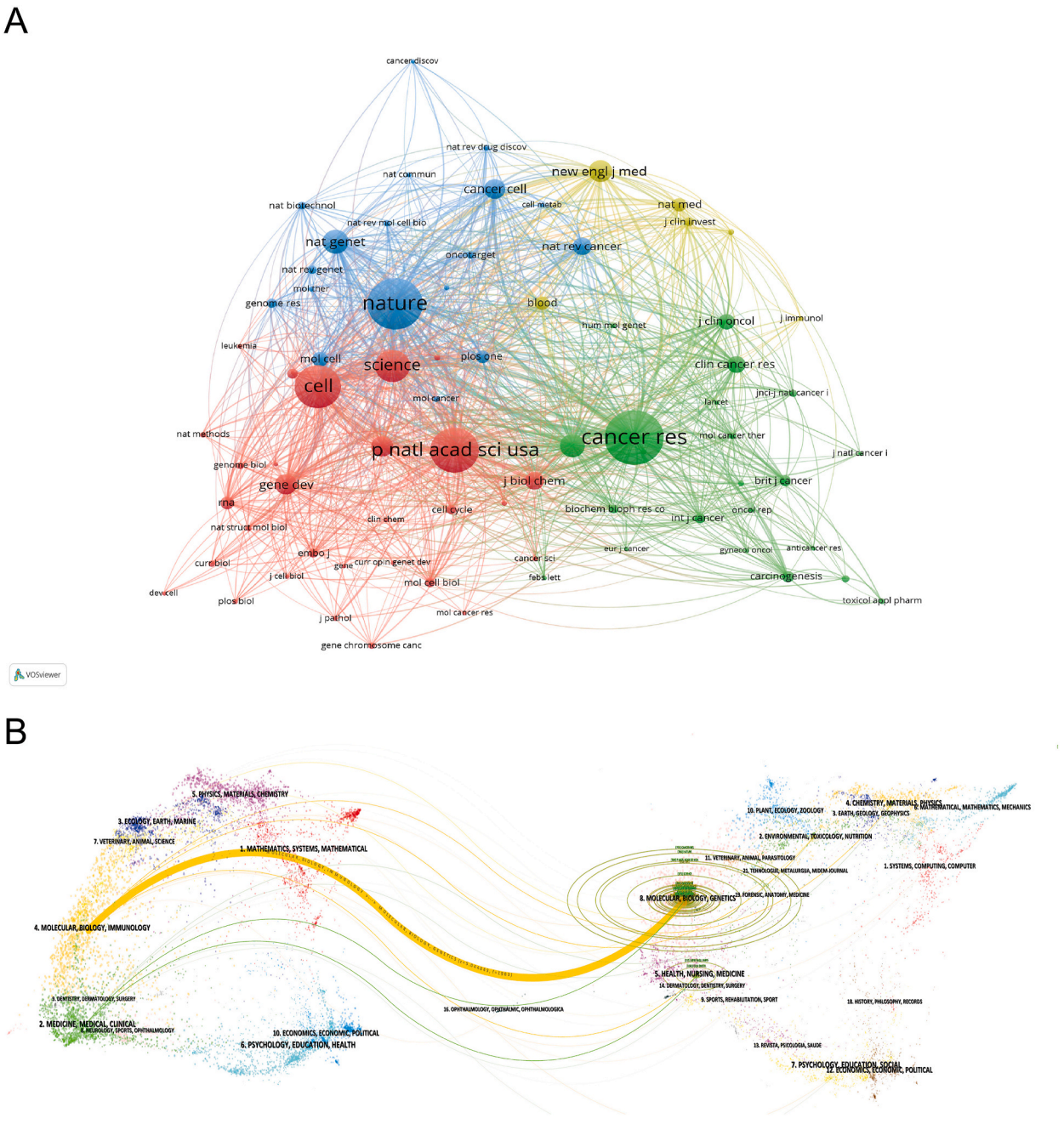


Fig. 4. Analysis of journals. (**A**) Visual analysis of cooperative networks between journals. (**B**) Double image overlay of journals.

4. Discussion

Lung cancer has been more prevalent worldwide and is currently considered one of the most frequent malignant tumors. Most lung cancer patients are discovered at an advanced stage of the disease, resulting in similar rates of both mortality and morbidity among persons with lung cancer [25]. Despite the existence of several therapies for lung cancer, they encounter substantial obstacles due to the absence of a precise and universally accepted criterion for the early detection of lung cancer, and the majority of treatments do not provide a cure [26,27]. Prior research has demonstrated that the development of lung cancer is caused by the accumulation of several variables, such as permanent genetic alterations and dynamic genetic changes in the absence of DNA sequence modifications [28]. The non-DNA sequence changes are called epigenetic changes. The research of epigenetics in relation to lung cancer has shown a significant and rapid growth in recent years. However, there are a large number of related research articles, so it is necessary to comprehensively evaluate the important achievements in this field with scientific and practical methods.

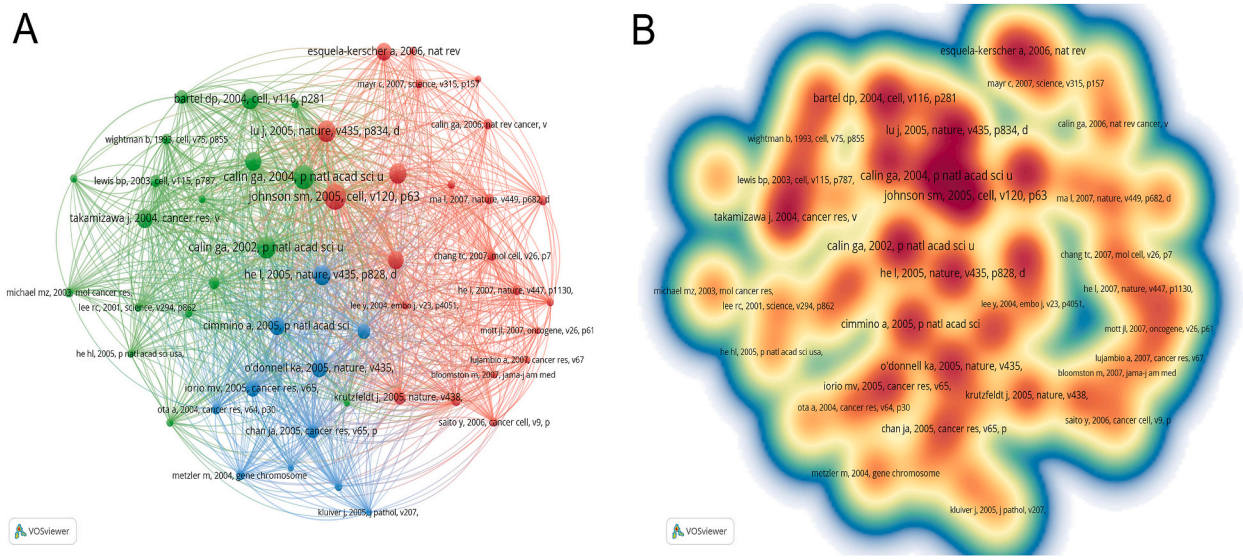


Fig. 5. Visualizaiton mapping of co-citation references. (**A**) Network visualization map. (**B**) Density visualization map.

Bibliometrics analysis originates from the field of information science. With the progress of the times, computers and the internet promoted bibliometrics to become an independent science major, which scholars in various fields widely use [29]. Bibliometric analysis and review articles enable the evaluation of the present condition and constraints of previous research findings. The literature review concentrates on the substance and offers a comprehensive analysis and subjective summary of the study, relying on a limited number of well selected sources. The objective of this bibliometric analysis research is to gather a comprehensive collection of publications from various sources in the subject of epigenetics of lung cancer, with the aim of identifying and selecting the top 100 most impactful articles. Objectively measure and evaluate the research results, quickly grasp the critical research hotspots and future research trends, and provide a reference for academic research.

As shown in Fig. 1, the research in the epigenetics of lung cancer is increasing rapidly yearly. Among the 100 top-ranked literature, the period is from 1998 to 2018. The majority of the publications span from 2006 to 2014, indicating a remarkable advancement in epigenetic research of lung cancer in recent years. These findings have gained widespread recognition among scholars. High-quality journals usually have high editorial standards and a rigorous review process to ensure that the articles published are of high scholarly value and quality, and also reflect the quality of the research. 40 % of the articles were heavily cited by subsequent scholars, with a total of more than 1000 citations, and these high quality articles are published in some of the top journals such as *Nat Rev Drug Discov* and *Nat Rev Cancer*.

Since the first article by Belinsky, SA, in 1998, it has been cited 784 times, the first article reporting methylation in the top 100 literature. The researchers discovered that carcinogens have the ability to cause abnormal methylation in the promoter region of the p16 (INK4a) tumor suppressor gene. This could potentially be an initial occurrence in the development of lung cancer and, to some degree, can be used to identify and forecast the advancement of lung cancer [30]. The most frequently cited is the review paper written by Calin, GA, in 2006, which was later quoted by many scholars. As of March 1, 2023, the number of citations was as high as 6316. This work presents a comprehensive analysis of the possible mechanisms by which changes in short RNA molecules might influence the development and advancement of cancer in humans. Scientists can employ the miRNA expression profile to predict the diagnosis, staging, prognosis, and treatment of cancer [31].

Keyword analysis of papers can help researchers find research patterns and anticipate future paths. According to the statistics on keyword trends, the data reveals that DNA methylation has the longest study duration. This suggests that DNA methylation has consistently been a primary area of attention in epigenetic research. DNA methylation refers to the addition of a methyl group to the 5-carbon position of cytosine in the genome, leading to the formation of 5-methylcytosine. Many cancer cells have a prevalent characteristic of abnormal DNA methylation [32,33]. In 2001, scholar Esteller,M studied the methylation profile of cancer genes [34]; the team found hypermethylation in the promoters of 12 genes, including p16, p15, p14, p73, and APC, which represent hundreds of tumour types. DNA methylation levels are significantly and differentially expressed in lung cancer tissues. It promotes cancer progression by silencing the expression of oncogene promoter regions through methylation levels. Intracellular DNA methylation at a high level plays a crucial function in lung cancer, serving as both an early event and a critical element in its progression [35]. Three types of DNA methyltransferases (DNMT) have been discovered to facilitate DNA methylation at cytosine. DNMT1 is primarily expressed at elevated levels in early-stage lung cancer tissues, and its direct activity results in decreased expression levels of numerous genes implicated in the development of lung cancer, such as CDKN2A and RASSF1A [36]. DNMT3a and DNMT3b initiate the creation of a fresh methylation pattern by specifically targeting unmethylated cytosine CpG sites. This process is strongly associated with the transformation of cancer cell lines and the enhancement of transcriptional activity of promoters. This targeted methylation activity not only impacts the expression pattern of genes but also directly influences the proliferation and differentiation of cells and facilitates the

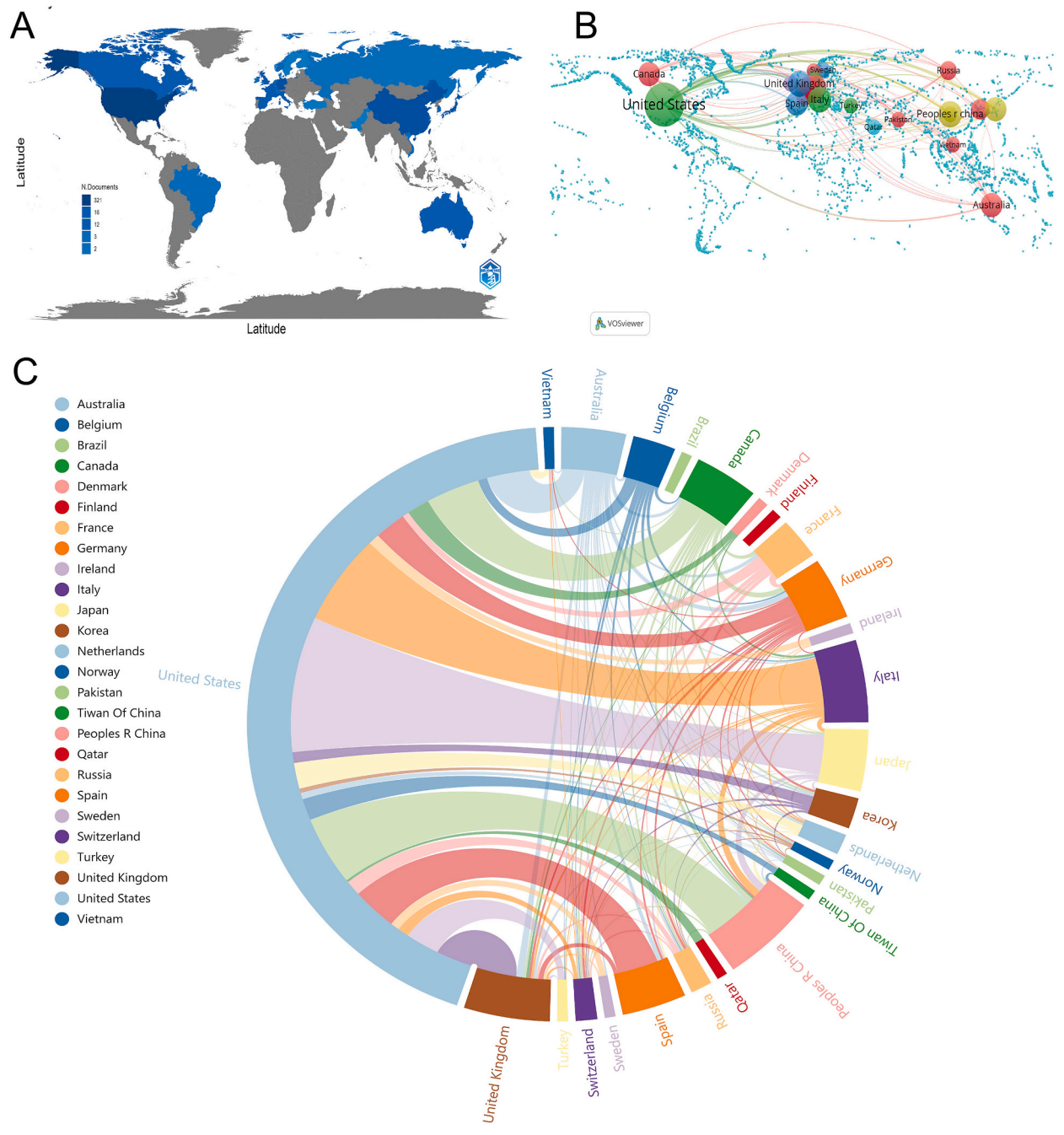


Fig. 6. Distribution and linkage of country composition related to lung cancer and epigenetics research. (**A**) Distribution of publications by country. (**B**) Visual map of international research collaborations in original articles. (**C**) Chord diagram evaluating international collaboration networks.

formation of tumors [37,38]. Furthermore, it was shown that several genes implicated in cellular function had significant methylation levels with the progression of lung cancer, including CDKN2A and PTPRN2 [39]. In the realm of scientific investigation, researchers have achieved notable progress in the comprehensive analysis of DNA methylation. The researchers have discovered specific molecular markers of methylation that play a critical role in the behaviour of cancer cells. Multiple studies have shown that the detection of hypermethylation in the promoters of the p16INK4A and CDH13 genes in blood can serve as a diagnostic technique for the early identification of lung cancer [40]. Furthermore, advanced detection techniques like PCR-SERS are employed to accurately measure methylation levels in plasma [41].

Recently, new terms have arisen, including non-coding RNA and epithelial-mesenchymal transition (EMT). Scientists have identified a new kind of RNA that does not code for proteins and has the potential to either promote or hinder the growth of cancer cells.

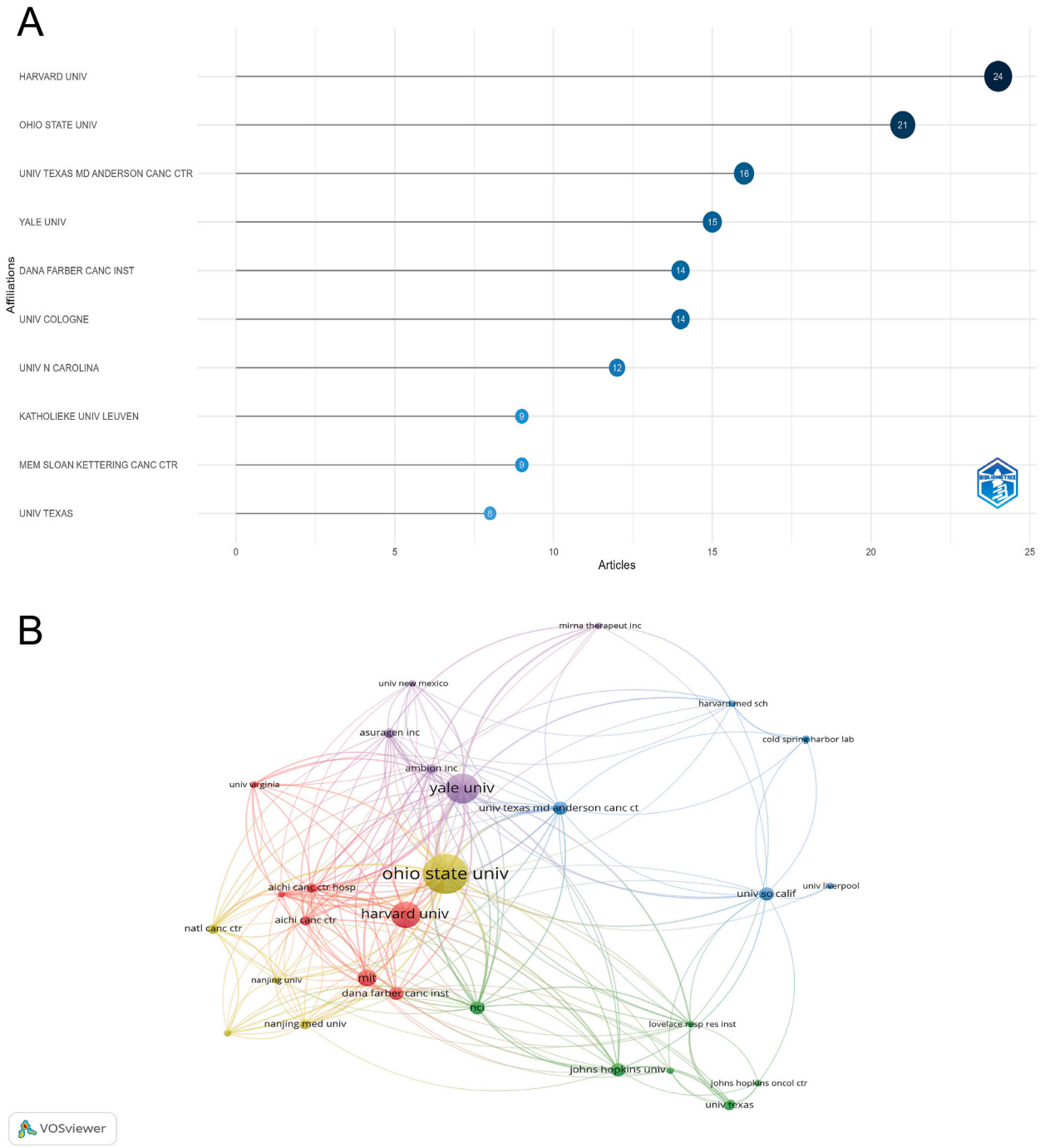


Fig. 7. Analysis of organizations. (**A**)The 10 most relevant institutions among the 100 top publications. (**B**) Co-authorship of the institutional network visualization map.

Moreover, the distinctive manner in which it is expressed in lung cancer may be employed for the purpose of diagnosing and predicting the course of the disease, as well as for identifying possible targets for the development of precise treatments [42–44]. With the advancement of science, high-throughput technology has helped scholars to make important progress in this field. Zhang L's analyzed the differences between two subtypes of squamous and adenocarcinoma of the lung at the individual cell level by single-cell sequencing technology [45], or comprehensively analysing the prediction and treatment of lung tumors through omic technologies (transcriptomic and proteomic technologies, epigenomic technologies and metabolomic technologies) [46]. Researchers have successfully assessed the degree of miRNA expression in both normal and tumor tissues using different genetic methods. MiRNA

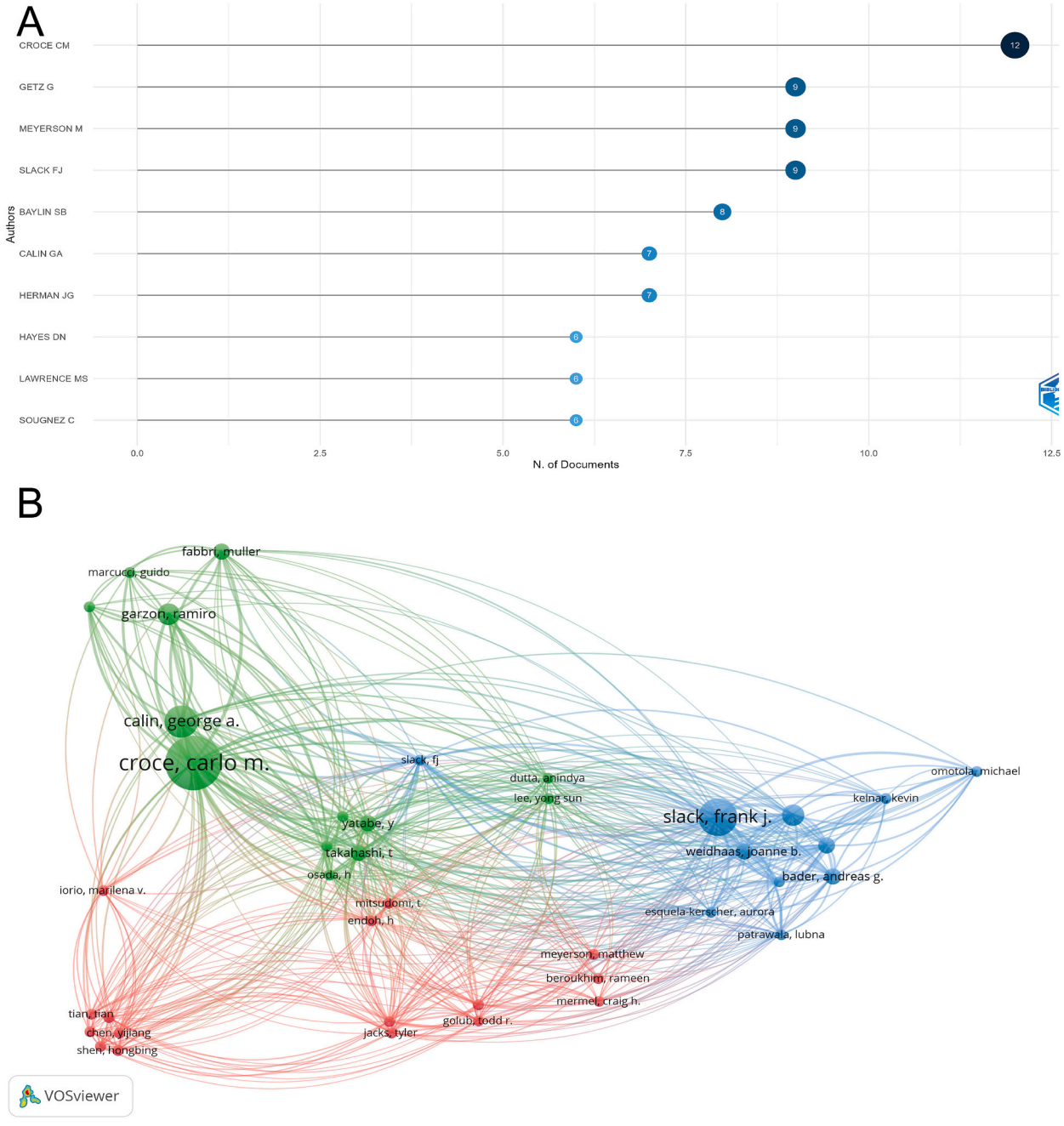


Fig. 8. Analysis of authors. (**A**) The 10 most relevant authors among the 100 top publications. (**B**)Author Collaboration Network Visualization Map.

expression patterns may be used to categorize several types of cancer, including lung cancer [47]. Additionally, miRNA may have a distinct function in this process. For instance, miRNA found in the amplification area of the cancer cell genome can facilitate the development of cancer, but miRNA placed in the absent chromosome of the cancer cell functions as a gene that suppresses tumor growth [48–50]. Even in their findings published in 2007, Fabbri M et al. talked about the down-regulation of miRNA-29 family levels in cancerous tissues, which can target DNA methyltransferases to normalize methylation in NSCLC [51]; This work establishes a foundation for the therapeutic approach to lung cancer that is centered around miRNA. Furthermore, both miRNA and lncRNA have a crucial function in regulating metastatic lung cancer cells. MALAT1 is the first identified LncRNA biomarker that has been discovered to be a negative prognostic predictor for NSCLC [52]. Many differentially expressed lncRNA have been identified, and these lncRNA play a role through tumour drive or tumour inhibition, respectively [53]. EMT is a recently explored area in the ongoing investigation of lung cancer. Recent research has demonstrated that EMT is the primary mechanism responsible for cancer cell invasion, metastasis,

and resistance to drugs [54,55]. Some non-coding RNA can regulate EMT in NSCLC [56–58]. For instance, the levels of miR-27b expression have an impact on the movement, growth, and change in cell structure from epithelial to mesenchymal in NSCLC tumor cells by specifically targeting Snail [59]. MiR-4739, a genetic factor that naturally drives cellular activity, causes the transition of mesenchymal cells and the invasion of NSCLC epithelial tissue through the Wnt/β-catenin signaling pathway [60]. This evidence suggests that there may also be a synergistic or inhibitory relationship between two or more epigenetic mechanisms.

In recent years and the next few years, more work has tended to optimize drug targets, improve pharmacological effects, achieve accurate lung cancer treatment, and even enhance drug resistance in lung cancer tissues [61]. With the help of single-cell omic technology, combining transcriptomic, proteomic and epigenomic data, it is expected that more personalized and accurate predictive targets will be developed. RNA expression patterns have use not only in diagnosing or prognosticating various subtypes of lung cancer [62]; recent studies have shown that significant breakthroughs are made in targeted therapy strategies based on miRNA drugs [63], even many miRNAs targeting drugs have been successfully introduced into clinical trials. Epigenetic targeted drugs should be combined with chemotherapy, immunotherapy or targeted therapy. Furthermore, scientists will conduct additional investigations into the comprehensive patterns of gene expression across the entire genome and the specific expression characteristics of non-coding RNA in different tissues. They will also explore the discovery and potential functions of other types of non-coding RNA, such as Circ RNA and long non-coding RNA. Additionally, they will further explore other mechanisms related to epigenetics in the future. We believe that with the future popularization of single-cell omic and even spatial transcriptomics technologies, the epigenetic expression profiles of individualized lung cancers may become more complete.

It is clear from the results that out of the 100 papers, the United States was involved in publishing the most research, with more collaboration with other countries. The United States cooperates more closely with Japan, Italy, and China than other countries. Scholars worldwide have widely recognized American research in this field. In addition to the 78 publications published by the United States, with 90300 citations, China, Canada, and other countries have also made significant contributions in this field. China has posted nine papers, with 8760 cited, ranking second. Then Canada published six articles, which were cited 8616 times. However, with the exception of the United States, there are fewer links between countries, and most of them are limited to developed countries, which indicates that further international cooperation is needed to promote the development of research.

Due to the fact that the United States has the largest share of the top 100 publications, most of the institutions belonging to these articles are from the United States, especially among the ten most relevant institutions; almost all of them are American institutions, of which Harvard University is the most frequently cited institution. In the cooperative network of various organizations around Yale University, Harvard University, and Ohio State University, other institutions also have a certain degree of connection. Among the top 100 articles, many researchers have outstanding achievements in this field, and Croce, CM scholar from Ohio State University, is the most relevant author. Croce, CM contributed articles in the WOS database, with 2417 articles. The Center has been steadily conducting epigenetic research on lung cancer for the past 20 years and has produced scientific results that have been cited 361582 times. Calin, GA of University of Texas Health Science Center Houston is a high level researcher with an h index of 130. WOSCC has included 556 articles that he has co-authored and has been cited 115023. Calin, GA, has a stable cooperative relationship with Croce, CM. The two authors are highly cited researchers in Cross-Field lung cancer and cell biology. In addition, there are many outstanding authors, most of whom work in oncology and cell biology, mostly from well-known institutions in the United States. Most of these authors conduct collaborative research through their institutions, suggesting that research in this area is concentrated among a certain group of collaborators.

There are some limitations in this study. First, all the documents retrieved in this paper are from the WOS database. Although we repeatedly adjust the search format, we inevitably need help finding excellent articles. Furthermore, historical writings are typically referenced due to their longstanding presence in the public domain. Subsequent writers are inclined to acknowledge works that have received significant attention in the past. Therefore, the number of citations alone cannot sufficiently gauge the depth and excellence of the piece. To solve this problem, we count the influence of the citation rate of these 100 top articles to reduce the time deviation. The citation rate is the average number of citations that each paper receives each year, which indicates its yearly scholarly impact [64,65]. In addition, the direct problem caused by this phenomenon is that this study has not been included in the research since 2018, and there is no lack of high-quality research results after 2018. Still, it has not been widely cited because of its short time or has yet to be found by the majority of scholars. Therefore, it does not appear in this top 100 paper. However, although the articles from 2019 to 2023 are not included, most of the high-citation articles in this year range are in the predicted research direction. Many research extensively investigate non-coding RNA, and other studies on non-coding RNAs [66] have also garnered significant attention from scholars [53,67]. The research tendency of epigenetics of lung cancer is to combine with modern technology, from experimental results to constructing computer models based on intelligent algorithms [68–70]. To develop supersensitive sensors for detecting non-coding RNA in cancer tissues [71–73]. Improve new molecular characterization strategies in addition to tumour DNA sequencing, including epigenetic analysis, multigroup analysis and single-cell sequencing, to find more possible markers [74–76]. In addition, it also includes research on drug development based on epigenetics and optimization of drug treatment strategies [77,78]. Although scholars have made many efforts in these directions, there is still a lot of room for exploration, and this is still a research hotspot for a long time. Given the above problems, it is necessary to continuously pay attention to the scientific research achievements in this field and keep abreast of the latest research trends in the next few years.

In our analysis of studies on lung cancer and epigenetics, we have effectively utilized a range of tools such as R software, Citespace, VOSviewer, and Excel. This study is the inaugural attempt to conduct a complete bibliometric assessment of the accomplishments in this particular subject. The following selection of 100 publications encompasses essential epigenetic research on lung cancer, with the majority of them being published prior to 2015. The United States has played a prominent role as a leader in this particular area of study. These esteemed institutions and accomplished writers have made significant contributions to the fields of lung cancer and

epigenetics. These articles present comprehensive research on DNA methylation, and recent advancements have been achieved in targeted therapeutic approaches using miRNA medicines. The convergence of emerging technologies and cutting-edge research is a prominent theme in future research. LncRNA and CircRNA also possess a greater scope for investigation. However, scientists have not yet fully recognized the importance of additional mechanisms in the field of epigenetics, such as chromatin remodeling and histone modification. The future is yet to be explored.

5. Conclusion

For over two decades, researchers have extensively investigated the epigenetics of lung cancer. To gain insights, a systematic data retrieval approach was used together with several bibliometric analytic methods to define and evaluate the 100 most often referenced works on the topic of lung cancer and epigenetics. These findings can offer academics a concise comprehension of the area and indicate potential avenues for further research.

Funding

This study did not get any financial support.

Data availability statement

The data from this study have not been stored in a publicly accessible repository since there are no appropriate databases to accommodate the data for this investigation. Furthermore, the data for this investigation are publicly available, and all photos and tables in this paper are authentic and may be acquired from the corresponding author.

CRediT authorship contribution statement

Wangzhouyang Lou: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yunsheng Li:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

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.

Abbreviations

SCLC Small cell lung cancer
NSCLC non-small cell lung cancer
MALAT1 adenocarcinoma transcript 1
HOTAIR HOX transcript antisense intergene RNA
INK4a tumour suppressor gene p16
miRNA microRNA
LncRNA Long noncoding RNA
DNMTs DNA methyltransferase enzymes
EMT Epithelial to mesenchymal trasition
MALAT1 The lncRNA metastasis-associated lung adenocarcinoma transcript 1
PCR-SERS Polymerase chain reaction - surface-enhanced Raman spectroscopy
WOS Web of Science
WOSCC Web of Science Core Collection
SCIE Science Citation Index Expanded
SSCI Social Science Citation Index
HARVARD UNIV Harvard University
OHIO STATE UNIV The Ohio State University
UNIV TEXAS MD ANDERSON CANC CTR The University of Texas MD Anderson Cancer Center
YALE UNIV Yale University
Nat Rev Cancer Nature Reviews Cancer
Cancer Res Cancer Research
Nat Rev Drug Discov Nature Reviews Drug Discovery
Cell Res Cell Research
Nat Rev Genet Nature Reviews Genetics
Dev Biol Developmental Biology

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35686.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] N. Duma, R. Santana-Davila, J.R. Molina, Non–small cell lung cancer: epidemiology, screening, diagnosis, and treatment, Mayo Clin. Proc. 94 (2019) 1623–1640, https://doi.org/10.1016/j.mayocp.2019.01.013.

[3] M. Thomas, S. Ponce-Aix, A. Navarro, J. Riera-Knorrenschild, M. Schmidt, E. Wiegert, K. Kapp, B. Wittig, C. Mauri, M. Dómine Gómez, et al., Immunotherapeutic maintenance treatment with toll-like receptor 9 agonist lefitolimod in patients with extensive-stage small-cell lung cancer: results from the exploratory, controlled, randomized, international phase II IMPULSE study, Ann. Oncol. 29 (2018) 2076–2084, https://doi.org/10.1093/annonc/mdy326.

[4] B.C. Bade, C.S. Dela Cruz, Lung cancer 2020, Clin. Chest Med. 41 (2020) 1–24, https://doi.org/10.1016/j.ccm.2019.10.001.

[5] Z. Chen, C.M. Fillmore, P.S. Hammerman, C.F. Kim, K.-K. Wong, Non-small-cell lung cancers: a heterogeneous set of diseases, Nat. Rev. Cancer 14 (2014) 535–546, https://doi.org/10.1038/nrc3775.

[6] R.S. Herbst, D. Morgensztern, C. Boshoff, The biology and management of non-small cell lung cancer, Nature 553 (2018) 446–454, https://doi.org/10.1038/nature25183.

[7] A.F. Gazdar, P.A. Bunn, J.D. Minna, Small-cell lung cancer: what we know, what we need to know and the path forward, Nat. Rev. Cancer 17 (2017) 725–737, https://doi.org/10.1038/nrc.2017.87.

[8] M. Duruisseaux, M. Esteller, Lung cancer epigenetics: from knowledge to applications, Semin. Cancer Biol. 51 (2018) 116–128, https://doi.org/10.1016/j.semcancer.2017.09.005.

[9] A. Nebbioso, F.P. Tambaro, C. Dell'Aversana, L. Altucci, Cancer epigenetics: moving forward, PLoS Genet. 14 (2018) e1007362, https://doi.org/10.1371/journal.pgen.1007362.

[10] T.B. Toh, J.J. Lim, E.K.-H. Chow, Epigenetics in cancer stem cells, Mol. Cancer 16 (2017) 29, https://doi.org/10.1186/s12943-017-0596-9.

[11] Y. Wang, Y. Han, Y. Jin, Q. He, Z. Wang, The advances in epigenetics for cancer radiotherapy, IJMS 23 (2022) 5654, https://doi.org/10.3390/ijms23105654.

[12] S. Zöchbauer-Müller, J.D. Minna, A.F. Gazdar, Aberrant DNA methylation in lung cancer: biological and clinical implications, Oncol. 7 (2002) 451–457, https://doi.org/10.1634/theoncologist.7-5-451.

[13] S.A. Selamat, J.S. Galler, A.D. Joshi, M.N. Fyfe, M. Campan, K.D. Siegmund, K.M. Kerr, I.A. Laird-Offringa, DNA methylation changes in atypical adenomatous hyperplasia, adenocarcinoma in situ, and lung adenocarcinoma, PLoS One 6 (2011) e21443, https://doi.org/10.1371/journal.pone.0021443.

[14] A. Van Den Broeck, E. Brambilla, D. Moro-Sibilot, S. Lantuejoul, C. Brambilla, B. Eymin, S. Gazzeri, Loss of histone H4K20 trimethylation occurs in preneoplasia and influences prognosis of non-small cell lung cancer, Clin. Cancer Res. 14 (2008) 7237–7245, https://doi.org/10.1158/1078-0432.CCR-08-0869.

[15] H. Sasaki, S. Moriyama, Y. Nakashima, Y. Kobayashi, M. Kiriyama, I. Fukai, Y. Yamakawa, Y. Fujii, Histone deacetylase 1 mRNA expression in lung cancer, Lung Cancer 46 (2004) 171–178, https://doi.org/10.1016/j.lungcan.2004.03.021.

[16] P. Guan, Z. Yin, X. Li, W. Wu, B. Zhou, Meta-analysis of human lung cancer microRNA expression profiling studies comparing cancer tissues with normal tissues, J. Exp. Clin. Cancer Res. 31 (2012) 54, https://doi.org/10.1186/1756-9966-31-54.

[17] X. Shi, M. Sun, H. Liu, Y. Yao, Y. Song, Long non-coding RNAs: a new frontier in the study of human diseases, Cancer Lett. 339 (2013) 159–166, https://doi.org/10.1016/j.canlet.2013.06.013.

[18] A. Lujambio, S. Ropero, E. Ballestar, M.F. Fraga, C. Cerrato, F. Setién, S. Casado, A. Suarez-Gauthier, M. Sanchez-Cespedes, A. Git, et al., Genetic unmasking of an epigenetically silenced microRNA in human cancer cells, Cancer Res. 67 (2007) 1424–1429, https://doi.org/10.1158/0008-5472.CAN-06-4218.

[19] Z. Wang, Z. Chen, Y. Gao, N. Li, B. Li, F. Tan, X. Tan, N. Lu, Y. Sun, J. Sun, et al., DNA hypermethylation of microRNA-34b/c has prognostic value for stage I non-small cell lung cancer, Cancer Biol. Ther. 11 (2011) 490–496, https://doi.org/10.4161/cbt.11.5.14550.

[20] R. Rousseau, Forgotten founder of bibliometrics, Nature 510 (2014) 218, https://doi.org/10.1038/510218e.

[21] Y. Liu, Y. Xu, X. Cheng, Y. Lin, S. Jiang, H. Yu, Z. Zhang, L. Lu, X. Zhang, Research trends and most influential clinical studies on anti-PD1/PDL1 immunotherapy for cancers: a bibliometric analysis, Front. Immunol. 13 (2022) 862084, https://doi.org/10.3389/fimmu.2022.862084.

[22] Y. Liu, J. Li, X. Cheng, X. Zhang, Bibliometric analysis of the top-cited publications and research trends for stereotactic body radiotherapy, Front. Oncol. 11 (2021) 795568, https://doi.org/10.3389/fonc.2021.795568.

[23] B. Shadgan, M. Roig, B. HajGhanbari, W.D. Reid, Top-cited articles in rehabilitation, Arch. Phys. Med. Rehabil. 91 (2010) 806–815, https://doi.org/10.1016/j.apmr.2010.01.011.

[24] J. Wang, W. Zhao, Z. Zhang, X. Liu, T. Xie, L. Wang, Y. Xue, Y. Zhang, A journey of challenges and victories: a bibliometric worldview of nanomedicine since the 21st century, Adv Mater 36 (2024) e2308915, https://doi.org/10.1002/adma.202308915.

[25] I. Balgkouranidou, T. Liloglou, E.S. Lianidou, Lung cancer epigenetics: emerging biomarkers, Biomarkers Med. 7 (2013) 49–58, https://doi.org/10.2217/bmm.12.111.

[26] Á. Quintanal-Villalonga, S. Molina-Pinelo, Epigenetics of lung cancer: a translational perspective, Cell. Oncol. 42 (2019) 739–756, https://doi.org/10.1007/s13402-019-00465-9.

[27] K. Wadowska, I. Bil-Lula, Ł. Trembecki, M. Śliwińska-Mossoń, Genetic markers in lung cancer diagnosis: a review, Int. J. Mol. Sci. 21 (2020) 4569, https://doi.org/10.3390/ijms21134569.

[28] C.M. Croce, Causes and consequences of microRNA dysregulation in cancer, Nat. Rev. Genet. 10 (2009) 704–714, https://doi.org/10.1038/nrg2634.

[29] M. Aria, C. Cuccurullo, Bibliometrix : an R-tool for comprehensive science mapping analysis, Journal of Informetrics 11 (2017) 959–975, https://doi.org/10.1016/j.joi.2017.08.007.

[30] S.A. Belinsky, K.J. Nikula, W.A. Palmisano, R. Michels, G. Saccomanno, E. Gabrielson, S.B. Baylin, J.G. Herman, Aberrant methylation of p16(INK4a) is an early event in lung cancer and a potential biomarker for early diagnosis, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 11891–11896, https://doi.org/10.1073/pnas.95.20.11891.

[31] G.A. Calin, C.M. Croce, MicroRNA signatures in human cancers, Nat. Rev. Cancer 6 (2006) 857–866, https://doi.org/10.1038/nrc1997.

[32] A. Nishiyama, M. Nakanishi, Navigating the DNA methylation landscape of cancer, Trends Genet. 37 (2021) 1012–1027, https://doi.org/10.1016/j.tig.2021.05.002.

[33] L.D. Moore, T. Le, G. Fan, DNA methylation and its basic function, Neuropsychopharmacology 38 (2013) 23–38, https://doi.org/10.1038/npp.2012.112.

[34] M. Esteller, P.G. Corn, S.B. Baylin, J.G. Herman, A gene hypermethylation profile of human cancer, Cancer Res. 61 (2001) 3225–3229.

[35] H. Heyn, M. Esteller, DNA methylation profiling in the clinic: applications and challenges, Nat. Rev. Genet. 13 (2012) 679–692, https://doi.org/10.1038/nrg3270.

[36] R.-K. Lin, H.-S. Hsu, J.-W. Chang, C.-Y. Chen, J.-T. Chen, Y.-C. Wang, Alteration of DNA methyltransferases contributes to 5'CpG methylation and poor prognosis in lung cancer, Lung Cancer 55 (2007) 205–213, https://doi.org/10.1016/j.lungcan.2006.10.022.

[37] F. Na, X. Pan, J. Chen, X. Chen, M. Wang, P. Chi, L. You, L. Zhang, A. Zhong, L. Zhao, et al., KMT2C deficiency promotes small cell lung cancer metastasis through DNMT3A-mediated epigenetic reprogramming, Nat. Can. (Ott.) 3 (2022) 753–767, https://doi.org/10.1038/s43018-022-00361-6.

[38] I. Teneng, C.S. Tellez, M.A. Picchi, D.M. Klinge, C.M. Yingling, A.M. Snider, Y. Liu, S.A. Belinsky, Global identification of genes targeted by DNMT3b for epigenetic silencing in lung cancer, Oncogene 34 (2015) 621–630, https://doi.org/10.1038/onc.2013.580.
[39] M. Wielscher, K. Vierlinger, U. Kegler, R. Ziesche, A. Gsur, A. Weinhäusel, Diagnostic performance of plasma DNA methylation profiles in lung cancer, pulmonary fibrosis and COPD, EBioMedicine 2 (2015) 929–936, https://doi.org/10.1016/j.ebiom.2015.06.025.
[40] P. Ulivi, W. Zoli, D. Calistri, F. Fabbri, A. Tesei, M. Rosetti, M. Mengozzi, D. Amadori, p16INK4A and CDH13 hypermethylation in tumor and serum of non-small cell lung cancer patients, J. Cell. Physiol. 206 (2006) 611–615, https://doi.org/10.1002/jcp.20503.
[41] X. Li, T. Yang, C.S. Li, Y. Song, D. Wang, L. Jin, H. Lou, W. Li, Polymerase chain reaction - surface-enhanced Raman spectroscopy (PCR-SERS) method for gene methylation level detection in plasma, Theranostics 10 (2020) 898–909, https://doi.org/10.7150/thno.30204.
[42] H. Ling, M. Fabbri, G.A. Calin, MicroRNAs and other non-coding RNAs as targets for anticancer drug development, Nat. Rev. Drug Discov. 12 (2013) 847–865, https://doi.org/10.1038/nrd4140.
[43] M.A. Cortez, C. Bueso-Ramos, J. Ferdin, G. Lopez-Berestein, A.K. Sood, G.A. Calin, MicroRNAs in body fluids—the mix of hormones and biomarkers, Nat. Rev. Clin. Oncol. 8 (2011) 467–477, https://doi.org/10.1038/nrclinonc.2011.76.
[44] S. Meng, H. Zhou, Z. Feng, Z. Xu, Y. Tang, P. Li, M. Wu, CircRNA: functions and properties of a novel potential biomarker for cancer, Mol. Cancer 16 (2017) 94, https://doi.org/10.1186/s12943-017-0663-2.
[45] L. Zhang, Y. Zhang, C. Wang, Y. Yang, Y. Ni, Z. Wang, T. Song, M. Yao, Z. Liu, N. Chao, et al., Integrated single-cell RNA sequencing analysis reveals distinct cellular and transcriptional modules associated with survival in lung cancer, Signal Transduct. Targeted Ther. 7 (2022) 9, https://doi.org/10.1038/s41392-021-00824-9.
[46] A. Quintanal-Villalonga, H. Taniguchi, Y.A. Zhan, M.M. Hasan, S.S. Chavan, F. Meng, F. Uddin, P. Manoj, M.T.A. Donoghue, H.H. Won, et al., Multiomic analysis of lung tumors defines pathways activated in neuroendocrine transformation, Cancer Discov. 11 (2021) 3028–3047, https://doi.org/10.1158/2159-8290.CD-20-1863.
[47] S.M. Hammond, microRNA detection comes of age, Nat. Methods 3 (2006) 12–13, https://doi.org/10.1038/nmeth0106-12.
[48] C.M. Croce, G.A. Calin, miRNAs, cancer, and stem cell division, Cell 122 (2005) 6–7, https://doi.org/10.1016/j.cell.2005.06.036.
[49] C. Caldas, J.D. Brenton, Sizing up miRNAs as cancer genes, Nat. Med. 11 (2005) 712–714, https://doi.org/10.1038/nm0705-712.
[50] C.-Z. Chen, MicroRNAs as oncogenes and tumor suppressors, N. Engl. J. Med. 353 (2005) 1768–1771, https://doi.org/10.1056/NEJMp058190.
[51] M. Fabbri, R. Garzon, A. Cimmino, Z. Liu, N. Zanesi, E. Callegari, S. Liu, H. Alder, S. Costinean, C. Fernandez-Cymering, et al., MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 15805–15810, https://doi.org/10.1073/pnas.0707628104.
[52] L.H. Schmidt, T. Spieker, S. Koschmieder, S. Schäffers, J. Humberg, D. Jungen, E. Bulk, A. Hascher, D. Wittmer, A. Marra, et al., The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth, J. Thorac. Oncol. 6 (2011) 1984–1992, https://doi.org/10.1097/JTO.0b013e3182307eac.
[53] M. Wang, C. Mao, L. Ouyang, Y. Liu, W. Lai, N. Liu, Y. Shi, L. Chen, D. Xiao, F. Yu, et al., Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA, Cell Death Differ. 26 (2019) 2329–2343, https://doi.org/10.1038/s41418-019-0304-y.
[54] S. Lamouille, J. Xu, R. Derynck, Molecular mechanisms of epithelial-mesenchymal transition, Nat. Rev. Mol. Cell Biol. 15 (2014) 178–196, https://doi.org/10.1038/nrm3758.
[55] Y. Li, C. Sun, Y. Tan, H. Zhang, Y. Li, H. Zou, ITGB1 enhances the radioresistance of human non-small cell lung cancer cells by modulating the DNA damage response and YAP1-induced epithelial-mesenchymal transition, Int. J. Biol. Sci. 17 (2021) 635–650, https://doi.org/10.7150/ijbs.52319.
[56] G.J. Hurteau, J.A. Carlson, S.D. Spivack, G.J. Brock, Overexpression of the microRNA hsa-miR-200c leads to reduced expression of transcription factor 8 and increased expression of E-cadherin, Cancer Res. 67 (2007) 7972–7976, https://doi.org/10.1158/0008-5472.CAN-07-1058.
[57] P. Ceppi, G. Mudduluru, R. Kumarswamy, I. Rapa, G.V. Scagliotti, M. Papotti, H. Allgayer, Loss of miR-200c expression induces an aggressive, invasive, and chemoresistant phenotype in non-small cell lung cancer, Mol. Cancer Res. 8 (2010) 1207–1216, https://doi.org/10.1158/1541-7786.MCR-10-0052.
[58] S. Ortiz-Cuaran, A. Swalduz, J.-P. Foy, S. Marteau, A.-P. Morel, F. Fauvet, G. De Souza, L. Michon, M. Boussageon, N. Gadot, et al., Epithelial-to-mesenchymal transition promotes immune escape by inducing CD70 in non-small cell lung cancer, Eur. J. Cancer 169 (2022) 106–122, https://doi.org/10.1016/j.ejca.2022.03.038.
[59] J. Zhang, X. Hua, N. Qi, G. Han, J. Yu, Y. Yu, X. Wei, H. Li, X. Chen, C. Leng, et al., MiR-27b suppresses epithelial-mesenchymal transition and chemoresistance in lung cancer by targeting Snail1, Life Sci. 254 (2020) 117238, https://doi.org/10.1016/j.lfs.2019.117238.
[60] W. Cen, Q. Yan, W. Zhou, M. Mao, Q. Huang, Y. Lin, N. Jiang, miR-4739 promotes epithelial-mesenchymal transition and angiogenesis in “driver gene-negative” non-small cell lung cancer via activating the Wnt/β-catenin signaling, Cell. Oncol. 46 (2023) 1821–1835, https://doi.org/10.1007/s13402-023-00848-z.
[61] M. Yuan, Y. Zhao, H.-T. Arkenau, T. Lao, L. Chu, Q. Xu, Signal pathways and precision therapy of small-cell lung cancer, Signal Transduct. Targeted Ther. 7 (2022) 187, https://doi.org/10.1038/s41392-022-01013-y.
[62] N. Yanaihara, N. Caplen, E. Bowman, M. Seike, K. Kumamoto, M. Yi, R.M. Stephens, A. Okamoto, J. Yokota, T. Tanaka, et al., Unique microRNA molecular profiles in lung cancer diagnosis and prognosis, Cancer Cell 9 (2006) 189–198, https://doi.org/10.1016/j.ccr.2006.01.025.
[63] R. Rupaimoole, F.J. Slack, MicroRNA therapeutics: towards a new era for the management of cancer and other diseases, Nat. Rev. Drug Discov. 16 (2017) 203–222, https://doi.org/10.1038/nrd.2016.246.
[64] L. Ma, X. Gao, W. Liu, Bibliometric analysis of the top-100 cited articles on oral potentially malignant disorders to guide research topic and direction, J. Dent. Sci. 15 (2020) 479–485, https://doi.org/10.1016/j.jds.2019.09.011.
[65] A. Mainwaring, N. Bullock, T. Ellul, O. Hughes, J. Featherstone, The top 100 most cited manuscripts in bladder cancer: a bibliometric analysis (review article), Int. J. Surg. 75 (2020) 130–138, https://doi.org/10.1016/j.ijsu.2020.01.128.
[66] Y. Chi, D. Wang, J. Wang, W. Yu, J. Yang, Long non-coding RNA in the pathogenesis of cancers, Cells 8 (2019) 1015, https://doi.org/10.3390/cells8091015.
[67] L.S. Kristensen, T. Jakobsen, H. Hager, J. Kjems, The emerging roles of circRNAs in cancer and oncology, Nat. Rev. Clin. Oncol. 19 (2022) 188–206, https://doi.org/10.1038/s41571-021-00585-y.
[68] X. Chen, D. Xie, Q. Zhao, Z.-H. You, MicroRNAs and complex diseases: from experimental results to computational models, Briefings Bioinf. 20 (2019) 515–539, https://doi.org/10.1093/bib/bbx130.
[69] X. Chen, T.-H. Li, Y. Zhao, C.-C. Wang, C.-C. Zhu, Deep-belief network for predicting potential miRNA-disease associations, Briefings Bioinf. 22 (2021) bbaa186, https://doi.org/10.1093/bib/bbaa186.
[70] W. Liu, H. Lin, L. Huang, L. Peng, T. Tang, Q. Zhao, L. Yang, Identification of miRNA–disease associations via deep forest ensemble learning based on autoencoder, Briefings Bioinf. 23 (2022) bbac104, https://doi.org/10.1093/bib/bbac104.
[71] T. Xue, W. Liang, Y. Li, Y. Sun, Y. Xiang, Y. Zhang, Z. Dai, Y. Duo, L. Wu, K. Qi, et al., Ultrasensitive detection of miRNA with an antimonene-based surface plasmon resonance sensor, Nat. Commun. 10 (2019) 28, https://doi.org/10.1038/s41467-018-07947-8.
[72] Y. Fan, W. Wu, N. Xie, Y. Huang, H. Wu, J. Zhang, X. Guo, S. Ding, B. Guo, Biocompatible engineered erythrocytes as plasmonic sensor initiators for high-sensitive screening of non-small cell lung cancer-derived exosomal miRNA in an integrated system, Biosens. Bioelectron. 219 (2023) 114802, https://doi.org/10.1016/j.bios.2022.114802.
[73] J. Zhang, C. Song, Y. Zhu, H. Gan, X. Fang, Q. Peng, J. Xiong, C. Dong, C. Han, L. Wang, A novel cascade signal amplification strategy integrating CRISPR/Cas13a and branched hybridization chain reaction for ultra-sensitive and specific SERS detection of disease-related nucleic acids, Biosens. Bioelectron. 219 (2023) 114836, https://doi.org/10.1016/j.bios.2022.114836.
[74] E.R. Malone, M. Oliva, P.J.B. Sabatini, T.L. Stockley, L.L. Siu, Molecular profiling for precision cancer therapies, Genome Med. 12 (2020) 8, https://doi.org/10.1186/s13073-019-0703-1.
[75] Y. Lu, X. Luo, Q. Wang, J. Chen, X. Zhang, Y. Li, Y. Chen, X. Li, S. Han, A novel necroptosis-related lncRNA signature predicts the prognosis of lung adenocarcinoma, Front. Genet. 13 (2022) 862741, https://doi.org/10.3389/fgene.2022.862741.

[76] M. Abu-Halima, A. Keller, L.S. Becker, U. Fischer, A. Engel, N. Ludwig, F. Kern, T.B. Rounge, H. Langseth, E. Meese, et al., Dynamic and static circulating cancer microRNA biomarkers – a validation study, RNA Biol. 20 (2023) 1–9, https://doi.org/10.1080/15476286.2022.2154470.
[77] Y. Fang, G. Liao, B. Yu, LSD1/KDM1A inhibitors in clinical trials: advances and prospects, J. Hematol. Oncol. 12 (2019) 129, https://doi.org/10.1186/s13045-019-0811-9.
[78] D. Morel, D. Jeffery, S. Aspeslagh, G. Almouzni, S. Postel-Vinay, Combining epigenetic drugs with other therapies for solid tumours — past lessons and future promise, Nat. Rev. Clin. Oncol. 17 (2020) 91–107, https://doi.org/10.1038/s41571-019-0267-4.