Systematic Review and Meta-Analysis

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Research trends for papillary thyroid carcinoma from 2010 to 2019

A systematic review and bibliometrics analysis

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Abstract

Background: Thyroid carcinoma comprises the fastest rising incidence of carcinomas over the past decade. Papillary thyroid carcinoma (PTC) is the most predominant type of thyroid carcinoma. This study aimed to assess the research trends in the field of PTC.

Methods: Publications from January 2010 to December 2019 were retrieved from the Web of Science Core Collection database using Thompson Reuters. Searching strategies were determined according to Medical Subject Heading terms. Different kinds of bibliometrics software, such as HistCite and VOSviewer, and online bibliometrics analysis platforms were utilized to evaluate and visualize the results.

Results: A total of 8102 publications across 93 countries were identified, with the annual number of publications showing an increasing trend. The United States, China, and South Korea showed their dominant position in PTC publication outputs, H-index, total citations, and international collaborations. *Thyroid* was the most productive journal. Akira Miyauchi published the most articles, and the most productive institution was *Yonsei University*. The hotspots keywords *proliferation*, *invasion and metastasis*, *diagnoses and prognoses*, *therapeutic resistance*, *recurrence*, and *microcarcinomas* appeared earlier and were sustained over the last 3 years.

Conclusions: This bibliometric study provides a comprehensive analysis delineating the scientific productivity, collaboration, and research hotspots within the PTC field, which will be very helpful when focusing on the direction of research over the next few years.

Abbreviations: ceRNA = competing endogenous RNA, H-index = Hirsch index, PTC = papillary thyroid carcinoma, SCI-E = Science Citation Index Expanded, TS = Theme Search.

Keywords: bibliometrics analysis, hotspot keywords, papillary thyroid carcinoma (PTC), research trends

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common histopathological thyroid carcinoma – accounting for 84% of all thyroid carcinomas – and its incidence rate has been rapidly rising over the past 3 decades.[1–3] Although PTC has a favorable prognosis with a 10-year survival rate exceeding 90%, a certain number of patients suffer from aggressive metastasis, recurrence, and iodine-131 therapy resistance, which can cause an unbearable economic burden at the personal and societal level and significantly decrease the patients' quality of life. These symptoms are almost entirely ascribed to the absence of an intensive evaluation of effective therapeutic measures and controllable risk factors.[4,5] Therefore, to develop more scientific research strategies that contribute to better prevention and treatment, integrated, systematic, and accurate assessments of the research status within the PTC field should be conducted.

Although a great number of systematic reviews and meta-analyses have extensively and clearly addressed the PTC field research status,[6–8] few studies have summarized this topic from the perspective of bibliometric analysis or provided the developing trends in this research domain. Bibliometric analysis involves analyzing the research performance of authors, countries, journals, subjects, institutions, and the development trends of publications within similar topics.[9] It is extremely important to capture the appropriate literature and to facilitate

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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an understanding of the characteristics and trends of a specific focus area. Bibliometric analysis can also present the most influential research quickly and accurately, which provides a theoretical basis for further research. Moreover, this information can provide policy guidance to decision-makers, which are widely applied in biomedical studies such as cancer research, macrophage polarization, radiation therapy, and reproductive and developmental toxicity of nanoparticles.[10–12]

Hence, the present study aimed to conduct a bibliometric analysis of the development trends, distribution pattern characteristics (such as institutions, subjects, funding, journals, countries, and authors), hotspot keywords, and frontier topics, published in PTC publications between 2010 and 2019. The study provided a brief overview of the achievements and landmarks in the PTC research domain as well as useful insights into the frontier hotspot trends, which would be beneficial when devising scientific research strategies in the coming years.[13]

2. Materials and methods

2.1. Data sources and search strategy

Data were obtained from the Web of Science Core Collection databases, the most well-known and influential scientific literature database, including from the Science Citation Index Expanded (SCI-E). In line with Medical Subject Heading terms, the search strategy conducted was "TS = (Cancer, Papillary Thyroid) or (Cancers, Papillary Thyroid) or (Papillary Thyroid Cancer) or (Papillary Thyroid Cancers) or (Thyroid Cancers, Papillary) or (Thyroid Carcinoma, Papillary) or (Carcinoma, Papillary Thyroid) or (Carcinomas, Papillary Thyroid) or (Papillary Thyroid Carcinomas) or (Thyroid Carcinomas, Papillary) or (Papillary Carcinoma Of Thyroid) or (Papillary Thyroid Carcinoma))." The time interval for the search was from 2010 to 2019 – a total of 10 years. The document type was "article," and the language was English. All electronic searches were performed in March 2020 and the year 2020 was eliminated from the analysis, as complete data for that year were unavailable. A flowchart of including and excluding publications is shown in Figure 1.

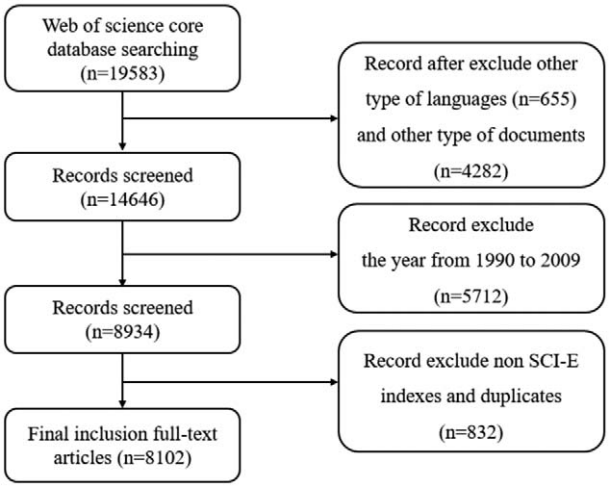

Figure 1. Flowchart of included and excluded publications.

2.2. Data collection

A total of 8102 bibliographic records were obtained from the database that met the inclusion criteria. The inclusive publications were downloaded and exported into different file formats for analysis. Analysis indicators included yearly and accumulative document numbers, average citations, funding, subjects, journals, institutions, countries of origin, authors, hotspot keywords, and frontier topics. Bradford law and Lotka law were introduced to describe and discover the "core journals" and "core authors" in this bibliometric analysis.

2.3. Statistical analysis

To assess different aspects of the obtained information, 2 programs were used to analyze the search results: HistCite (version 2.0), developed by Eugene Garfield, and VOSviewer (version 1.6.6), a tool for constructing and visualizing bibliometric networks, run by the Centre for Science and Technology Studies at Leiden University. The online bibliometric analysis software https://bibliometric.com/ was used to analyze international collaboration between countries. We used SPSS 21.0 software to analyze the trends of the publications according to the year. A regression model was used to fit the curve of the cumulative number of articles. GraphPad Prism and Sigma Plot software were used to create graphics. The 2019 impact factor (IF) of journals was obtained from the Journal Citation Reports of Thomson Reuters on June 29, 2020. Hirsch index (H-index) and average citations were consulted by citation reports from the Web of Science database.

2.4. Ethical approval

All data in this bibliometric analysis were extracted from a public database, and no ethical approval or patient consent was required.

3. Results

3.1. Publications and citations

In total, 8102 articles were published in the Web of Science database with the SCI-E index of the PTC research domain from 2010 to 2019, accounting for 57.93% (8102/13,986) of all publications from 1900 to 2019. The growth trends of the cumulative documents accorded with the quadratic function growth curve model, with the formula $f(x) = 29.01(t-2009)^2 + 519.40(t-2009) + 19.70$ ($R^2 = 1.00$, $P < 0.01$). Accordingly, it could be predicted that in 2020, 9243 (1141 new articles) cumulative articles would be published. Based on the Gompertz growth model $f(x) = e^{6.554+0.269(t-2009)}$ ($R^2 = 0.936$, $P < 0.01$), it could be predicted that 2016 would be the year with the highest publication growth rate. After 2016, the growth rate would decrease; however, the cumulative number of publications would continue to grow. The average citation trends continually decreased from 29.49 in 2010 to 1.22 in 2019. We speculated that this might be attributed to the large volume of new articles, with citations lagging behind (Fig. 2).

3.2. Publication distribution among funding bodies, subjects, journals, and institutions

The most productive funding body was the *National Natural Science Foundation of China*, contributing to the largest number

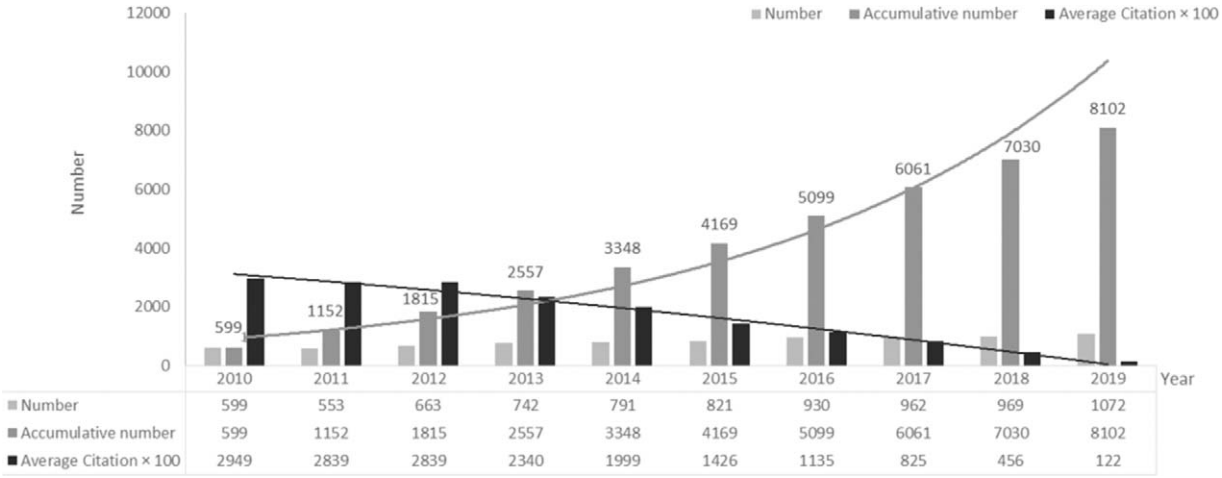

Figure 2. Publications of articles in the field of PTC research from 2010 to 2019. The grey curve represents the cumulative growth trend and the black curve represents the average citation trend. PTC = papillary thyroid carcinoma.

of publications (593 articles). Articles funded by the *United States Department of Health and Human Services* and *National Institutes of Health (NIH) USA* had the highest H-index (35.13 and 35.15, respectively) and had average citations (both with 62) among the top 10 most productive funding bodies (Fig. 3A). The subjects *oncology*, *endocrinology metabolism*, *surgery*, and *pathology* were the most productive research fields (subjects were defined as per their description in Web of Science) (Fig. 3B).

All the articles obtained belonged to a total of 901 SCI journals. According to Bradford law, the top 10 most productive journals – with 2083 published articles – should be considered as the "core journals" in the PTC research field. Based on the citation network, we divided the top 100 journals into 4 clusters and found that the same research field journals tended to cluster under the same categories – mainly focusing on *Thyroid* (in yellow), *World Journal of Surgery* (in green), *Oncology Letters* (in red), and *Endocrine Pathology* (in blue). Accordingly, *Thyroid* (534 articles) had the largest number of publications, followed by the *Journal of Clinical Endocrinology* (which had the highest average citations at 41.52) and *the World Journal of Surgery* (Fig. 3C and D).

Furthermore, we evaluated the most productive institutions and authors in our study. The 8102 obtained articles were contributed by 5376 institutions. Yonsei University, situated in South Korea, was the most productive institution, with 221 articles published. Mem Sloan Lettering Cancer Center, situated in the United States, possessed the highest H-index (44) and the highest average citations (49.35) among the top 10 most productive institutions, followed by the University Texas MD Anderson Cancer Center, situated in the United States and University of Pisa, situated in Italy. Based on co-authorship networks, we divided the top 100 institutions into 5 clusters and discovered the closer collaboration between institutions inclined into enrichment in the same categories. We identified Yonsei University (yellow), Mem Sloan Lettering Cancer Center (red), Shanghai Jiao Tong University (blue), University of Naples Federico II (green), and University Roma La Sapienza (purple) as the most influential institutions in their respective co-authorship groups (Fig. 3E and F).

3.3. Publication distribution among author analysis

In total, 26,454 authors participated in the PTC-published works, with each article co-written by 3.26 authors on average. The top 10 most productive authors were almost exclusively from Asian research institutions, particularly from South Korea. According to Lotka law, these authors should be regarded as the "core authors" in the PTC research field. Based on co-authorship networks, we divided the top 100 most productive authors into 6 clusters, identifying Akira Miyauchi (Kuma Hospital, indigo), Jung-Han Yoon (Chonnam National University Hwasun Hospital, blue), Ji-Hoon Kim (Seoul National University Hospital, green), Zhang Le (Zhongshan School of Medicine, purple), Won Bae Kim (University of Ulsan College of Medicine, yellow), and R. Michael Tuttle (Memorial Sloan Kettering Cancer Center, red) as the most influential authors in their respective co-authorship categories. In addition, according to citation networks, we determined that Akira Miyauchi, R. Michael Tuttle, Yuri E. Nikiforov, Zhang Le, Tae Yong Kim, Ji-Hoon Kim, and Young Kee Shong were the most important contributors because their articles have been most cited by the top 100 most productive authors (Table 1 and Fig. 4).

3.4. Analysis of countries

A total of 93 countries participated in PTC publication, with the top 10 most productive countries responsible for 91.11% (7382/8102) of the total publications. Some articles were co-written by collaborators from different countries. The United States (1904 articles), China (1885 articles), Korea (1128 articles), Italy (763 articles), and Japan (419 articles) were the top 5 most productive countries by the number of publications. In addition, the growth rates were significantly distinct across the top 10 most productive countries, with China having the most sustained rate of increase of PTC publication outputs since 2012. The United States had the most international collaboration (Fig. 5).

3.5. Visualization of keywords

According to co-occurrence networks, a total of 8807 author keywords were identified. We found that the keywords "immunohistochemistry, prognosis, microcarcinoma, metasta-

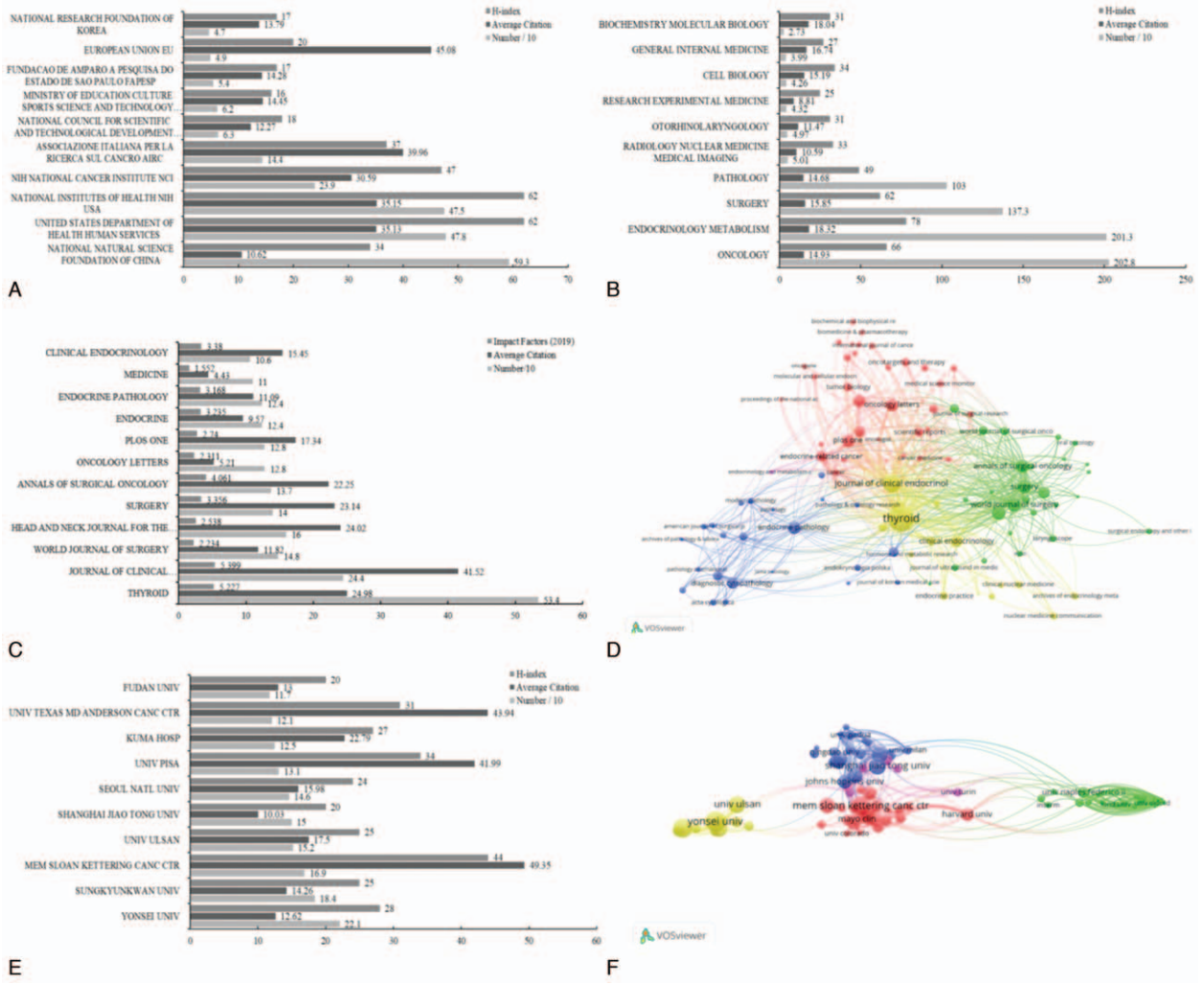

Figure 3. Article distribution among funding bodies, subjects, journals, and institutions in the field of PTC from 2000 to 2019. (A)-(C) and (E) are the publication number, average citation, and H-index of the top 10 productive funding bodies, subjects, journals, and institutions, respectively. (D) The visualization of citation networks of the top 100 most productive journals. (F) The visualization of co-authorships networks of the top 100 most productive institutions. Bar length reflects the numerical size of each parameter. Dots represent journals or institutions and larger dots indicate a larger number of publications of journal or institution. The clusters are labeled using different colors and the links represent the citation or co-authorships of journals or institutions, respectively. H-index = Hirsch index, PTC = papillary thyroid carcinoma.

Table 1

Top 10 authors most frequently appearing in the publications.

Rank	Author	N (%)	H-index	Citation	TLCS*	TGCS†	Institution	Country
1	Akira Miyauchi	112 (1.38)	25	23.03	1031	2342	Kuma Hospital	Japan
2	Ji-Hoon Kim	100 (1.23)	19	11.52	418	1094	Seoul National University Hospital	Korea
3	Michael Tuttle	88 (1.09)	34	62.26	2197	5255	Memorial Sloan Kettering Cancer Center	United States
4	Zhang Le	83 (1.02)	19	12.14	267	930	ZhongShan School of Medicine	China
5	Tae Yong Kim	82 (1.01)	18	15.32	504	1084	University of Ulsan College of Medicine	Korea
5	Young Kee Shong	82 (1.01)	20	23.02	635	1716	University of Ulsan College of Medicine	Korea
6	Jung-Han Yoon	80 (0.99)	18	11.96	384	901	Chonnam National University Hwasun Hospital	Korea
7	Yasuhiro Ito	79 (0.97)	25	29.72	958	2129	Kuma Hospital	Japan
8	Won Bae Kim	78 (0.96)	18	12.37	392	879	University of Ulsan College of Medicine	Korea
9	Wang Yan	75 (0.93)	16	11.09	250	819	The Sixth People's Hospital Affiliated to Shanghai Jiao Tong University	China
10	Yuri E. Nikiforov	71 (0.88)	34	65.87	1687	4539	University of Pittsburgh School of Medicine	Pennsylvania

H-index = Hirsch index.

* TLCS (total local citation score) represents the citation score in which cited by the same collection.

† TGCS (total global citation score) represents the citation score in which cited by all database.

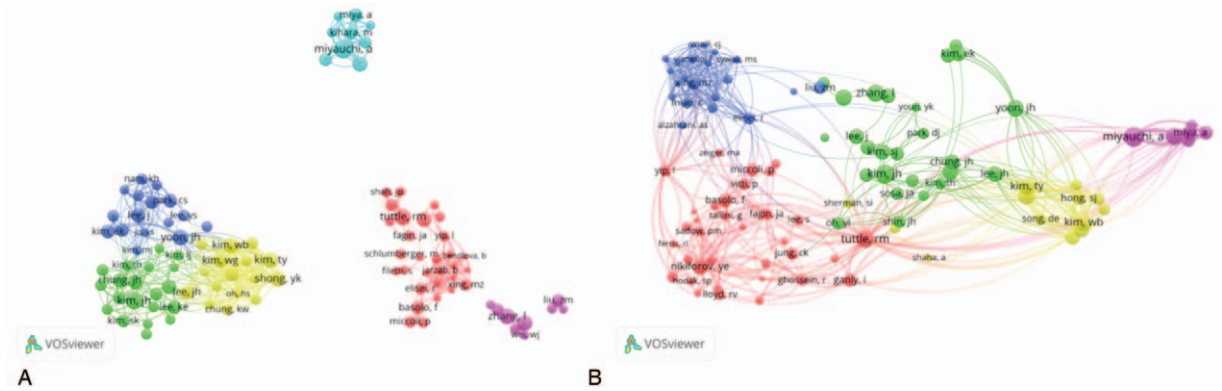

Figure 4. Visualization of the top 100 productive authors among publications in the field of PTC from 2010 to 2019. (A) Represents the co-authorship network and (B) represents the citation network. Dots represent authors, and larger dots indicate a higher number of publications. The clusters are labeled using different colors and the links represent author collaborations. PTC = papillary thyroid carcinoma.

sis, recurrence, differentiated thyroid cancer" were the most prominent keywords from 2010 to 2019. Meanwhile, an analysis of the development of keywords from 2017 to 2019 showed that hotspot keywords appeared and remained concentrated on "immunohistochemistry, prognosis, thyroglobulin, thyroidectomy, microcarcinoma, braf mutation" in 2017, "metastasis, survival, ultrasonography, prognosis, lymph node metastasis, invasion, proliferation, apoptosis" in 2018, and "prognosis, metastasis, microcarcinoma, recurrence, proliferation" in 2019 (Fig. 6).

3.6. Frontier topics analysis

Based on citation networks, we identified that the most influential article, with an impact factor of 32.242, was written by Nishant Agrawal et al and published in *Cell* in 2014. This article indicated clearly that PTC was a MAPK-driven endocrine carcinoma that was promoted by the mutation and fusion of BRAF, RAS, RET, EIF1AX, PPM1D, CHEK2, and regulated by oncomiRs (miR-21, miR-146b, miR-221, and miR-222), as well as by tumor suppressor microRNAs (let-7 family, miR-204, and miR-375), detected by genomic landscape technology.

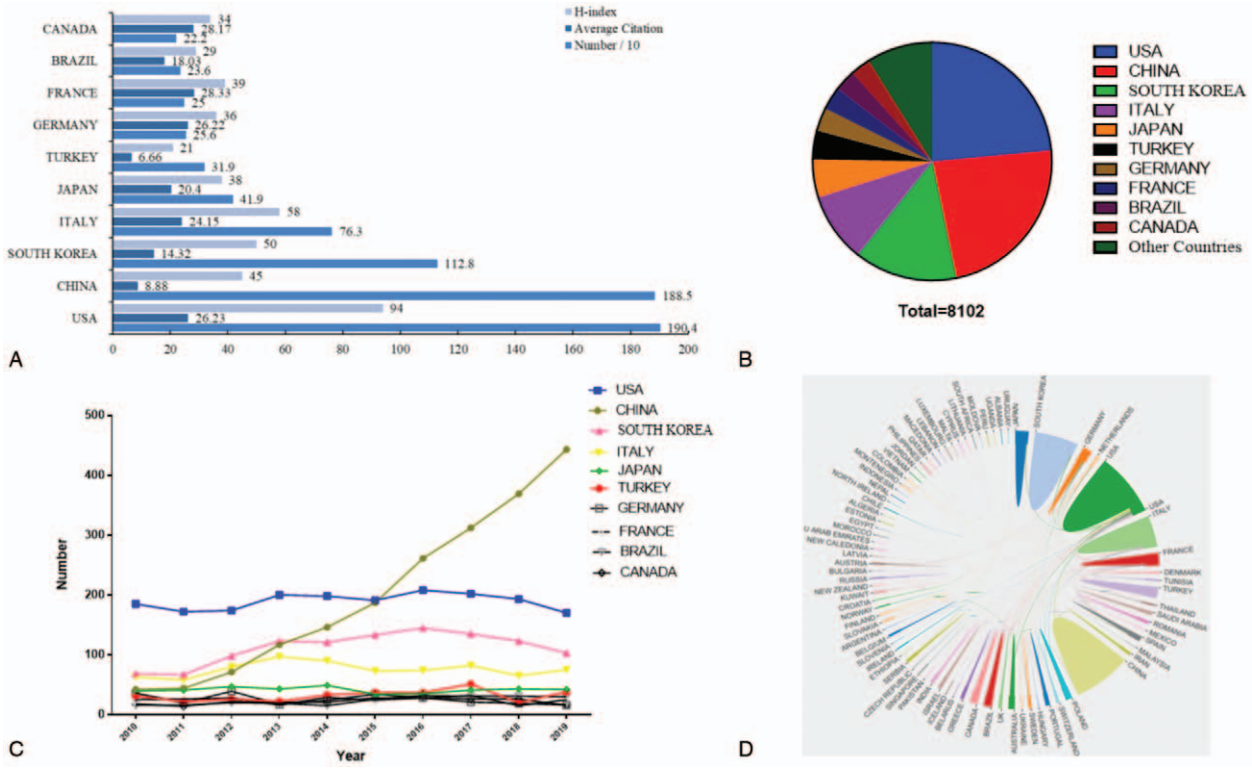

Figure 5. The top 10 most productive countries within PTC research from 2000 to 2019. (A) The number of publications, average citation, and H-index. (B) The relative proportion. (C) The publication's output trend. (D) Represents the international collaboration relationship networks. H-index = Hirsch index, PTC = papillary thyroid carcinoma.

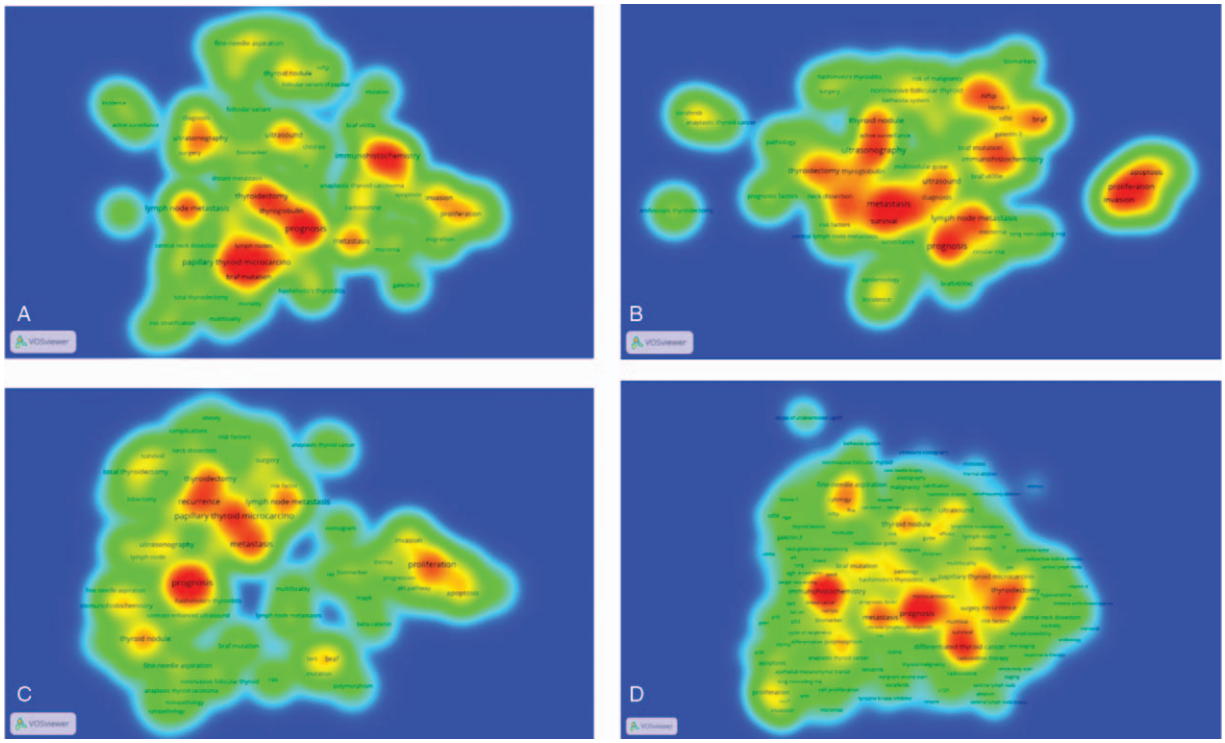

Figure 6. Heatmap visualization related to PTC research from 2000 to 2019. (A) to (C) The top 100 hotspot keywords in 2017, 2018, and 2019, respectively. (D) The top 500 hotspot keywords from 2010 to 2019. Redder spots indicate hotter research keywords and greener spots indicate colder keywords. PTC = papillary thyroid carcinoma.

We stratified the top 100 most frequently cited articles for nearly 3 years from 2017 to 2019. This subgroup analysis discovered that almost 60% (54% in 2017, 65% in 2018, and 60% in 2019) of the prominent frontier topics focused on "tumorigenesis, progression, invasion, metastasis, diagnosis and prognosis, therapeutic resistance," and most co-existed with miRNA-lncRNA-circRNA ceRNA (competing endogenous RNAs) networks and PI3K/AKT/mTOR, MAPK, MEK/ERK, wnt/beta-catenin, JAK/STAT, and NF-kappa B signal pathways (Fig. 7).

4. Discussion

4.1. Principal findings

In this study, using visualization software, we aimed to explore the research trends and hotspots in the field of PTC publications from 2010 to 2019. Our results suggested that the number of publications showed a growth trend over this period, with 2016 as the possible year with the highest publication growth rate. This means that this research field may remain relevant over the next few years, until the arrival of the platform period. The current publication trend was consistent with patient needs, given that the number of PTC diagnoses has tripled over the past decade, while thyroid cancer (of which PTC is the most dominant type) is 1 of the fastest-growing cancers.[1–3] The analysis of yearly citation numbers showed that the closer an article's time of publication was to the time of the data collection, the lower the average citation number. This phenomenon may be attributed to the fact that newer publications continued to increase rapidly, while the citations of these articles lagged significantly.

Secondly, we found that 40% of the top 10 most productive funding bodies were located in the United States, indicating the high quality of articles published by the USA funding bodies. Meanwhile, the journal distribution of the publications was concentrated to the top 10 journals. The subject journals can be divided into 4 categories: thyroid professional journals, clinical surgery journals, endocrinology-related journals, and comprehensive oncology journals. The average citation of these journal publications was higher than the IF (2019) of the journals. This means that PTC is an emerging hotspot research area that may be consistent with the patients' needs, and the publications will be cited more frequently in the coming years.

We discovered, thirdly, that among the top 10 productive institutions, 50% are located in South Korea, indicating the high quality of articles published by South Korean institutions. The most productive institutions, such as Yonsei University, Mem Sloan Kettering Cancer Center, Shanghai Jiao Tong University, and University of Naples Federico II, are all relatively mature in this research field and can be considered as important institutions for collaboration. Authors Akira Miyauchi, Michael Tuttle, Jung-Han Yoon, Ji-Hoon Kim, Zhang Le, and Won Bae Kim have published many publications and collaborated closely, and can be regarded as leaders in this professional research field.

Lastly, the publications present a dynamic time trend varying with the years as well as show differences among different countries. The United States, China, Korea, Italy, and Japan ranked as the top 5 most productive countries, accounting for 75.28% of the total number of publications. The United States, China, and South Korea showed their dominant position in the PTC research field, reflected in their publication output, H-index,

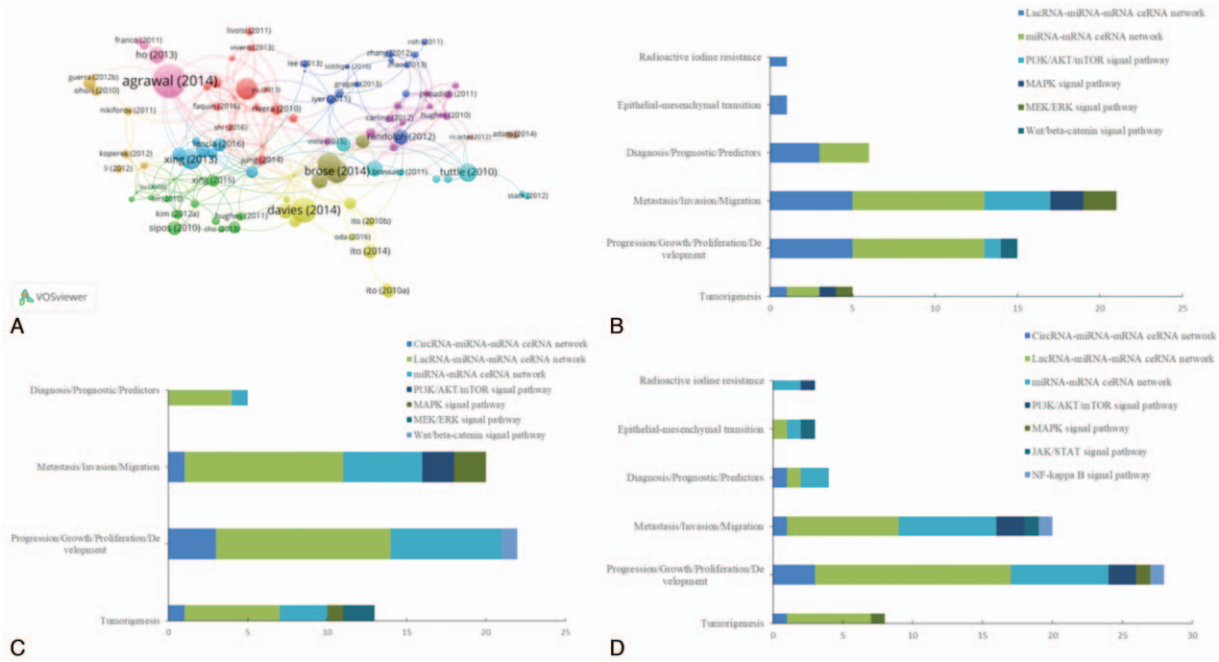

Figure 7. The frontier topics in the top 100 most-cited PTC articles from 2010 to 2019. (A) Represents the article citation network from 2010 to 2019. (B) to (D) The frontier topics in 2017, 2018, and 2019, respectively. The longer the bar length, the more frequently the topic occurred. Dots represent articles, and larger dots indicate a higher frequency of cited articles. The clusters are labeled using different colors, and the links represent the citation of articles. Bar color represents the relative proportions. PTC = papillary thyroid carcinoma.

average citation, and international collaboration. Notably, compared with the unchanged cumulative number of publications in the United States and Korea, publications in China have increased dramatically since 2012. This phenomenon indicates that China is developing rapidly in this research domain, indicating that the Chinese population might suffer from serious public health problems relating to the widespread prevalence of thyroid cancer. However, at this stage, the relative number of average citations in Chinese publications is lower. Therefore, the quality of China's outputs should be greatly improved in the future.

4.2. Potential implications

Bibliometrics is a rapidly advancing field that promises to incorporate an objective element into a long-standing process of measuring scholarly impact. The availability of electronic databases and downloadable tools to aid these calculations will likely increase their use and add an objective measure to the subjective letter of reference.[14,15] Web of Science is the most respected and widely used bibliometric database. This bibliometric analysis provides a comprehensive analysis of research hotspots in the field of PTC, which is very helpful in formulating the next research direction for PTC researchers.[16,17]

4.2.1. Clinical research. Results of keyword co-occurrence analysis, conducted over nearly 3 years, revealed that hotspot keywords appeared to maintain focus on 3 categories, represented by (1) proliferation, invasion, and apoptosis, (2) microcarcinoma, diagnosis, immunohistochemistry, and prognosis, and (3) recurrence, metastasis, therapeutic resistance, and survival. These 3 hotspot classes fully demonstrate the main concentrated aspects of the recent research field. This research field is still in the developing stage, and it will undoubtedly develop rapidly in the future. Notably, approximately half of the PTC cases were classified as microcarcinoma (PTC measuring 10 mm or less in diameter, defined by the World Health Organization) and therefore the rapid increase in the incidence of PTC patients is mostly attributed to the increase in microcarcinoma.[18] Although microcarcinoma generally follows an indolent clinical course and carries an excellent prognosis, patients recently reported displaying metastasis, recurrence, and therapeutic resistance.[19] Therefore, some studies have begun to explore an accurate method to distinguish stable microcarcinoma from aggressive microcarcinoma and to investigate effective therapies.[20,21] This has been neglected in previous studies.[18–19]

4.2.2. Mechanism research. From the frequency of occurrence of topics among the top 100 most-cited articles over nearly 3 years from 2017 to 2019, we discovered that "metastasis, invasion, migration," and "progression, growth, proliferation, development" were the most prominent frontiers topics, and most co-existed with "ceRNA networks, MAPK, PI3K/AKT/mTOR, MEK/ERK, wnt/beta-catenin, JAK/STAT, and NF-kappa B signal pathways." This demonstrates that biology mechanism pathways are currently the most mainstream research area in the PTC field and will remain a topic of research in the next few years.

We can explain biology mechanism from the following 2 aspects. On the one hand, Song et al[22] employed whole-exome sequencing and next-generation gene-panel approach of PTC and identified that gene mutants associated with cell adhesion could be used to predict aggressiveness. Cell adhesion molecules, which are regulated by various miRNAs, play pivotal roles in the

immune-inflammatory response.[23] Importantly, tumorigenesis and the progression of carcinoma depend on foci immune microenvironment disorder, which could modulate tumor aggressiveness.[24,25] Therefore, we speculated that ceRNA networks might disturb cell adhesion reactions, provoking foci surrounding immune microenvironment disorder, which should be responsible for the malignant behaviors of PTCs.

On the other hand, Sun et al verified that cell adhesion alteration of hepatocytes could be blocked by the ERK1/2 pathway inhibitor (U0126) in the human liver cell line-HL7702.[26] Zheng et al[27] indicated that mi-30e inhibited cell adhesion by suppressing the activation of the MAPK signaling pathway in prostate cancer. Moreover, they supposed that the Wnt/β-catenin signaling pathway might play a critical role in adherens junctions cell regeneration[28] and that both NF-kappa B and JAK/STAT pathways could inhibit endothelial cell adhesion.[29] Furthermore, downregulation of the PI3K/AKT/mTOR signaling pathway can suppress cancer cell adhesion reactions.[30,31] Notably, cell adherence to the extracellular matrix is an essential condition for unlimited tumor proliferation and has been identified as the key determinant for radioresistance and drug resistance.[32,33] It is not only significantly correlated with aggressiveness but also linked to shortened disease-free survival.[34,35] Thus, it can be speculated that biological signaling pathways – through the mediated expression of cell adhesion molecules, perturbing tumor unlimited proliferation – contribute to the occurrence of therapeutic resistance, such as radio-resistance and drug resistance, and poor prognoses, such as shortened disease-free survival. Further studies are needed to explore and validate these biological mechanisms.

4.3. Limitations

Some weaknesses should be considered when interpreting the results of our study. First, the publications are only derived from SCI-E of the Web of Science. Second, we only introduced English publications into our analysis. In addition, a certain bias in the selection of publications should not be excluded. Despite these limitations, the study does, to some extent, reveal the future research trends and hotspots in this research field.

4.4. Conclusion

PTC publications have provided insight into important areas of research. The annual number of publications has grown rapidly in the past decade and will continue to grow in the coming years. The United States is the leading country in this research field. China and South Korea also achieved important research results and played a role in promoting the development of PTC research. Future research hotspot topics might include clinical micro-carcinoma and the mechanism of biological pathways. We believe that these findings will offer useful information for researchers in further exploration of PTCs.

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Investigation: Fengyan Huang.
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Project administration: Fengyan Huang.
Software: Hongying Jia, Lihua Wang.
Visualization: Fengyan Huang, Lihua Wang.
Writing – original draft: Fengyan Huang.
Writing – review & editing: Hongying Jia.

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