International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

The Application of microRNAs in Papillary Thyroid Cancer: A Bibliometric and Visualized Analysis

Tinghua Zhang[1], Bo Yuan[2], Shaofu Yu[3]

[1]Department of Clinical Laboratory, the Second People's Hospital of Huaihua City, Huaihua, Hunan, People's Republic of China; [2]Department of Clinical Laboratory, Southern University of Science and Technology Hospital, Guangdong, Shenzhen, People's Republic of China; [3]Department of Clinical Pharmacy, the Second People's Hospital of Huaihua, Huaihua, Hunan, People's Republic of China

Correspondence: Shaofu Yu, Department of Clinical Pharmacy, the Second People's Hospital of Huaihua, Huaihua, Hunan, People's Republic of China, Tel +86-13974531958, Email yushaofuanjing@163.com

Objective: Thyroid cancer is the most common malignant endocrine tumor, with papillary thyroid carcinoma (PTC) being the most prevalent type, accounting for 85% of thyroid cancer cases. Here, we conducted a bibliometric analysis of the literature in the field of microRNAs in PTC research to demonstrate current trends and research hotspots, and present a visual map of past and emerging trends.

Methods: We searched the Web of Scientific Core Collection (WoSCC) database for publications from 1999 to 2023 centered on this field. Next, we employed visualization tools such as VOSviewer, CiteSpace, and Microsoft Excel 2019 to present co-occurrence and co-citation analyses, trends, hotspots, and visual representations of contributions from authors, institutions, journals, and countries/regions.

Results: The bibliometric analysis encompassed the period from 1999 to 2023, with 994 papers from 54 countries/regions. The country with the most publications and highest total citations was the People's Republic of China, but the United States held the highest average citation rate. Among the top ten productive institutions, the Ohio State University (Ohio State Univ) was the most prominent contributor to this field. The JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM (J Clin Endocrinol Metab) ranked first in terms of citation counts and average citations among the top ten productive journals. In terms of keywords, "circular RNAs", "promotes", and "progression" have become prominent research areas.

Conclusion: This study elucidates current trends, hotspots, and emerging frontiers in miRNA research within PTC, and provides new insights and guidance for future identification of new PTC biomarkers and clinical trials.

Keywords: microRNAs, papillary thyroid cancer, bibliometric, VOSviewer, CiteSpace

Introduction

Thyroid cancer is the most common malignant tumor in endocrine tumors. According to pathological classification, it can be divided into papillary thyroid carcinoma (PTC), medullary thyroid carcinoma, follicular thyroid carcinoma, and undifferentiated thyroid carcinoma. The most malignant is undifferentiated thyroid carcinoma, while medullary thyroid carcinoma has moderate malignancy. PTC and follicular thyroid carcinoma have lower malignancy levels. PTC, follicular thyroid carcinoma, and undifferentiated thyroid carcinoma originate from follicular cells, while medullary thyroid carcinoma originates from non-follicular cells.[1] PTC is the most common type of thyroid cancer,[2] accounting for 85% of thyroid cancer cases.[3] In recent years, the incidence of PTC has been rapidly increasing in many countries worldwide.[4] Due to its highly invasive and metastatic nature, the incidence of PTC is increasing faster than other solid tumors globally.[5] The rising incidence of PTC has raised significant concerns in global public health.

Most well-differentiated thyroid cancer patients are asymptomatic and are usually discovered during routine physical examinations or incidentally during imaging studies. For tumors smaller than or equal to 1 cm, surgery may not be

Received: 27 August 2024
Accepted: 2 October 2024
Published: 15 October 2024

necessary; for tumors larger than 1 cm, surgery is usually required regardless of lymph node involvement.[6] After surgery, PTC patients have a longer survival time, with a five-year relative survival rate of approximately 98.5% in the United States.[6] Despite advances in the diagnosis and treatment of thyroid cancer, the increasing detection rate of PTC due to advancements in diagnostic technologies, there is still room for improvement in the accuracy of screening and diagnosis. The common methods for early screening and diagnosis of thyroid cancer are ultrasound and fine-needle aspiration biopsy (FNA).[3] FNA is the gold standard for diagnosing thyroid cancer, but it may not always provide a complete picture of the cancer, leading to misdiagnosis. Furthermore, it is a complex and invasive procedure. Due to the complexity and stealthiness of thyroid cancer, there is a need to explore new biomarkers, with microRNAs (miRNAs) being one of the promising research targets. Identifying and validating reliable biomarkers can help assess the risk of vascular invasion in PTC patients, predict disease progression, and optimize treatment decisions.[2]

MiRNA is a type of short non-coding RNA containing around 22 nucleotides, which can regulate gene expression by degrading messenger RNA or inhibiting messenger RNA translation. Research has found that the expression of most miRNAs is severely dysregulated in thyroid cancer, and miRNAs play a crucial role in the proliferation, differentiation, apoptosis, angiogenesis, invasion, and metastasis of thyroid cancer cells.[7]

Bibliometric analysis is a commonly used method in scientific publication and quantitative research, involving the collection, processing, and management of data from previous scientific publications to summarize the progress of research topics. Additionally, bibliometric analysis can identify hotspots and emerging trends in specific fields. However, few studies have applied bibliometric analysis to the field of miRNA in PTC.

Therefore, in this study, we conducted a systematic bibliometric analysis of research literature on miRNA and PTC from 1999 to 2023. We visually analyzed the annual publication output, authors, institutions, journals, contributions by country or region, publication trends, international collaborations, references, and keywords. Furthermore, we provided an outlook on research progress and identified research hotspots and trends in this field. In summary, our aim is to summarize past research and provide a research foundation or new frontiers for further studies on miRNA in PTC.

Materials and Methods

Search Strategy and Data Collection

We conducted an advanced search in the Web of Scientific Core Collection (WoSCC) database using the following search terms to identify publications primarily related to miRNA: TS = (“microRNA” OR “miRNA” OR “miR”) and TS = (“papillary thyroid cancer” OR “papillary thyroid carcinoma”). The search period was limited from January 1, 1999, to December 31, 2023. Subsequently, we restricted the document types to original articles and review articles. The identified publications meeting the inclusion criteria were exported in a plain text format as “full records and cited references”.

Data Analysis

Import publications into VOSviewer (version 1.6.20) and CiteSpace (version 6.2.6) to retrieve titles, keywords, authors, institutions, countries or regions, journals, publication years, citation counts, average citation counts, and cited references. Export the corresponding bibliometric parameters to Microsoft Excel 2019 to determine publication trends, distribution of document types, and major contributors, including prolific authors, institutions, countries or regions, and journals. VOSviewer is used to illustrate maps and describe the collaboration strength among authors, institutions, countries, and journals to demonstrate their scientific influence in the field. Finally, by utilizing author keywords in VOSviewer, keywords with the strongest citation bursts, and co-cited references in CiteSpace, visualize the knowledge evolution, hot topics, and potential research frontiers in the field. In the network visualization map generated by VOSviewer, node colors represent clusters, node sizes represent the number of publications or frequency of keywords, links between nodes represent collaboration or co-occurrence relationships, and link thickness represents strength. In the overlay visualization map generated by VOSviewer, node colors represent the average publication year, where purple represents earlier years and yellow represents more recent years. In CiteSpace, a blue line represents a cyclical pattern, and a red line represents a burst cycle.

Results

General Data

We retrieved 994 publications from the WoSCC database, covering the period from January 1, 1999, to December 31, 2023, with publication types limited to original articles and review articles. During this period, a total of 994 articles were published, including 912 (91.75%) original articles and 82 (8.25%) review articles. No articles were retrieved for the years 2000–2004, with only 1 article each found for 1999 and 2005. The number of articles published showed an increasing trend from 1999 to 2020, with the highest number of articles published in 2020 (155 articles), followed by a decreasing trend from 2021 onwards (Figure 1A). A total of 54 countries/regions published papers in this research field during the period from January 1, 1999, to December 31, 2023, with the top three countries/regions being the People's Republic of China (646 articles), the United States (117 articles), and Italy (67 articles) (Figure 1B).

Active Countries or Regions

When the minimum number of documents was set at 5, only 28 countries/regions reached the threshold. We constructed a map of their collaborative relationships (Figure 2A), with the People's Republic of China being the most active country in this field. As shown in Figure 2B, we summarized the number of publications, total citations, and average citations for the top 10 prolific countries/regions. The People's Republic of China had the highest total citations with 13,637 citations and an average of 21.11 citations. The United States followed with 11,634 total citations and an average of 99.44 citations. Italy ranked third with 3427 total citations and an average of 51.15 citations. However, it is noteworthy that among the top 10 prolific countries/regions, China had the highest number of publications and total citations, but had the lowest average citation count at 21.11, while the United States had the highest average citation count at 99.44.

Active Organizations

69 organizations have published 5 or more papers, and we have constructed a map of their collaboration relationships (Figure 3A). Figure 3B shows the top ten productive institutions. The Ohio State University (Ohio State Univ) stands out as the most prominent contributor in the field, with a total citation count of 4210, averaging 191.36 citations. The National

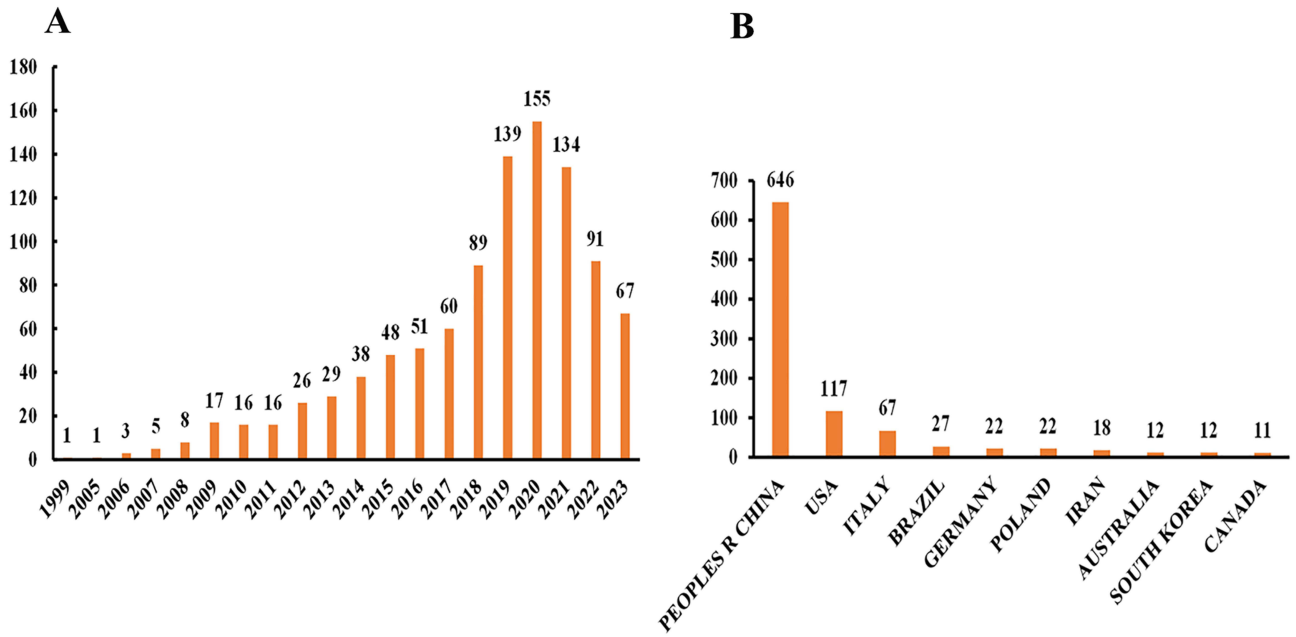


Figure 1 General data analysis. (**A**) Number of articles published each year. (**B**) Top ten countries/regions in terms of the number of published articles from January 1, 1999, to December 31, 2023.

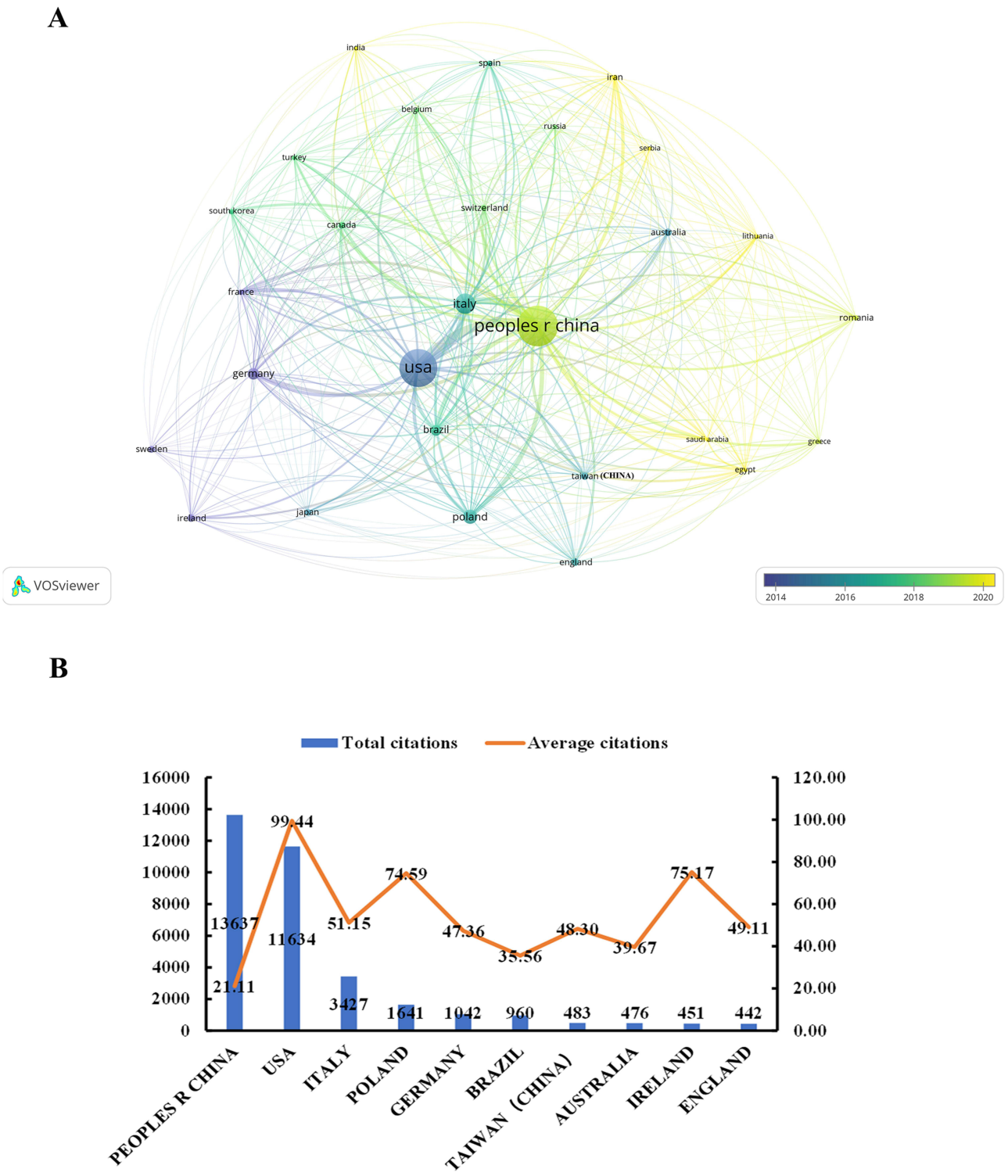
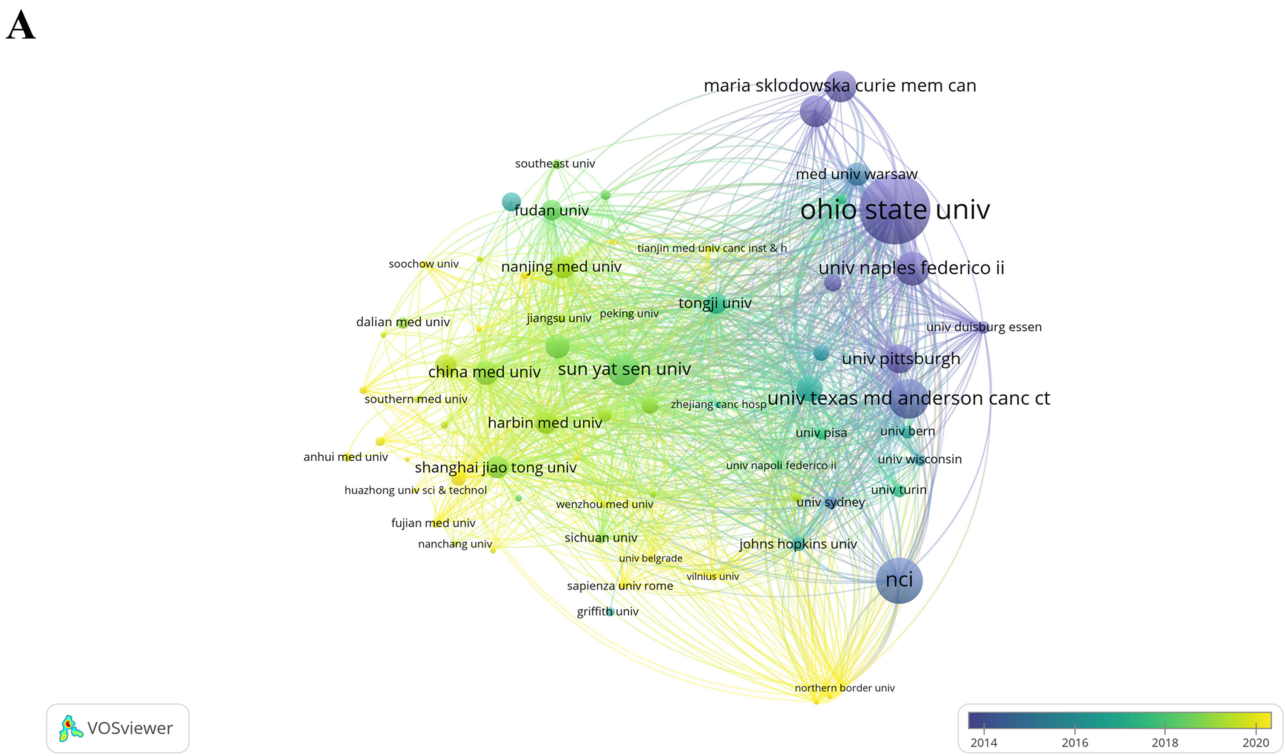


Figure 2 Active countries/regions in the field. (**A**) Network map visualization of active countries/regions in the field. (**B**) Total citations and average citations for the top 10 countries/regions.

Cancer Institute (NCI) ranks second in total citations, and the University of Texas MD Anderson Cancer Center (Univ Texas Md Anderson Canc Ctr) ranks third. However, it is worth noting that the highest average citation count belongs to the Maria Sklodowska-Curie Memorial Cancer Center (Maria Sklodowska Curie Mem Canc Ctr), with an average of 232.40 citations.



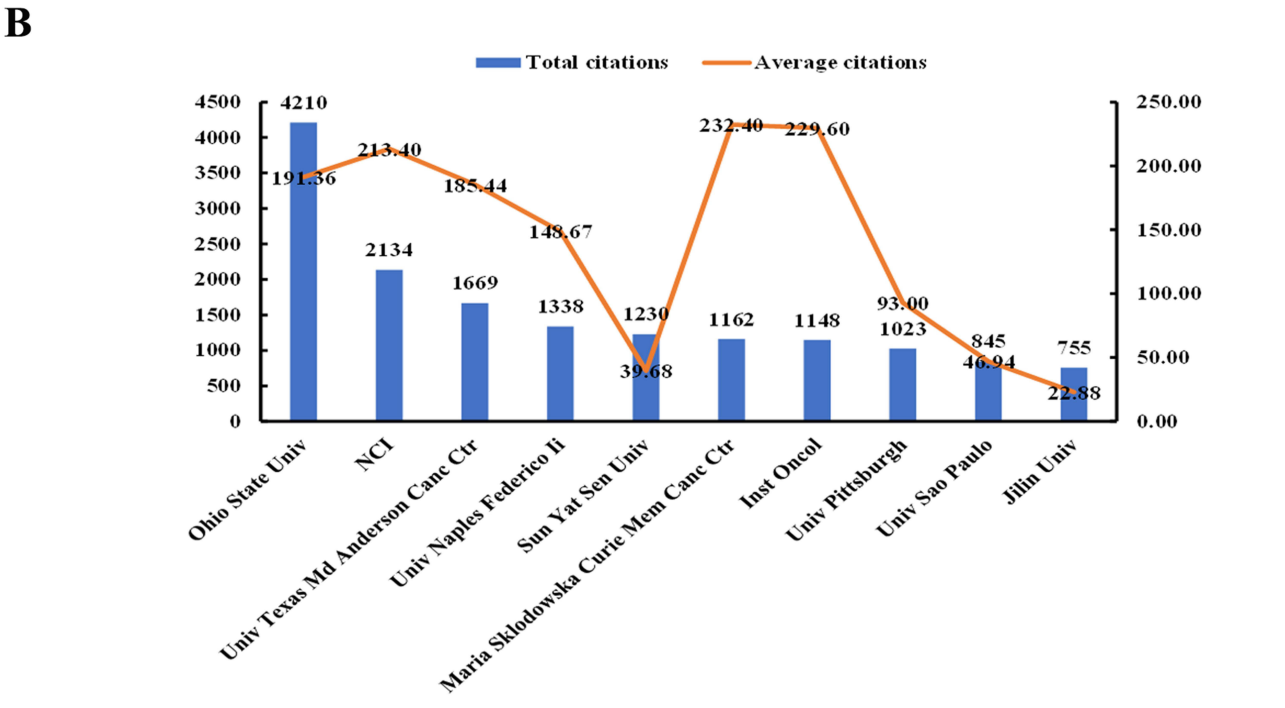


Figure 3 (**A**) Visualization map of organizational collaboration networks. (**B**) Citations and average citations in the top 10 active organizations.

Journals and Co-Cited Journals

Using VOSviewer, we identified 53 journals that have published at least 5 articles, and the journal collaboration network visualization map is shown in Figure 4A. Figure 4B summarizes the top ten productive journal citation counts and average citation counts. JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM (J CLIN ENDOCRINOL METAB) leads in citation count with 1767 citations and an average of 73.63 citations, ranking first. ENDOCRINE-RELATED CANCER and THYROID rank second and third in total citations. However, the highest average citation count goes to ENDOCRINE-RELATED CANCER, with an average of 76.16 citations. The co-cited journals collaboration network visualization map is shown in Figure 4C. Figure 4D summarizes the top ten co-cited journals. As shown in Figure 4D, JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM has the highest number of co-citations with 1719, followed by THYROID (1361 co-citations) and CANCER RESEARCH (1172 co-citations).

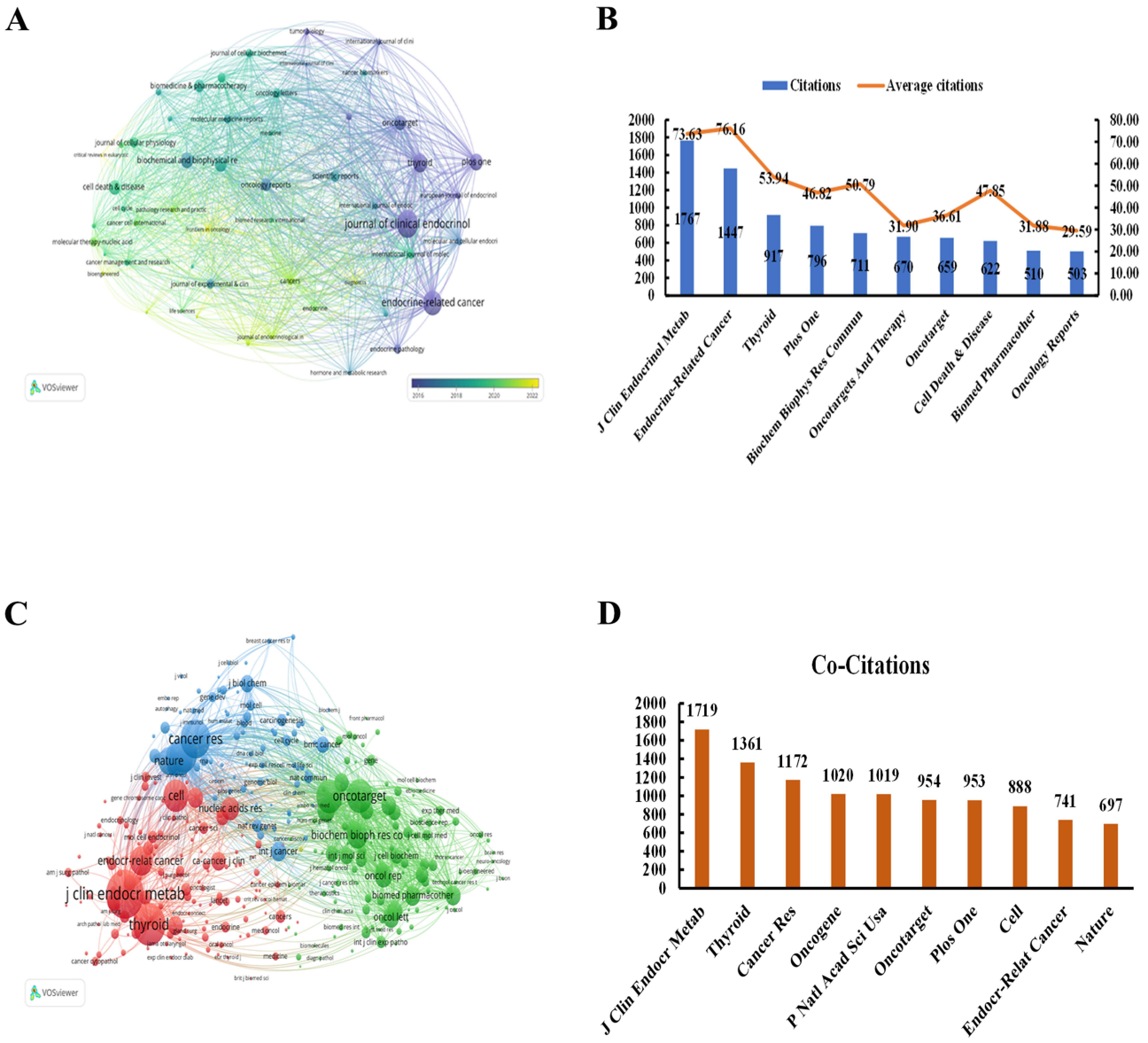


Figure 4 (**A**) Visualization map of journal collaboration networks. (**B**) Citations and average citations in the top 10 productive journals. (**C**) Co-Cited journals collaboration network visualization map. (**D**) Co-Citations in the top 10 co-cited journals.

Active Authors

In this study, we analyzed the author network visualization map (Figure 5A). The top 10 active authors are shown in Figure 5B. The top three authors in terms of citations are Jazdzewski Krystian (1452 citations), De La Chapelle Albert (1395 citations), Nikiforov Yuri E. (952 citations), with the highest average citation count belonging to De La Chapelle Albert, averaging 155.00 citations. In terms of co-citations (Figure 5C), Nikiforova Mn, Xing Mz, and He Hl rank in the top three (Figure 5D). Among the 62 authors who have published three or more articles, we analyzed the collaboration relationships based on the average publication year (Figure 5E). Zhang Hao has the highest total link strength (Figure 5F).

Publications and Reference Articles

Figure 6A shows the visualization map of publication network relationships. In Figure 6B, the top 10 referenced publications are listed, with the highest citation count (1758 citations) going to the article "Integrated genomic characterization of papillary thyroid carcinoma" (doi: 10.1016/j.cell.2014.09.050).[8] The second and third most cited articles are "MicroRNAs in body fluids–the mix of hormones and biomarkers" (doi: 10.1038/nrclinonc.2011.76)[9] and "The role of microRNA genes in papillary thyroid carcinoma" (doi:10.1073/pnas.0509603102).[10]

Through CiteSpace, we obtained a graph of the most cited reference articles (Figure 6C) and the top 10 reference articles with the highest burst frequencies (Figure 6D). In Figure 6D, the article "The role of microRNA genes in papillary thyroid carcinoma" (doi:10.1073/pnas.0509603102)[10] published by He H et al in 2005 still has the highest burst intensity. The reference article "Prognostic implications of miR-146b expression and its functional role in papillary thyroid carcinoma" (doi: 10.1210/jc.2012–2666)[11] has the longest burst duration.

Figure 6E shows the visualization map of co-cited publication network relationships. In Figure 6F, the top 10 co-cited publications are listed, with the article "The role of microRNA genes in papillary thyroid carcinoma" (doi:10.1073/pnas.0509603102)[10] having the highest citation count (233 co-citations). The second and third most co-cited articles are "MicroRNA deregulation in human thyroid papillary carcinomas" (doi:10.1677/erc.1.01209)[12] and "MicroRNA expression profiling of thyroid tumors: biological significance and diagnostic utility" (doi:10.1210/jc.2007–2696).[13]

Keywords

We analyzed the bibliometric information of these documents using VOSviewer. A total of 296 keywords appeared at least 5 times, categorized into 7 clusters (Figure 7A), with shades indicating the proximity to the present or earlier stages. As shown in Figure 7B, we analyzed the top 10 keywords, finding that they mainly include "expression" (n=368), "cancer" (n=312), "papillary thyroid carcinoma" (n=274), "invasion" (n=246), "carcinoma" (n=224), "proliferation" (n=222), "metastasis" (n=193), "migration" (n=186), "papillary thyroid cancer" (n=174), and "microRNA" (n=166). These keywords reflect the main topics related to the investigators.

Using CiteSpace, we conducted keyword cluster analysis (Figure 7C), keyword timeline analysis (Figure 7D), and identified the top 34 keywords with the highest burst frequencies (Figure 7E). Figure 7C shows 9 keyword clusters. In Figure 7D, keywords like "fine needle aspiration" and "tall cell variant loss of heterozygosity cancer" reflect the earliest interests of scholars in the field. Additionally, through detecting burst keywords in specific periods, CiteSpace helped identify major themes. In Figure 7E, blue lines indicate the time from their first appearance to 2023, and red lines indicate burst times. "Fine needle aspiration" has the longest burst duration and earliest appearance, starting in 1999 and ending in 2013, with the highest burst intensity attributed to "tumors", "papillary carcinomas", and "deregulation". In the last three years (2021–2023), bursting keywords include "circular RNAs", "promotes", and "progression".

Discussion

General Information

Our analysis includes 994 articles published between 1999 and 2023, originating from 54 countries/regions. These numbers indicate that this research field has garnered global attention. The quantity of annual publications can reflect the development of a specific field, and we found that from 1999 to 2020, this research field showed an overall upward trend;

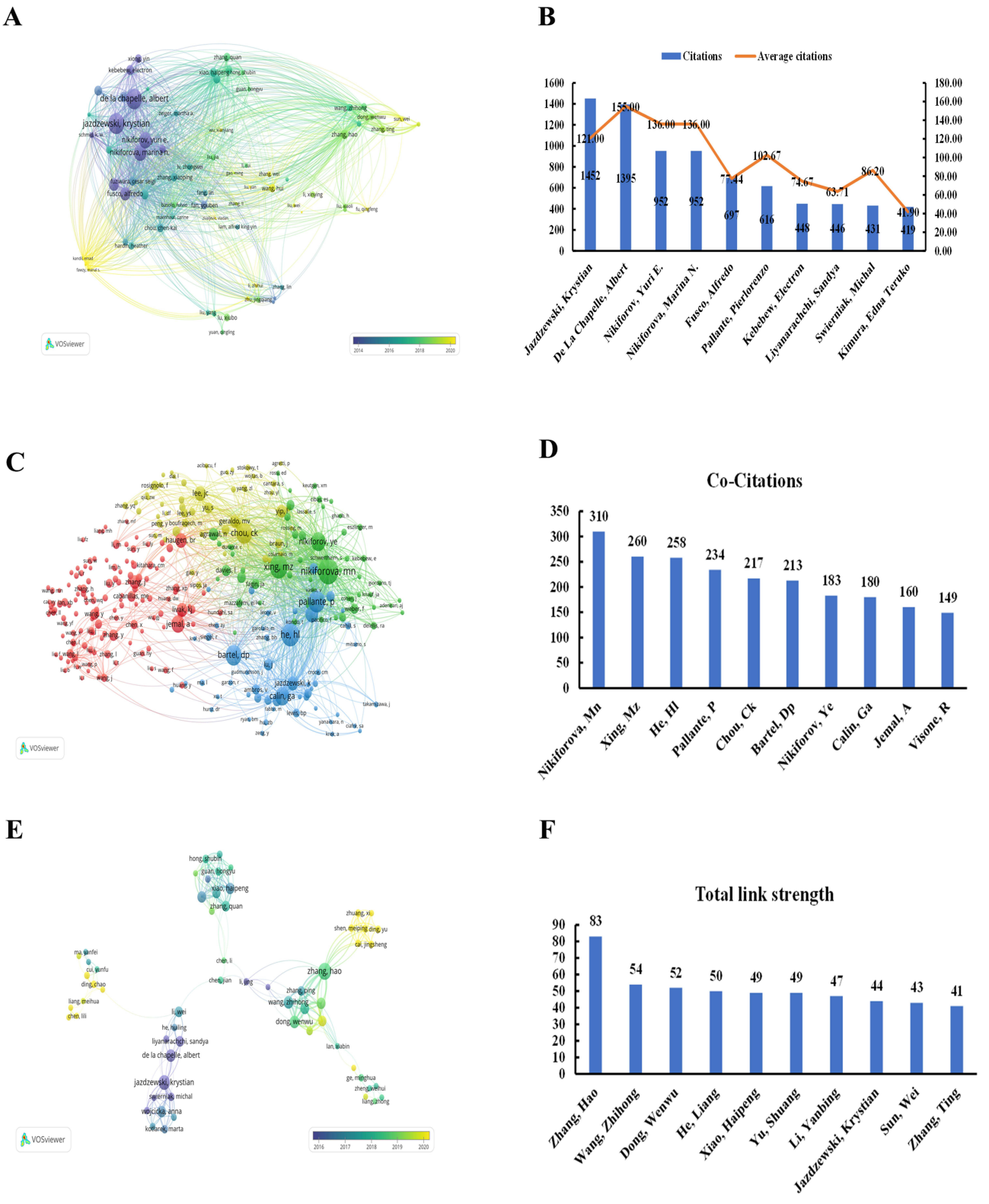


Figure 5 (**A**) Network distribution map of authors relevant to the field. (**B**) Top 10 active authors. (**C**)Network distribution map of co-cited authors in the field. (**D**) Top 10 active co-cited authors. (**E**) Collaboration relationships among authors. (**F**) Top 10 authors by total link strength.

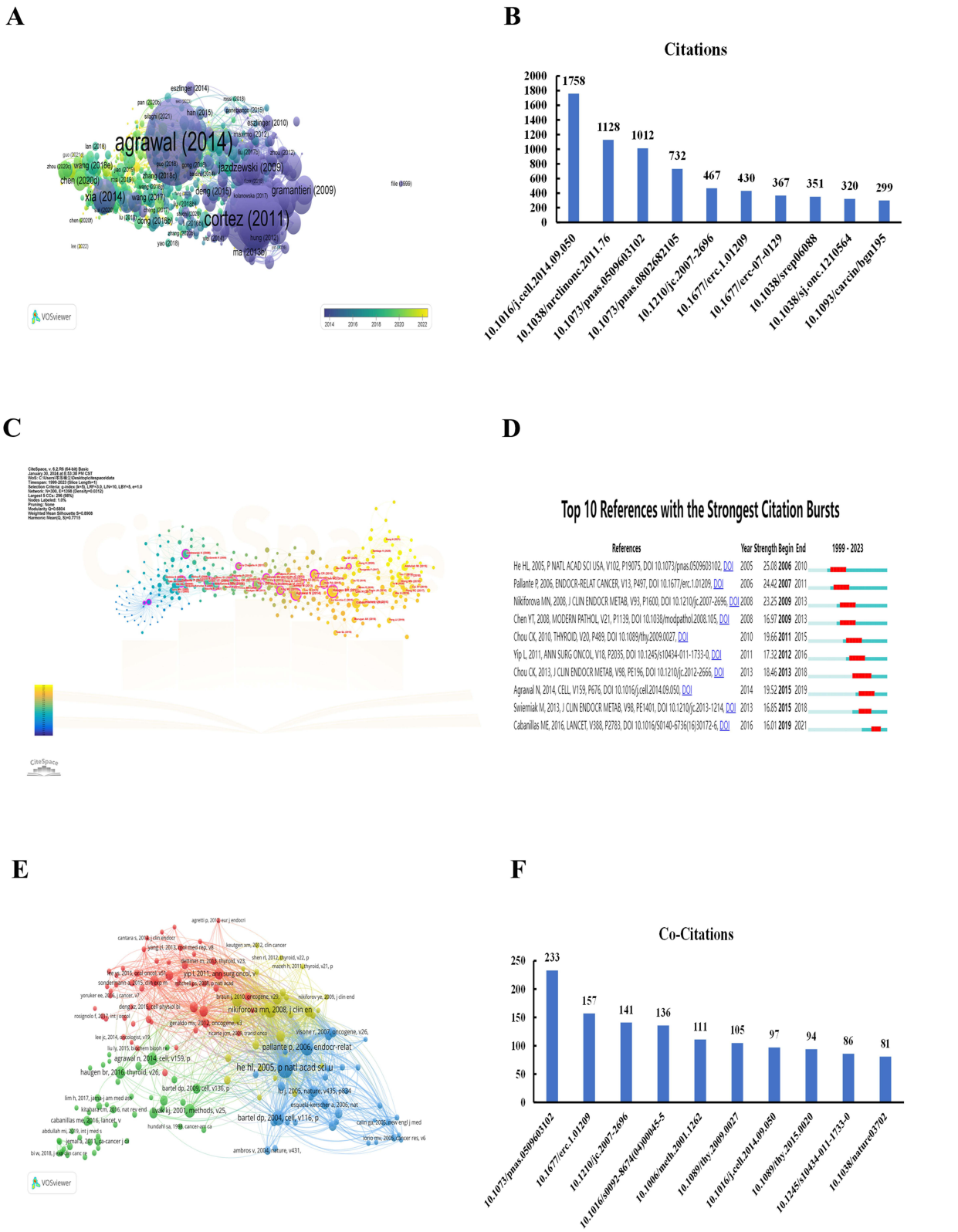
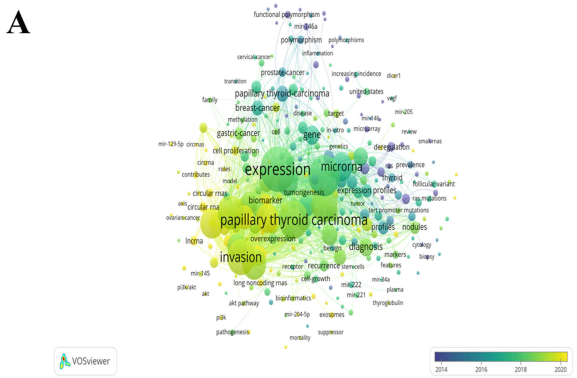
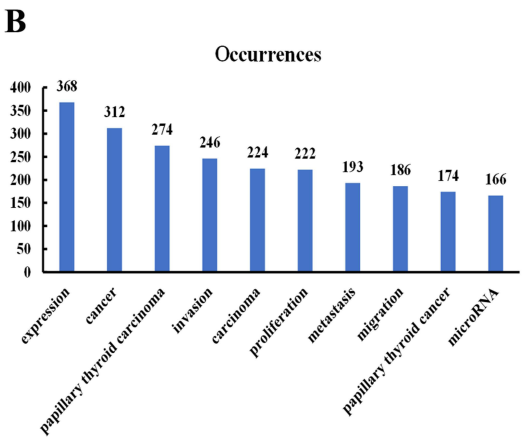
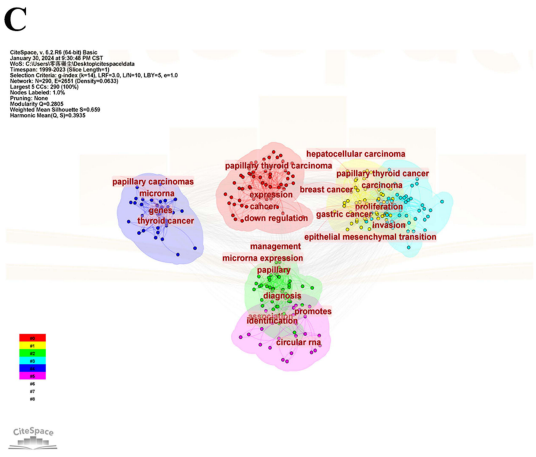
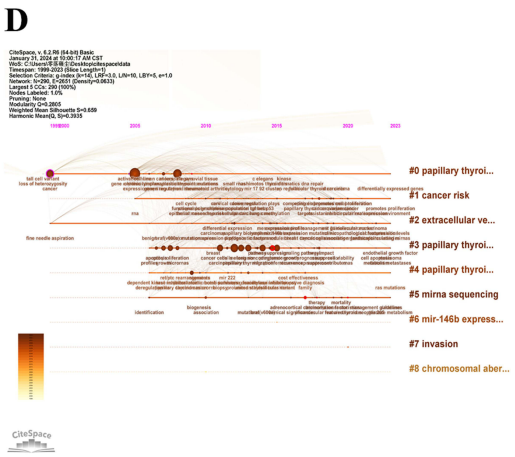


Figure 6 (**A**) Visualization map of publication network relationships. (**B**) Top 10 referenced publications. (**C**) Most cited reference articles. (**D**) Top 10 reference articles with highest burst frequencies. (**E**) Visualization map of co-cited publication network relationships. (**F**) Top 10 co-cited publications.









E

Top 34 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1999 - 2023
fine needle aspiration	1999	3.3	1999	2013	
gene expression	2005	9.07	2005	2015	
braf mutations	2005	8.18	2005	2017	
activation	2005	3.72	2005	2010	
deregulation	2006	9.87	2006	2013	
chronic lymphocytic leukemia	2007	4.51	2007	2011	
papillary carcinomas	2008	10.61	2008	2015	
braf mutation	2008	6.35	2008	2013	
mirnas	2008	4.53	2008	2017	
nf kappa b	2008	4.23	2008	2012	
braf(v600e) mutation	2008	3.97	2008	2014	
tumors	2009	12.79	2009	2016	
microrna expression	2009	8.32	2009	2016	
gene	2006	4.03	2009	2015	
in vivo	2009	4.03	2009	2014	
ret/ptc rearrangements	2009	3.64	2009	2013	
prevalence	2009	3.47	2009	2013	
functional polymorphism	2010	6.3	2010	2016	
genes	2007	5.96	2010	2017	
breast cancer	2009	6.74	2011	2015	
expression profiles	2011	5.21	2011	2014	
prostate cancer	2011	4.82	2011	2015	
differential expression	2012	3.97	2012	2017	
profiles	2006	4.87	2013	2016	
down regulation	2007	4.24	2014	2017	
biomarkers	2014	3.41	2014	2017	
benign	2006	3.37	2015	2017	
tumor growth	2016	3.65	2016	2017	
poor prognosis	2017	3.6	2017	2018	
biomarker	2018	4.35	2020	2021	
association guidelines	2020	3.53	2020	2023	
circular rnas	2020	5.97	2021	2023	
promotes	2017	5.42	2021	2023	
progression	2015	4.57	2021	2023	

Figure 7 (**A**) Visualization map of publication network relationships. (**B**) Top 10 keywords. (**C**) Keyword cluster analysis. (**D**) Keyword timeline analysis. (**E**) Top 34 keywords with highest burst frequencies.

however, there was a decrease in the number of new publications in 2021. We speculate that this may be due to the field shifting towards other directions. Indeed, the top three countries/regions in terms of the number of published articles were the People's Republic of China (646 articles), the United States (117 articles), and Italy (67 articles). Among the top ten most productive institutions, the Ohio State University (Ohio State Univ) stood out as the most prominent contributor in the field, with a total citation count of 4210 and an average of 191.36 citations. The National Cancer Institute (NCI) ranked second in total citations, and the University of Texas MD Anderson Cancer Center (Univ Texas Md Anderson Canc Ctr) ranked third. However, it is noteworthy that the institution with the highest average number of citations was the Maria Sklodowska-Curie Memorial Cancer Center (Maria Sklodowska Curie Mem Canc Ctr), with an average of 232.40 citations. Among the top ten productive journals, JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM (J CLIN ENDOCRINOL METAB) had 1767 citations, with an average of 73.63 citations, ranking first. ENDOCRINE-RELATED CANCER and THYROID ranked second and third, respectively.

Research Trends and Hotspots

The analysis and discussion of the general information above indicate that influential authors and references mainly consist of articles from reputable institutions and journals. By combining keyword co-occurrence, clustering, and burst analysis of references, we identified the continued hotspots and research trends of miRNA in the field of PTC research. In the early years, research primarily focused on "fine needle aspiration", "gene expression", and "tall cell variant loss of heterozygosity cancer". However, as medical technologies continue to advance, "circular RNAs", "promotes", and "progression" are becoming important areas of research. The following topics may be worth further investigation in the future: The application of miRNA in PTC screening and diagnosis; The application of miRNA in PTC regulation and treatment; The application of miRNA in PTC prognosis; The application of circular RNAs in PTC; The application of immunotherapy in PTC.

The Application of miRNA in PTC Screening and Diagnosis

Currently, the common method for diagnosing PTC still involves performing a biopsy on patients and conducting cytological examinations to confirm the diagnosis. This method is complex and highly invasive.[14] Although thyroid biopsy is the gold standard for PTC diagnosis, it may not provide a comprehensive view of the cancer, leading to a certain probability of misdiagnosis. Detecting abnormally expressed miRNA in PTC tissues may serve as a new complementary screening diagnostic marker to improve the specificity and sensitivity of PTC diagnosis. Studies have shown that compared to normal thyroid tissues from the same patients, miR-146b, miR-181a, miR-187, miR-221, and miR-222 are significantly upregulated in PTC tissues.[15] These miRNAs are also upregulated in PTC tissues compared to nodular goiter tissues. Monitoring the expression levels of these dysregulated miRNAs may facilitate early diagnosis and differential diagnosis of PTC. While testing individual miRNAs may lack diagnostic accuracy, researchers have proposed using miRNA ratios or combinations to further improve the accuracy of PTC diagnosis. Studies indicate that compared to individual miR-221 and miR-222, the sensitivity and specificity of the miR-221/222 ratio in PTC diagnosis can reach 75% and 80%, respectively, with an area under the receiver operating characteristic curve of 0.85.[16] Another study analyzed the miRNA expression profile of PTC tissues and found that a combination of miRNAs (miR-152-3p, miR-221-3p, miR-551b-3p, and miR-7-5p) had an area under the curve of 0.841, making it a potential diagnostic tool for PTC.[4] A study also confirmed that a combination of miR-138 and miR-21 increased the sensitivity of thyroid cancer diagnosis to 73.3% and the specificity to 76.5%, surpassing the diagnostic value of individual biomarkers, making them a valuable tool for distinguishing PTC from benign thyroid lesions.[17] In PTC tissue samples, the expression levels of miR-551b, miR-146b, miR-221, miR-222, and miR-375 are highly upregulated, while the expression levels of miR-873 and miR-204 are downregulated, potentially serving as potential biomarkers for the diagnosis of PTC.[18] Additionally, the expression level of miR-300 in tissue samples is elevated, and the expression level of BCL2L11 is reduced, both of which have clinical predictive value for the diagnosis of PTC.[19]

Although tissue miRNA can differentiate between benign and malignant thyroid lesions, and also exhibit differential expression at different stages and locations of thyroid cancer, the invasiveness of biopsy remains a significant issue. Researchers have started exploring less invasive thyroid cancer screening diagnostic markers such as circulating

miRNAs. Studies have reported significant dysregulation of miRNAs in the blood serum or plasma of PTC patients, and their detection can improve the sensitivity and specificity of PTC diagnosis, potentially serving as new screening diagnostic markers for PTC.[20] Serum miRNAs show good diagnostic performance in distinguishing patients with PTC, patients with benign nodules, and healthy controls, thus holding considerable potential as a new type of minimally invasive tool for detecting PTC.[21] A study has established a combination of seven miRNAs in plasma through the random forest algorithm, which has significant performance in distinguishing PTC from healthy or benign groups.[22] In the blood plasma of PTC patients, the expression levels of let-7 family members (let-7a, let-7c, let-7d, and let-7f) are significantly higher than those in healthy controls.[23] The expression levels of miR-146b-3p, miR-222-3p, miR-221-5p, and miR-21a-3p in plasma can serve as candidate biomarkers for the early diagnosis and monitoring of PTC.[24] MiR-221, miR-181b, miR-146b, miR-21, and miR-222 are also significantly overexpressed in plasma and can serve as non-invasive diagnostic biomarkers for PTC.[25] In the differential diagnosis of thyroid cancer, studies have found that compared to benign thyroid nodules, the expression levels of miR-222, miR-181a, and miR-146a in the blood plasma of PTC patients are significantly increased, indicating their potential diagnostic value in distinguishing benign and malignant thyroid nodules.[26] Compared to existing screening diagnostic methods, blood serum or plasma miRNAs have the advantages of wide distribution, easy sampling, stable nature, and by detecting their expression levels, not only can patient invasiveness be reduced, but it can also save patients' economic costs and achieve higher accuracy. Recent research suggests that detecting the expression levels of serum or plasma miRNAs is becoming a practical and non-invasive screening diagnostic method for PTC patients.[27] The development of detection methods for abnormally expressed miRNAs in serum may be a promising minimally invasive diagnostic tool for the early diagnosis of PTC. This approach could enhance diagnostic sensitivity and specificity, as well as improve preoperative patient counseling and therapeutic guidance.[28]

Extracellular vesicles are intracellular vesicles that play a crucial role in cell-to-cell communication. They are easy to obtain, stable in nature, and have a certain specificity in their source. They play a critical role in the occurrence, development, and metastasis of cancer. Among them, miRNAs in extracellular vesicles are considered as biomarkers for tumor screening and diagnosis. In recent years, research on extracellular vesicle miRNA in PTC has been increasing, mainly focusing on the potential applications of extracellular vesicle miRNA as biological markers for PTC screening and diagnosis. Studies have found that compared to normal thyroid cell lines, five miRNAs (miR-21-5p, miR-31-5p, miR-221-3p, miR-222-3p, and let-7i-3p) in extracellular vesicles from PTC cells show significant dysregulation, indicating their diagnostic value.[29] A combination of three miRNAs (miR-146b-5p, miR-223-5p, and miR-182-5p) isolated from blood extracellular vesicles showed an area under the curve of 0.981, with a sensitivity of 93.8% and a specificity of 92.9%.[30] Testing this combination has high sensitivity and specificity in distinguishing thyroid cancer from normal individuals and may be the best diagnostic combination for this purpose. New research has shown that compared to benign thyroid tumors and healthy controls, expression of miR-130a-3p in serum extracellular vesicles is significantly reduced in thyroid malignant tumors.[31] The reduced levels are significantly correlated with the malignancy of the tumors and can serve as diagnostic biomarkers for thyroid malignant tumors.

Application of miRNA in the Regulation and Treatment of PTC

Dysregulated miRNAs can not only serve as screening and diagnostic markers for PTC, but also play critical regulatory roles in the proliferation and apoptosis of PTC cells. Most miRNAs directly regulate their target genes to exert anti-cancer effects, with a few playing oncogenic roles. Research has found that overexpression of miR-524-5p can inhibit the migration and proliferation of thyroid cancer cells.[1] MiR-145 is significantly downregulated in PTC and can directly target the RAB5C gene to inhibit PTC cell proliferation, migration, and promote apoptosis.[32] MiR-643 is significantly upregulated in PTC tissues and can target the CYP11B1 gene to promote thyroid cancer cell proliferation and inhibit apoptosis.[33] MiR-200c is an anti-cancer miRNA that directly regulates the DACH1 gene to promote PTC cell proliferation.[34] Overexpression of miR-144-3p in thyroid cancer tissues can affect cell proliferation, invasion, and apoptosis through the PTEN gene.[35] Overexpression of miR-144-5p can inhibit thyroid cancer cell proliferation by targeting the ITGA3 gene and promote apoptosis.[36] Overexpression of miR-9-5p can inhibit the viability of PTC cells by inducing apoptosis.[37] MiR-4728 is downregulated in PTC tissues and cell lines, and its overexpression can inhibit PTC

cell proliferation.[38] Downregulation of miR-363-3p can directly target the NOB1 gene to inhibit PTC cell proliferation.[39] In PTC and thyroid follicular carcinoma, reduced expression of miR-369-3p can target the TSPAN13 gene to inhibit PTC cell proliferation and promote apoptosis.[40] MiR-30a exerts anti-cancer effects in PTC by directly targeting the E2F7 gene.[41] Dysregulated miR-21-3p and miR-21-5p are closely related to the development of thyroid cancer, and their overexpression can downregulate the TIMP3, MAT2A, TGFBR2, and PLAT genes, which may be promising intervention strategies in thyroid cancer diagnosis and treatment.[42] MiR-592 is significantly upregulated in medullary thyroid cancer tissues and cell lines, promoting carcinogenesis by reducing CDK8 expression.[43] miRNAs can also activate entire signaling pathways by targeting one or more genes in the pathway to exert tumor regulatory effects. Research indicates that miRNAs play important regulatory roles as key regulators of signaling pathways in thyroid cancer, mainly targeting the MAPK, PI3K, and TGFβ pathways.[44] MiR-128 can inhibit thyroid cancer cell proliferation and promote apoptosis by suppressing the CXCR4/RhoA signaling pathway.[45] These studies show that miRNAs play a crucial role in regulating downstream target genes and signaling pathways in the proliferation and apoptosis of thyroid cancer cells. MiR-34 therapy, currently used in clinical studies, is a well-known miRNA treatment method where upregulated miRNAs can be inhibited by artificial antagonists, and downregulated miRNAs can be supplemented by synthetic miRNA mimics. In thyroid cancer research, it has been found that increasing the expression levels of miR-363-3p may be a candidate method for treating PTC.[39] These miRNA treatment methods are gradually becoming common strategies in cancer research, with miRNAs and their target genes in thyroid cancer potentially becoming new targets for regulation and potential therapeutic drugs.

Application of miRNA in the Progression and Prognosis of PTC

In recent years, despite advances in the diagnosis and treatment of PTC, the postoperative recurrence and metastasis rates of PTC remain high. miRNAs are key regulatory factors in the migration and invasion of PTC cancer cells, closely associated with tumor size, lymphovascular invasion, lymph node metastasis, and distant metastasis. Compared to other biomarkers, miRNAs are gradually becoming non-invasive prognostic biomarkers for thyroid cancer patients due to their accessibility, non-invasiveness, and stability. MiR-144-5p,[36] miR-363-3p,[39] miR-30a,[41] and miR-299-5p[5] can inhibit the invasion and migration of thyroid cancer cells. The expression level of miR-146b is directly correlated with tumor size and stage, with its overexpression promoting the migration and invasion of PTC cells.[46] Upregulation of miR-96-3p can promote the invasion and migration of PTCcells through regulation of the SDHB/AKT/mTOR pathway.[47] In vitro, miR-3121-3p promotes tumor invasion and migration in PTC by inhibiting the Rap1GAP gene.[48] MiR-625-3p, miR-564, miR-205, and miR-34c-5p play important regulatory roles in the migration and invasion of thyroid cancer cells.[49] Eight miRNAs, including miR-1179, miR-133b, miR-3194, miR-3912, miR-548j, miR-6720, miR-6734, and miR-6843, may impact the prognosis of PTC through the Hedgehog and calcium signaling pathways.[50] MiR-483-3p is upregulated in undifferentiated thyroid carcinoma and can predict the prognosis by targeting the Pard3 gene to promote TGFβ1-induced cell migration, invasion, and epithelial-mesenchymal transition.[51] Numerous miRNAs are associated with thyroid cancer recurrence and lymph node metastasis. MiR-146 is one of the most studied miRNAs in thyroid cancer, and a deeper study of its target genes can predict PTC lymph node metastasis.[7] Overexpression of miR-221 is significantly associated with PTC recurrence.[15] MiR-181p, miR-182, miR-183, miR-204, miR-206, miR-128-3p, and miR-375 can significantly influence the progress of PTC, while miR-193-3p, miR-182-5p, and miR-3607-3p are significantly associated with PTC metastasis.[46] MiR-136, miR-21, and miR-127 are significantly associated with distant metastasis and recurrence in thyroid cancer.[52] These reported miRNAs may become new prognostic biomarkers for PTC, playing a crucial role in prognosis. In-depth study of miRNA prognoses can help clinical doctors in their follow-up and patients in monitoring themselves, effectively avoiding unnecessary secondary invasive treatments.

The Application of Circular RNAs in PTC

Circular RNAs (circRNAs) constitute a large class of non-coding RNAs (ncRNAs) and are considered to be competitive endogenous RNAs (ceRNAs). They regulate gene expression and play a crucial role in various stages of cancer. Multiple circRNAs are vital in the development of PTC and may serve as important new biomarkers and/or targets for the diagnosis and treatment of PTC. The presence of miRNA binding sites or response elements in circRNAs enables them to

regulate miRNA function by acting as ceRNAs or "miRNA sponges".[53] High iodine levels exacerbate the malignancy of PTC through the circ_0004851/miR-296-3p/FGF11 axis.[54] CircLIFR inhibits the progression of PTC by regulating the miR-429/TIMP2 axis and may become a potential therapeutic target for PTC.[55] The downregulation of circPHGDH inhibits the progression of PTC through the miR122-5p/PKM2 axis.[56] CircSEMA6A affects the invasion and migration of PTC cells by targeting MiR-520h/ELAVL1.[57] CircNDST1 promotes the development of PTC by activating the PI3K–Akt pathway and EMT through interaction with CSNK2A1.[58] Circ_0003747 promotes the progression of thyroid cancer by upregulating PLCD3 expression through the absorption of miR-338-3p.[59] Circ_0058129 accelerates the progression of PTC through the miR-873-5p/FSTL1 pathway.[60] CircNRIP1 can act as a sponge for the oncomiRs miR-541-5p and miR-3064-5p, upregulate the expression of PKM2, and serve as a prognostic biomarker and therapeutic target for PTC.[61] Circ-CDC6 promotes the proliferation, migration, invasion, and tumor growth of PTC by adsorbing miR-129-5p and promoting the expression of LARP1.[62] CircPTPRM accelerates the malignancy of PTC through the miR-885-5p/DNMT3A axis.[63] CircPVT1 can act as a molecular sponge for miR-195 and promote the malignant progression of PTC.[64] CircLDLR promotes the tumorigenesis of PTC by regulating the miR-637/LMO4 axis.[65] Circ_0041829 and circ_0092299 play important roles in the progression of PTC.[66] Knocking down the expression of circ_0082182 significantly inhibits the activity, proliferation, migration, and invasion of TPC-1 cells.[67] Circ_0000144 promotes malignancy and angiogenesis in PTC by regulating the miR-1178-3p/YWHAH axis.[68] Circ_0000644 promotes the progression of thyroid papillary cancer by adsorbing miR-1205 and regulating the expression of E2F3.[69] It is known that circRNAs may be potential biomarkers for PTC, although they need to be verified before being implemented in clinical practice. With the development of new technologies for screening circular RNAs, they may one day be widely used for the diagnosis and monitoring of PTC.[53]

The Application of Immunotherapy in PTC

Immunotherapy is a promising avenue for the treatment of advanced thyroid cancer.[70,71] The prognosis of thyroid cancer patients varies significantly depending on different pathological types or different clinical conditions. Although immunotherapy has been applied in clinical practice, its therapeutic effect is still far from satisfactory. The response of PTC to immune checkpoint inhibitors (ICIs) is highly variable, and the response to ICIs depends on the immune system status of the treated individual, and the regulation of the immune system should be explored as a tool to improve the response of PTC patients to ICIs.[72] Researching the expression of immune checkpoint molecules in PTC and their correlation with clinical pathological characteristics and prognosis will help develop new treatment strategies. The expression of programmed death ligand 1 (PD-L1) is an established prerequisite for checkpoint inhibitor therapy, and PD-L1 expression is significantly associated with reduced disease-free survival (DFS), making it a potential prognostic biomarker for disease recurrence in PTC patients.[73] PD-L1 and B7-H3 are effective prognostic factors and potential therapeutic targets for high-risk thyroid cancer.[74] B7-H3 and ICAM-1, as two important immune checkpoint proteins (ICPs), are potential therapeutic targets for thyroid cancer and may pave the way for combination therapy in advanced thyroid cancer.[70] IRX5 can stimulate the transition of macrophages towards M2 in the immunological environment of thyroid cancer growth, providing a potential new focus for immunotherapy for thyroid cancer.[75] The expression of LPAR5 is associated with the prognosis of PTC and may provide a new target for PTC immunotherapy.[76] SIGLEC10 and SIGLEC15 can serve as important prognostic markers for PTC and attractive targets for immunotherapy.[77] The glucose metabolism-related gene PGBD5 may be a relatively important oncogene in PTC, and constructing a prognostic prediction model with it provides a new idea for guiding immune checkpoint blockade therapy in PTC.[78] PTC cases with BRAF mutations have higher expression of immune checkpoint markers CD274 and CTLA4, and BRAF-mutated or highly expressed PTC cases may be related to an immunologically "hot" signal and may benefit from immunotherapy strategies.[79] Researching immune cells and immune-related genes in the tumor microenvironment will help to more accurately identify low-risk PTC, which will greatly promote the development of immunotherapy for high-risk PTC.[80] Four types of immune cells (M1 macrophages, NK cells, $CD4^+$ memory T cells, and $CD8^+$ T cells) can be used to identify low-risk PTC, while six types of immune cells (M0 macrophages, M2 macrophages, γδT cells, resting mast cells, resting dendritic cells, and activated dendritic cells) and six immune-related genes (CSF2, CXCL5, CCL17, ICAM1, CCL19, and CD40LG) are closely related to high-risk PTC. In-depth research on immune cells and immune-related genes can provide a theoretical basis for

developing improved immunotherapy strategies.[80] The interaction between LAMP3+ dendritic cells and T cell subsets promotes the immune escape of papillary thyroid cancer, providing a new effective idea and strategy for immunotherapy in patients with progressive PTC.[81] Establishing a prognostic immune-related signature (IRS) to predict the progression-free survival (PFS) of PTC, the IRS shows stronger prognostic power and accurate survival prediction compared to conventional clinical and pathological characteristics.[82] Combining the expression of immune checkpoints and drug sensitivity, the cell senescence-related signature (CSRS) is a reliable predictor of prognosis in PTC patients, and patients with high-risk scores may benefit from immunotherapy, potentially becoming immune therapy response and prognostic biomarkers that affect the tumor immune microenvironment of PTC.[83] Patients with high tumor mutation burden (TMB) have poor prognosis, and stratifying PTC patients by TMB can select advanced PTC patients suitable for immunotherapy.[71] Many miRNAs are also closely related to genes associated with immunotherapy in PTC. In thyroid cancer, miR-148a targets PD-L1 to downregulate its expression.[84] MiR-199a-5p plays an important role in the progression and metastasis of follicular thyroid cancer by regulating the expression of PD-L1.[85] MiR-335-5p targeting ICAM-1 inhibits invasion and metastasis of thyroid cancer cells.[86] LPAR5 is a target gene of miR-513c-5p and has the ability to eliminate the effects of miR-513c-5p on thyroid cancer cells.[87] MiR-31 is important in the dedifferentiation of PTC induced by $BRAF^{V600E}$, possibly due to its regulation of the Wnt/β-catenin pathway.[88] The $BRAF^{V600E}$ oncogene regulates miR-222-3p, promoting cell migration of PTC as well as Snail-induced EMT, and is associated with lymph node metastasis in PTC patients.[89] It is hypothesized that the above immune therapy-related cells and genes can serve as biomarkers for predicting prognosis and can be used to identify biomarkers for high-risk and low-risk PTC, which will help clinicians determine prognosis early and further develop personalized immunotherapy regimens.

Considerations on the Application of miRNA in PTC Research

MiRNA has been proven to play an important role in screening, diagnosis, regulation, treatment, and prognosis of PTC. However, there are still certain limitations in research on miRNA in PTC. The detection methods of miRNA are not mature enough, they are diverse in form, yet there is no unified detection standard. Many miRNAs are widely distributed in the human body, besides being dysregulated in PTC, they also show abnormal expression in other cancers and diseases. Therefore, further research is needed on the specificity of miRNA detection. Moreover, in order to establish criteria for the screening, diagnosis, and prognosis of PTC using miRNA in populations, larger sample size studies and multi-center studies are still required to obtain reliable threshold standards. There are multiple target points in the regulation of miRNA for PTC treatment. miRNA can target and regulate multiple genes and signaling pathways, as well as regulate various physiological and pathological mechanisms. Therefore, the safety and specificity of using miRNA in clinical treatment of thyroid cancer still need further validation. In addition, a significant amount of prospective research is required on issues such as the dose, method of administration, and site of administration for miRNA therapy for PTC. In conclusion, miRNA has a promising application prospect in the diagnosis and treatment of thyroid cancer, but further research is needed on the regulatory effects of miRNA and its target genes. Only by continuously transforming laboratory research into clinical diagnosis and treatment, can miRNA provide new ideas and methods for the screening, regulation, treatment, and prognosis of PTC.

Limitations

In this study, we used bibliometrics and visualization analysis to elucidate the current application status of miRNA in PTC research, making this study relatively detailed and objective. However, there are still some inevitable limitations in this research. Firstly, the literature data of this study all come from the WoSCC database, which is the most widely used and authoritative database; however, there are still some publications that are not included in the WoSCC database. Secondly, non-English publications were not included in this study. Additionally, this study only analyzed original articles and reviews, overlooking the value of other publications.

Conclusion

In summary, over the past twenty years, the annual number of publications on miRNA in PTC research has shown an increasing trend from 1999 to 2020, with the highest number of articles published in 2020, followed by a gradual

decrease in publications after 2021. The results of this study, by summarizing and visualizing publication trends, research hotspots, collaborative relationships, and cutting-edge research, provide a foundation and new frontiers for future research on miRNA in PTC, enabling readers to quickly and effectively access useful information in this field. These findings will help the research community explore emerging topics and mechanisms, and provide guidance for future clinical trials in PTC.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Approval

This study was prepared in accordance with the Committee on Publication Ethics (COPE) guidelines to respect third parties' rights such as copyright and/or moral rights. Ethical approval was not required to conduct this project, as data are not individualized and primary data were not collected.

Consent for Publication

All authors have read and approved the content and agree to submit the final manuscript for consideration and publication in your journal.

Acknowledgments

We acknowledge that all authors participated sufficiently in the work and take public responsibility for its content.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Jiang S, Yan J, Chen X, et al. Ginsenoside Rh2 inhibits thyroid cancer cell migration and proliferation via activation of miR-524-5p. *Arch Med Sci*. 2022;18(1):164–170. doi:10.5114/aoms.2020.92871
2. Buczyńska A, Kościuszko M, Krętowski AJ, Popławska-Kita A. Exploring the clinical utility of angioinvasion markers in papillary thyroid cancer: a literature review. *Front Endocrinol*. 2023;14:1261860. doi:10.3389/fendo.2023.1261860
3. Ruiz-Pozo VA, Cadena-Ullauri S, Guevara-Ramírez P, Paz-Cruz E, Tamayo-Trujillo R, Zambrano AK. Differential microRNA expression for diagnosis and prognosis of papillary thyroid cancer. *Front Med Lausanne*. 2023;10:1139362. doi:10.3389/fmed.2023.1139362
4. Rogucki M, Sidorkiewicz I, Niemira M, et al. Expression profile and diagnostic significance of microRNAs in papillary thyroid cancer. *Cancers*. 2022;14(11):2679. doi:10.3390/cancers14112679
5. Wang Z, He L, Sun W, et al. miRNA-299-5p regulates estrogen receptor alpha and inhibits migration and invasion of papillary thyroid cancer cell. *Cancer Manag Res*. 2018;10:6181–6193. doi:10.2147/CMAR.S182625
6. Boucai L, Zafereo M, Cabanillas ME. Thyroid cancer: a review. *JAMA*. 2024;331(5):425–435. doi:10.1001/jama.2023.26348
7. Santiago K, Chen Wongworawat Y, Khan S. Differential microRNA-signatures in thyroid cancer subtypes. *J Oncol*. 2020;2020:2052396. doi:10.1155/2020/2052396
8. Network CGAR, Akbani R, Aksoy B. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676–690. doi:10.1016/j.cell.2014.09.050
9. Cortez MA, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. MicroRNAs in body fluids--The mix of hormones and biomarkers. *Nat Rev Clin Oncol*. 2011;8(8):467–477. doi:10.1038/nrclinonc.2011.76
10. He H, Jazdzewski K, Li W, et al. The role of microRNA genes in papillary thyroid carcinoma. *Proc Natl Acad Sci U S A*. 2005;102(52):19075–19080. doi:10.1073/pnas.0509603102

11. Chou CK, Yang KD, Chou FF, et al. Prognostic implications of miR-146b expression and its functional role in papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2013;98(2):E196–205. doi:10.1210/jc.2012-2666
12. Pallante P, Visone R, Ferracin M, et al. MicroRNA deregulation in human thyroid papillary carcinomas. *Endocr Relat Cancer*. 2006;13(2):497–508. doi:10.1677/erc.1.01209
13. Nikiforova MN, Tseng GC, Steward D, Diorio D, Nikiforov YE. MicroRNA expression profiling of thyroid tumors: biological significance and diagnostic utility. *J Clin Endocrinol Metab*. 2008;93(5):1600–1608. doi:10.1210/jc.2007-2696
14. Rogucki M, Buczynska A, Kretowski AJ, Poplawska-Kita A. The Importance of miRNA in the diagnosis and prognosis of papillary thyroid cancer. *J Clin Med*. 2021;10(20):4738. doi:10.3390/jcm10204738
15. Celakovsky P, Kovarikova H, Chrobok V, et al. MicroRNA deregulation in papillary thyroid cancer and its relationship with BRAF V600E mutation. *In Vivo*. 2021;35(1):319–323. doi:10.21873/invivo.12262
16. Cai S, Ma J, Wang Y, et al. Biomarker value of miR-221 and miR-222 as potential substrates in the differential diagnosis of papillary thyroid cancer based on data synthesis and bioinformatics approach. *Front Endocrinol*. 2021;12:794490. doi:10.3389/fendo.2021.794490
17. Wang L, Duan Y, Peng W, et al. miR-21 facilitates the diagnostic value of miR-138 for papillary thyroid cancer in formalin-fixed paraffin-embedded tissues. *Transl Cancer Res*. 2019;8(5):1718–1726. doi:10.21037/tcr.2019.08.14
18. Armos R, Bojtor B, Papp M, et al. MicroRNA profiling in papillary thyroid cancer. *Int J Mol Sci*. 2024;25(17):9362. doi:10.3390/ijms25179362
19. Shen Y, Li X, Xie R, et al. Expression levels of microRNA-300/BCL2L11 in papillary thyroid cancer and their clinical diagnostic values. *Eur Surg Res*. 2023;64(3):342–351. doi:10.1159/000530682
20. Papaioannou M, Chorti AG, Chatzikyriakidou A, Giannoulis K, Bakkar S, Papavramidis TS. MicroRNAs in papillary thyroid cancer: what is new in diagnosis and treatment. *Front Oncol*. 2021;11:755097. doi:10.3389/fonc.2021.755097
21. Chen Y, Dong B, Huang L, Huang H. Serum microRNAs as biomarkers for the diagnosis of papillary thyroid carcinoma: a meta-analysis. *Bosnian J Basic Med Sci*. 2022;22(6):862–871. doi:10.17305/bjbms.2022.7343
22. Cui W, Xuan T, Liao T, Wang Y. From sequencing to validation: NGS-based exploration of plasma miRNA in papillary thyroid carcinoma. *Front Oncol*. 2024;14. doi:10.3389/fonc.2024.1410110.
23. Perdas E, Stawski R, Kaczka K, Zubrzycka M. Analysis of let-7 family miRNA in plasma as potential predictive biomarkers of diagnosis for papillary thyroid cancer. *Diagnostics*. 2020;10(3). doi:10.3390/diagnostics10030130
24. Kazlauskiene M, Klimaite R, Kondrotiene A, et al. Plasma miRNA-146b-3p, −222-3p, −221-5p, −21a-3p expression levels and TSHR methylation: diagnostic potential and association with clinical and pathological features in papillary thyroid cancer. *Int J Mol Sci*. 2024;25(15):8412. doi:10.3390/ijms25158412
25. Kondrotiene A, Dauksa A, Pamedytyte D, et al. Plasma-derived miRNA-222 as a candidate marker for papillary thyroid cancer. *Int J Mol Sci*. 2020;21(17):6445. doi:10.3390/ijms21176445
26. Rezaei M, Khamaneh AM, Zarghami N, Vosoughi A, Hashemzadeh S. Evaluating pre- and post-operation plasma miRNAs of papillary thyroid carcinoma (PTC) patients in comparison to benign nodules. *BMC Cancer*. 2019;19(1):690. doi:10.1186/s12885-019-5849-0
27. Ghafouri-Fard S, Shirvani-Farsani Z, Taheri M. The role of microRNAs in the pathogenesis of thyroid cancer. *Noncoding RNA Res*. 2020;5(3):88–98. doi:10.1016/j.ncrna.2020.06.001
28. Geropoulos G, Psarras K, Papaioannou M, et al. Circulating microRNAs and clinicopathological findings of papillary thyroid cancer: a systematic review. *In Vivo*. 2022;36(4):1551–1569. doi:10.21873/invivo.12866
29. Maggisano V, Capriglione F, Verrienti A, et al. Identification of exosomal microRNAs and their targets in papillary thyroid cancer cells. *Biomedicines*. 2022;10(5):961. doi:10.3390/biomedicines10050961
30. Toraih EA, Elshazli RM, Trinh LN, et al. Diagnostic and prognostic performance of liquid biopsy-derived exosomal microRNAs in thyroid cancer patients: a systematic review and meta-analysis. *Cancers*. 2021;13(17):4295. doi:10.3390/cancers13174295
31. Yin G, Kong W, Zheng S, et al. Exosomal miR-130a-3p promotes the progression of differentiated thyroid cancer by targeting insulin-like growth factor 1. *Oncol Lett*. 2021;21(4):283. doi:10.3892/ol.2021.12544
32. Zhang W, Ji W, Li T, Liu T, Zhao X. MiR-145 functions as a tumor suppressor in papillary thyroid cancer by inhibiting RAB5C. *Int J Med Sci*. 2020;17(13):1992–2001. doi:10.7150/ijms.44723
33. Yin H, Shao J. MicroRNA-643 promotes proliferation and inhibits apoptosis of papillary thyroid carcinoma by down-regulating the cytochrome P450 family member 11B1. *Transl Cancer Res*. 2020;9(3):1465–1475. doi:10.21037/tcr.2020.01.43
34. Ren ZF, Du MF, Fu H, et al. MiR-200c promotes proliferation of papillary thyroid cancer cells via Wnt/beta-catenin signaling pathway. *Eur Rev Med Pharmacol Sci*. 2020;24(10):5512–5518. doi:10.26355/eurrev_202005_21336
35. Cao HL, Gu MQ, Sun Z, Chen ZJ. miR-144-3p contributes to the development of thyroid tumors through the PTEN/PI3K/AKT pathway. *Cancer Manag Res*. 2020;12:9845–9855. doi:10.2147/CMAR.S265196
36. Zhang J, Zhong Y, Sang Y, Ren G. miRNA-144-5p/ITGA3 suppressed the tumor-promoting behaviors of thyroid cancer cells by downregulating ITGA3. *Comput Math Methods Med*. 2021;2021:9181941. doi:10.1155/2021/9181941
37. Guo F, Hou X, Sun Q. MicroRNA-9-5p functions as a tumor suppressor in papillary thyroid cancer via targeting BRAF. *Oncol Lett*. 2018;16(5):6815–6821. doi:10.3892/ol.2018.9423
38. Liu Z, Zhang J, Gao J, Li Y. MicroRNA-4728 mediated regulation of MAPK oncogenic signaling in papillary thyroid carcinoma. *Saudi J Biol Sci*. 2018;25(5):986–990. doi:10.1016/j.sjbs.2018.05.014
39. Dong S, Xue S, Sun Y, et al. MicroRNA-363-3p downregulation in papillary thyroid cancer inhibits tumor progression by targeting NOB1. *J Investig Med*. 2021;69(1):66–74. doi:10.1136/jim-2020-001562
40. Li P, Dong M, Wang Z. Downregulation of TSPAN13 by miR-369-3p inhibits cell proliferation in papillary thyroid cancer (PTC). *Bosn J Basic Med Sci*. 2019;19(2):146–154. doi:10.17305/bjbms.2018.2865
41. Guo H, Zhang L. MicroRNA-30a suppresses papillary thyroid cancer cell proliferation, migration and invasion by directly targeting E2F7. *Exp Ther Med*. 2019;18(1):209–215. doi:10.3892/etm.2019.7532
42. Nwadiugwu MC. Thyroid tumor: investigating microRNA-21 gene suppression in FTC and FTA. *Cancer Inform*. 2020;19:1176935120948474. doi:10.1177/1176935120948474
43. Liu T, Meng J, Zhang Y. miR592 acts as an oncogene and promotes medullary thyroid cancer tumorigenesis by targeting cyclin-dependent kinase 8. *Mol Med Rep*. 2020;22(4):3316–3326. doi:10.3892/mmr.2020.11392

44. Ramirez-Moya J, Santisteban P. miRNA-directed regulation of the main signaling pathways in thyroid cancer. *Front Endocrinol*. 2019;10:430. doi:10.3389/fendo.2019.00430
45. Zheng X, Wang S, Hong S, et al. CXCR4/RhoA signaling pathway is involved in miR-128-regulated proliferation and apoptosis of human thyroid cancer cells. *Int J Clin Exp Pathol*. 2017;10(9):9213–9222.
46. Ulisse S, Baldini E, Lauro A, et al. Papillary thyroid cancer prognosis: an evolving field. *Cancers*. 2021;13(21). doi:10.3390/cancers13215567
47. Zhao X, Li Y, Zhou Y. MicroRNA-96-3p promotes metastasis of papillary thyroid cancer through targeting SDHB. *Cancer Cell Int*. 2019;19:287. doi:10.1186/s12935-019-1003-y
48. Xu M, Zhou J, Zhang Q, et al. MiR-3121-3p promotes tumor invasion and metastasis by suppressing Rap1GAP in papillary thyroid cancer in vitro. *Ann Transl Med*. 2020;8(19):1229. doi:10.21037/atm-20-4469
49. Hamidi AA, Taghehchian N, Basirat Z, Zangouei AS, Moghbeli M. MicroRNAs as the critical regulators of cell migration and invasion in thyroid cancer. *Biomark Res*. 2022;10(1):40. doi:10.1186/s40364-022-00382-4
50. Yi W, Liu J, Qu S, Fan H, Lv Z. An 8 miRNA-based risk score system for predicting the prognosis of patients with papillary thyroid cancer. *Technol Cancer Res Treat*. 2020;19:1533033820965594. doi:10.1177/1533033820965594
51. Zhang X, Liu L, Deng X, et al. MicroRNA 483-3p targets Pard3 to potentiate TGF-beta1-induced cell migration, invasion, and epithelial-mesenchymal transition in anaplastic thyroid cancer cells. *Oncogene*. 2019;38(5):699–715. doi:10.1038/s41388-018-0447-1
52. Park JL, Kim SK, Jeon S, Jung CK, Kim YS. MicroRNA profile for diagnostic and prognostic biomarkers in thyroid cancer. *Cancers*. 2021;13(4). doi:10.3390/cancers13040632
53. Zhang Y, Jia -D-D, Zhang Y-F, et al. The emerging function and clinical significance of circRNAs in thyroid cancer and autoimmune thyroid diseases. *Int J Biol Sci*. 2021;17(7):1731–1741. doi:10.7150/ijbs.55381
54. J-j L, Z-x R, Yang X, et al. Circ_0004851 regulates the molecular mechanism of miR-296-3p/FGF11 in the influence of high iodine on PTC. *J Transl Med*. 2024;22(1). doi:10.1186/s12967-024-05405-2
55. Zhang F, Li J, Xu J, Jiang X, Chen S, Nasser QA. Circular RNA circLIFR suppresses papillary thyroid cancer progression by modulating the miR-429/TIMP2 axis. *J Cancer Res Clin Oncol*. 2024;150(6). doi:10.1007/s00432-024-05839-7
56. Shen J, Ma Z, Yang J, et al. CircPHGDH downregulation decreases papillary thyroid cancer progression through miR-122-5p/PKM2 axis. *BMC Cancer*. 2024;24(1). doi:10.1186/s12885-024-12199-5
57. Liu Y, Xin Y, Shang X, Tian Z, Xue G. CircSEMA6A upregulates PRRG4 by targeting MiR-520h and recruiting ELAVL1 to affect cell invasion and migration in papillary thyroid carcinoma. *Arch Endocrinol Metab*. 2024;68. doi:10.20945/2359-4292-2021-0541.
58. Shu C, Wang S, Hu J, et al. CircNDST1 promotes papillary thyroid cancer progression via its interaction with CSNK2A1 to activate the PI3K–Akt pathway and epithelial–mesenchymal transition. *J Endocrinol Invest*. 2022;46(3):545–557. doi:10.1007/s40618-022-01928-x
59. Dou X-L, Xia F-D, X-Y L. Circ_0003747 promotes thyroid cancer progression by sponging miR-338-3p to upregulate PLCD3 expression. *Epigenetics*. 2023;18(1). doi:10.1080/15592294.2023.2210339
60. Tan X, Zhao J, Lou J, Zheng W, Wang P. Hsa_circ_0058129 regulates papillary thyroid cancer development via miR-873-5p/follistatin-like 1 axis. *J Clin Lab Anal*. 2022;36(5). doi:10.1002/jcla.24401
61. Ji X, Lv C, Huang J, Dong W, Sun W, Zhang H. ALKBH5-induced circular RNA NRIP1 promotes glycolysis in thyroid cancer cells by targeting PKM2. *Cancer Sci*. 2023;114(6):2318–2334. doi:10.1111/cas.15772
62. Li P, Chen J, Zou J, Zhu W, Zang Y, Li H. Circular RNA coiled-coil domain containing 66 regulates malignant development of papillary thyroid carcinoma by upregulating La ribonucleoprotein 1 via the sponge effect on miR-129-5p. *Bioengineered*. 2022;13(3):7181–7196. doi:10.1080/21655979.2022.2036304
63. Chen D, Jiang X, Luo H, Hua Q, Zhang F. CircPTPRM accelerates malignancy of papillary thyroid cancer via miR-885-5p/DNMT3A axis. *J Clin Lab Anal*. 2022;36(10). doi:10.1002/jcla.24688
64. Zeng L, Yuan S, Zhou P, Gong J, Kong X, Wu M. Circular RNA Pvt1 oncogene (CircPVT1) promotes the progression of papillary thyroid carcinoma by activating the Wnt/β-catenin signaling pathway and modulating the ratio of microRNA-195 (miR-195) to vascular endothelial growth factor A (VEGFA) expression. *Bioengineered*. 2021;12(2):11795–11810. doi:10.1080/21655979.2021.2008639
65. Y-m J, Liu W, Jiang L, Chang H, Tu W-J. CircLDLR promotes papillary thyroid carcinoma tumorigenicity by regulating miR-637/LMO4 axis. *Dis Markers*. 2021;2021:1–12. doi:10.1155/2021/3977189
66. Kim JY, Lee Y, Dho SH, et al. Integrative analysis of circular RNA regulatory network in papillary thyroid carcinoma. *Am J Cancer Res*. 2023;13(9):4446–4465.
67. Wang B, Shen W, Yan L, et al. Reveal the potential molecular mechanism of circRNA regulating immune-related mRNA through sponge miRNA in the occurrence and immune regulation of papillary thyroid cancer. *Ann Med*. 2023;55(2). doi:10.1080/07853890.2023.2244515
68. Ma Y, Yang D, Guo P. Circ_0000144 acts as a miR-1178-3p decoy to promote cell malignancy and angiogenesis by increasing YWHAH expression in papillary thyroid cancer. *J Otolaryngol - Head Neck Surg*. 2022;51(1). doi:10.1186/s40463-022-00574-w
69. Nie C, Han J, Bi W, et al. Circular RNA circ_0000644 promotes papillary thyroid cancer progression via sponging miR-1205 and regulating E2F3 expression. *Cell Cycle*. 2021;21(2):126–139. doi:10.1080/15384101.2021.2012334
70. Song P, Xu Y, Ye G. B7-H3 and ICAM-1 are potentially therapeutic targets for thyroid carcinoma. *Diagn Pathol*. 2024;19(1). doi:10.1186/s13000-024-01504-2
71. Xie Z, Li X, Lun Y, et al. Papillary thyroid carcinoma with a high tumor mutation burden has a poor prognosis. *Int Immunopharmacol*. 2020;89:107090. doi:10.1016/j.intimp.2020.107090
72. Pani F, Yasuda Y, Rousseau ST, et al. Preconditioning of the immune system modulates the response of papillary thyroid cancer to immune checkpoint inhibitors. *J ImmunoTher Cancer*. 2022;10(12):e005538. doi:10.1136/jitc-2022-005538
73. Girolami I, Pantanowitz L, Mete O, et al. Programmed death-ligand 1 (PD-L1) is a potential biomarker of disease-free survival in papillary thyroid carcinoma: a systematic review and meta-analysis of PD-L1 immunoexpression in follicular epithelial derived thyroid carcinoma. *Endocr Pathol*. 2020;31(3):291–300. doi:10.1007/s12022-020-09630-5
74. Zhu X, Hu C, Zhang Z, et al. PD-L1 and B7-H3 are effective prognostic factors and potential therapeutic targets for high-risk thyroid cancer. *Endocr Pathol*. 2024;35(3):230–244. doi:10.1007/s12022-024-09822-3
75. Qin L, Chen C, Gui Z, Jiang Y. IRX5's influence on macrophage polarization and outcome in papillary thyroid cancer. *Front Oncol*. 2024;14. doi:10.3389/fonc.2024.1399484.

76. Zhang B, Zhang L, Qi P, et al. Potential role of LPAR5 gene in prognosis and immunity of thyroid papillary carcinoma and pan-cancer. *Sci Rep*. 2023;13(1). doi:10.1038/s41598-023-32733-y
77. Jin T, Wang W, Ge L, Li X, Ge M. The expression of two immunosuppressive SIGLEC family molecules in papillary thyroid cancer and their effect on prognosis. *Endocrine*. 2023;82(3):590–601. doi:10.1007/s12020-023-03452-1
78. Xie W, Zeng Y, Hu L, et al. Based on different immune responses under the glucose metabolizing type of papillary thyroid cancer and the response to anti-PD-1 therapy. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.991656
79. Mohanty A, Afkhami M, Reyes A, et al. Exploring markers of immunoresponsiveness in papillary thyroid carcinoma and future treatment strategies. *J ImmunoTher Cancer*. 2024;12(7):e008505. doi:10.1136/jitc-2023-008505
80. Li X, Jian J, Zhang A, Xiang J, Huang J, Chen Y. The role of immune cells and immune related genes in the tumor microenvironment of papillary thyroid cancer and their significance for immunotherapy. *Sci Rep*. 2024;14(1). doi:10.1038/s41598-024-69187-9
81. Wang Z, Ji X, Zhang Y, et al. Interactions between LAMP3+ dendritic cells and T-cell subpopulations promote immune evasion in papillary thyroid carcinoma. *J ImmunoTher Cancer*. 2024;12(5):e008983. doi:10.1136/jitc-2024-008983
82. Sun J, Shi R, Zhang X, et al. Characterization of immune landscape in papillary thyroid cancer reveals distinct tumor immunogenicity and implications for immunotherapy. *Oncoimmunology*. 2021;10(1). doi:10.1080/2162402x.2021.1964189
83. Huang Y, Jiang H, Xu G, et al. Comprehensive analysis of cellular senescence and immune microenvironment in papillary thyroid carcinoma. *Aging*. 2024;16(3):2866–2886. doi:10.18632/aging.205520
84. Wang X, Zhang Y, Zheng J, Yao C, Lu X. LncRNA UCA1 attenuated the killing effect of cytotoxic CD8 + T cells on anaplastic thyroid carcinoma via miR-148a/PD-L1 pathway. *Cancer Immunol Immunother*. 2021;70(8):2235–2245. doi:10.1007/s00262-020-02753-y
85. Lin J, Qiu Y, Zheng X, Dai Y, Xu T. The miR-199a-5p/PD-L1 axis regulates cell proliferation, migration and invasion in follicular thyroid carcinoma. *BMC Cancer*. 2022;22(1). doi:10.1186/s12885-022-09838-0
86. Luo L, Xia L, Zha B, et al. miR-335-5p targeting ICAM-1 inhibits invasion and metastasis of thyroid cancer cells. *Biomed Pharmacother*. 2018;106:983–990. doi:10.1016/j.biopha.2018.07.046
87. Tong C, Wang C, Wang Y, Xiao X. TNRC6C-AS1 promotes thyroid cancer progression by upregulating LPAR5 via miR-513c-5p. *Cancer Manage Res*. 2021;13:6141–6155. doi:10.2147/cmar.S312621
88. Zhang P, Guan L, Sun W, et al. Targeting miR-31 represses tumourigenesis and dedifferentiation of BRAFV600E-associated thyroid carcinoma. *Clin Transl Med*. 2024;14(5). doi:10.1002/ctm2.1694
89. Gao Y, Xiang D, Li W, et al. BRAFV600E mutation-responsive miRNA-222-3p promotes metastasis of papillary thyroid cancer cells via snail-induced EMT. *Front Endocrinol*. 2022;13. doi:10.3389/fendo.2022.843334