Original Article

Research trends and hotspots on human papillomavirus: a bibliometric analysis of 100 most-cited articles

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Background: The study aimed to investigate the research trends and hotspots in the field of human papillomavirus (HPV) from the top-cited articles.

Methods: The database Web of Science (WOS) was utilized to retrieve articles closely related to HPV, and 100 articles with the most citations were selected. Bibliometric analysis along with visualization tools was applied to analyze citation, publication time, journal, author, geographic distribution, institutional and international cooperation, title, abstract, and keyword co-occurrence cluster.

Results: The articles were mainly published from 2003 to 2012 (56%) and most articles were published in 2007 (13 papers). The citations ranged from 506 to 6,426, with a median citation of 798.5. The United States contributed 68% of the papers, and most articles were published in North America and Europe continent. Boash FX, Meijer CLJM, and Munoz N owned most authorship (13 papers). The most highlighted research category was oncology (34%), and the most aggregated topics were epidemiology (34%) and etiology (32%). The emerging trends on subtopics including vaccination, intention, screening, and man, were raising.

Conclusions: Emerging trends in epidemiology, etiology, and HPV-related cancers remained central to the field. For decades, the focus of HPV research has shifted from identification to screening and prevention. With the implementation of vaccination, future studies may focus on its practice as well as public intention.

Keywords: Human papillomavirus (HPV); vaccination; bibliometric; visualization

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Introduction

Human papillomavirus (HPV), especially high-risk HPV (hrHPV) types, has been identified as the leading cause of cervical cancer, which caused approximately 341,800 new deaths in 2020 (1,2). To date, more than 200 genotypes have been recorded by the International HPV Reference Center, and 12 HPVs [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59] have been defined by the World Health Organization as high-risk cancerous types, with HPV68 and HPV73 recognized as possible cancerous types. The genome of hrHPV is liable to integrate into the host genome, resulting in E2 gene breakage and E6/E7 oncogene transcriptional dysregulation, thus participating in the carcinogenic process (3,4). The incidence of HPV infection did decrease under wide HPV vaccination, but it still posed a burden on cancer prevention (5,6). In addition, the infection of the vaccine-covered HPV types after vaccination did occur (7). Most HPV infections undergo a spontaneous clearance process, but persistent and recurrent infections are not uncommon (8). Those unanswered questions constitute diverse fields of research for scientists.

The research on HPV began when zur Hausen H first

discovered that HPV causes cervical cancer in 1974 (9), and nearly 50,000 papers closely related to HPV have been published so far. The vast number of publications cast difficulties for scientists and researchers to obtain high-quality relevant information. Therefore, it is necessary to sort out monumental publications and focused topics to simplify literature retrieval. Also, an overview of research trends over the years can be of great help in perceiving the circumstance and current state of research. Bibliometric analysis serves as a useful tool to measure the quality of publications and find links between different articles. It has been widely used in several scientific fields to evaluate publications and explore research hotspots and trends (10-12). The trends and hotspots of medical research are constantly changing with the new progress of the vast majority of medical research. In the case of HPV, the implementation of vaccination has dramatically changed the focus of research. The recent bibliometric study on HPV concentrated on HPV vaccination and illustrated the exponential dynamics of the publications with clinical trials providing evidence of the efficacy and safety of the HPV vaccine (13). While vaccination is one of the most high-profile topics in the HPV field, other subjects such as HPV-related cancers, infection populations, and cervical cancer screening also dominate.

Here, we conducted a bibliometric study and attempted to seek hotspots and trends in HPV research. To depict the overall perspective of the HPV research field, we analyzed 100 of the most cited papers closely related to HPV. Highly relevant articles published since 2013 were also analyzed to convey the recent research directions.

Methods

Data source and search strategies

The study was conducted on the basis of the Web of Science (WOS) database, which is a well-established and credible resource for biomedical research, especially for its ability to obtain citation information. Since citations in WOS are used to calculate the impact factor, we consider the citation retrieved from WOS to be accurate. We conducted a comprehensive search of the Web of Science Core Collection on October 12, 2021. Searches were performed independently by two reviewers (YG and YX) with the strategy syntax TI = (human papillomavirus) OR TI = (HPV). Inclusion criteria were as follows: (I) clinical (longitudinal, cohort, case-control, etc.) or laboratory studies with HPV as the research core; (II) systematic reviews; (III) English-written articles. Exclusion criteria were: (I) HPV was not the central focus of the topic; (II) abstracts, conferences, correspondence, errata, and editorial materials; (III) non-English written papers. The disagreement between the two reviewers was discussed to reach an agreement.

Data collection

A total of 39,134 items were retrieved, and 26,460 items were left after excluding article types other than research articles or systematic reviews. The top 250 articles were sorted by citation frequency, and 227 articles met the inclusion and exclusion criteria. Finally, we selected the 100 most-cited articles for bibliometric analysis, and the items including author, year of publication, journal, title, keywords, abstract, country, institution, times of citation were thoroughly collected and recorded in an Excel sheet (https://cdn.amegroups.cn/static/public/atm-22-463-1.xlsx).

In addition, we screened out papers published after 2013 from the 26,460 articles retrieved to update the current trends and hotspots and included a total of 13,646 articles. The information was also collected and recorded in the same way. The complete workflow was shown in *Figure 1*.

Data visualization

The primary analysis was performed on the online bibliometric platform (https://bibliometric.com/) to visualize the keywords trends, collaborations, and citation networks of publications. Geographical analysis was performed through the dycharts analysis platform (https://dycharts.com/). VOSviewer v1.6.17 was applied to conduct cluster analysis and construct institutional cooperation networks, title and abstract network, and keywords network. The size of the node in the network maps represented the weight of the item, and the distance between nodes showed their relevance. Links between nodes showed co-occurrence, co-authorship, or co-citation. Different colors in network visualization and density visualization represented different clusters. Overlay visualization scored each item, revealing research trends. Microsoft Excel 365 was applied to construct statistical graphs.

Statistical analysis

The differences between groups were tested by One-Way ANOVA. The trend between citation density and time was analyzed by Mann-Kendall trend analysis. Spearman's

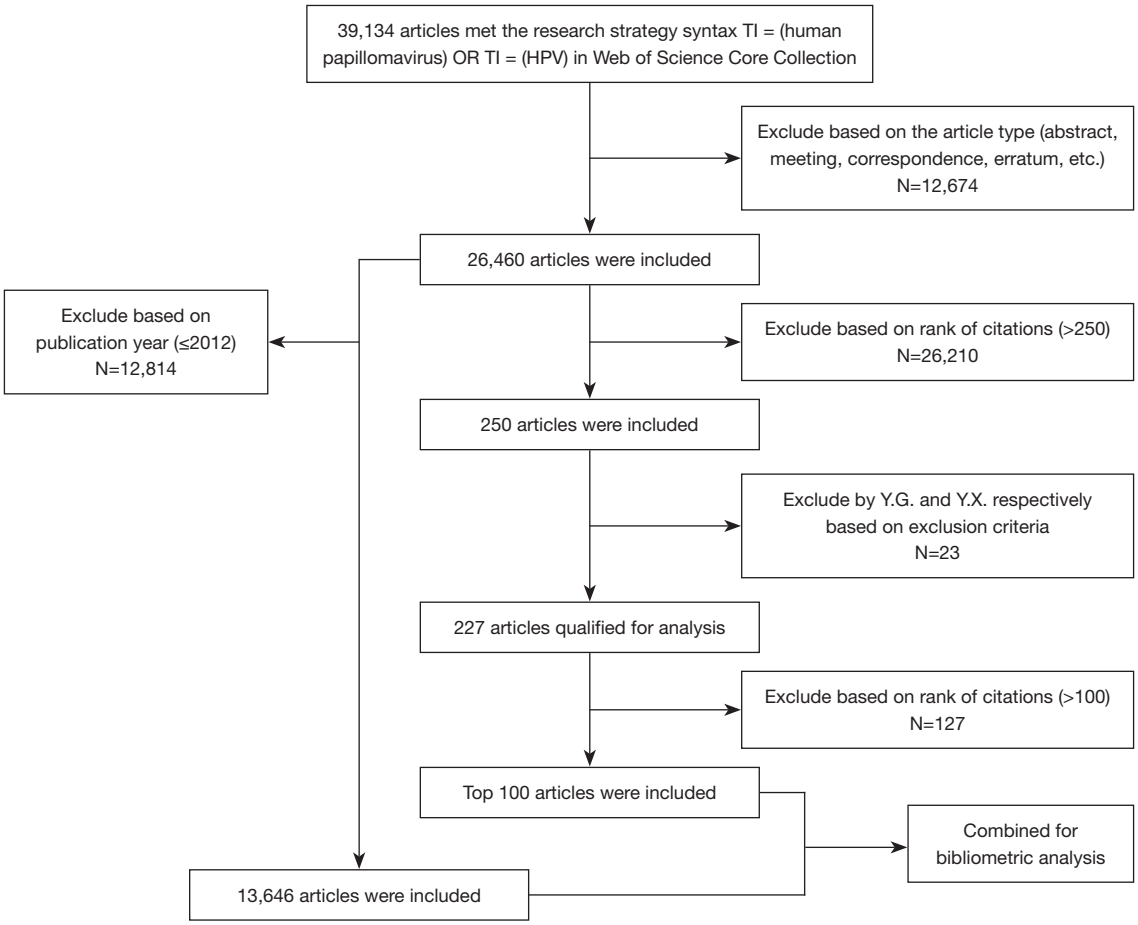

Figure 1 Flowchart illustrating the process of screening and enrollment of articles.

Rank correlation was applied for correlation analysis. Those statistical analyses were implemented in R v4.0.5 and GraphPad Prism v9.2.0. P value lower than 0.05 was considered statistically significant.

Result

Analysis of citation

The citations of the 100 most-cited articles ranged from 506 to 6,426. The total citation reached 108,270 and the median was 798.5 citations. The most cited paper was published in 1999, entitled "*Human papillomavirus is a necessary cause of invasive cervical cancer worldwide*". In this article, Walboomers *et al.* (14) demonstrated that the incidence of HPV infection in cervical carcinoma reached 99.7%, which was underestimated due to the failure of L1-based assays on account of the fragmentation and integration of the L1 gene. The second-ranked paper was "*Epidemiologic classification of human papillomavirus types associated with cervical cancer*" with 4,613 citations, which clustered 13 HPV types other than HPV16 and 18 into the high-risk group (15). The third most cited article was "*Human papillomavirus and survival of patients with oropharyngeal cancer*", which discussed the relationship between HPV status and prognosis in patients with oropharyngeal cancer (16). *Table 1* listed the top ten most cited articles.

Analysis of publication year

The 100 most cited articles were published from 1983 to 2017. Thirty-four percent of the articles were published between 2003 to 2007, compared with only 37 papers in the 20 years preceding 2003 (*Figure 2A*). Since 2013, merely 7% of the articles were published. The number of publications

Table 1 Top ten articles in HPV field with most citations

Rank	Year	Citations	Article title	Journal
1	1999	6,426	*Human papillomavirus is a necessary cause of invasive cervical cancer worldwide*	*JOURNAL OF PATHOLOGY*
2	2003	4,613	*Epidemiologic classification of human papillomavirus types associated with cervical cancer*	*NEW ENGLAND JOURNAL OF MEDICINE*
3	2010	4,004	*Human papillomavirus and survival of patients with oropharyngeal cancer*	*NEW ENGLAND JOURNAL OF MEDICINE*
4	1990	3,520	*The E6 oncoprotein encoded by human papillomavirus type-16 and type-18 promotes the degradation of p53*	*CELL*
5	1995	2,734	*Prevalence of human papillomavirus in cervical-cancer: a worldwide perspective*	*JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE*
6	2002	2,509	*The causal relation between human papillomavirus and cervical cancer*	*JOURNAL OF CLINICAL PATHOLOGY*
7	1990	2,304	*Association of human papillomavirus type-16 and type-18 e6 proteins with p53*	*SCIENCE*
8	2011	2,235	*Human papillomavirus and rising oropharyngeal cancer incidence in the United States*	*JOURNAL OF CLINICAL ONCOLOGY*
9	2000	2,165	*Evidence for a causal association between human papillomavirus and a subset of head and neck cancers*	*JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE*
10	2009	1,911	*Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial*	*JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE*

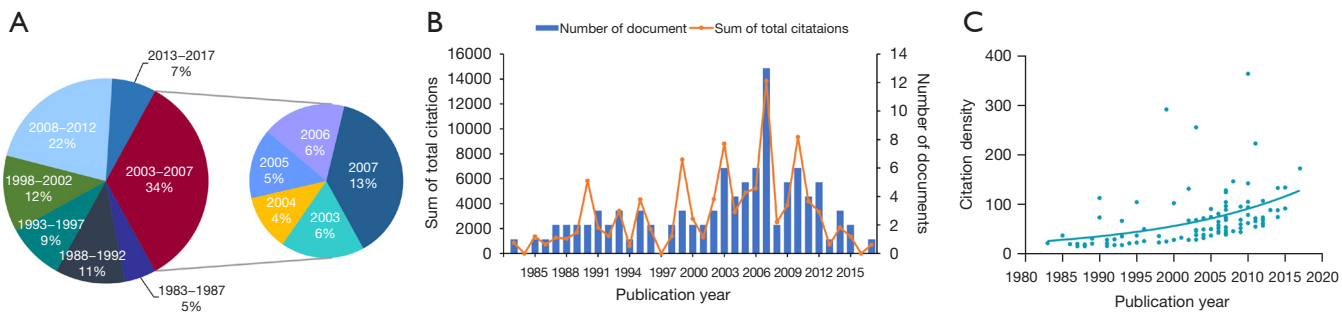

Figure 2 Time analysis of 100 top-cited articles in HPV. (A) A majority of articles were published in 2003–2012 (56%, n=56). (B) Number of documents published each year and the corresponding citations of those documents. The bars show the number of documents published each year and the nodes on the line chart represent the summed citations. (C) Time-dependent citation density trend. Mann-Kendall trend test showed an increasing trend between the citation density and the time (P=1.99e-11). HPV, human papillomavirus.

presented a parabolic trend over time (*Figure 2B*). Thirteen high-quality publications were published in the year 2007, which was the highest ever. In 2003, 2007, and 2010, the annual summed citations exceeded 8,000. Mann-Kendall trend analysis showed that the trend between citations and time was not significant (P=0.37), but there was an upward trend between citation density and time (z =6.7067, P=1.99e-11). Nonparametric Spearman's rank analysis revealed that citation density was positively correlated with time (r^2 =0.4286, P<0.0001), as shown in *Figure 2C*.

Analysis of journal

A total of 36 journals were included, with impact factors

ranging from 2.493 to 91.245 (*Table 2*). *NEW ENGLAND JOURNAL OF MEDICINE*, *INTERNATIONAL JOURNAL OF CANCER*, *JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE*, and *LANCET* were the top four journals with the most articles. Correlation analysis of Spearman's rank test showed that the impact factor was positively correlated with the number of citations (r^2 =0.092, P=0.021).

Analysis of geographic distribution, institution, and international cooperation

These articles were distributed in 64 countries, with the USA contributing the most papers (*Figure 3A*), followed by France (n=22), Spain (n=17), The Netherlands (n=17), and Canada (n=17). In the geographic distribution shown in *Figure 3B*, most articles were published in North America and continental Europe. Other publications were scattered across South America, Asia, Africa, and Australia. Most publications were contributed by industrialized countries. Cooperation between countries was common and more common among countries with highly cited articles, such as USA and Canada, which were the closest of all countries (*Figure 3C*). The overlay visualization in *Figure 3D* showed that the time of publications in USA was earlier than that in most countries. In addition, China and Austria were related to the most recent published articles. The institutional cooperation was visualized in *Figure 3E*. The International Agency for Research on Cancer (IRAC), Johns Hopkins University, National Cancer Institute (NCI), and the University of Washington had the most outputs. The links between these institutions were strong, and the articles from Johns Hopkins University were published earlier than others in general.

Analysis of authorship

The authorships of the most frequently cited articles were listed in *Table 3*. A total of 20 authors had authorship of five or more papers, of which Boash FX, Meijer CLJM, and Munoz N owned authorship of 13 articles. The connections between Boash FX, Meijer CLJM, Munoz N, and Shan KV were extremely strong. Twelve authors had the first authorship of two or more papers. Both Boach FX and Munoz N were the first authors of three articles. Boach FX focused on the relationship between HPV and cervical cancer, and Munoz N was more interested in HPV types. The number of authors ranged from one to 142, with an average number of 11. Most articles had fewer than 12 authors, and only three articles had more than 30 authors. Spearman's rank test showed that there was no significant correlation between citation and number of the author (P=0.175).

Analysis of article type, category, and topic

Among the 100 most-cited articles, 82 were research articles and the remaining 18 were systematic reviews. There was no significant difference in citation times between research articles and reviews (P=0.952). The WOS categories of these articles were mainly oncology, general internal medicine, and biology (*Figure 4A*). As can be seen from *Figure 4B*, there was no significant difference in citations among WOS categories (P=0.6837). According to the research topic, these articles can be divided into five groups: epidemiology, etiology, vaccination, detection, and sequence (*Figure 4C*). As shown in *Figure 4D*, there was no significant difference in citations among article topics (P=0.2638). Sixty-four percent of these papers dealt with epidemiology and etiology, followed by vaccination. The oncogenic mechanism of HPV and its oncoproteins took a major part of its etiological research.

Analysis of title and abstract co-occurrence cluster

Overlay visualization visualized trends in titles and abstracts over time, with 98 items appearing at least ten times (*Figure 5*). The word "vaccine" accounted for the largest proportion and was closely related to "population" and "efficacy". The color of the bubbles represented the average time of the occurrence of the item. The yellow bubble was the most recent topic, while the purple bubble was the oldest. "Vaccine", "man", "oral HPV infection" and "CIN2/3" were recent topics. The terms "specimen", "CIN", "p53", "risk factor" and "association" appeared earlier, followed by "patient", "cytology", "HPV testing", "colposcopy", "anal cancer" and "HNSCC", before "oropharyngeal cancer", "invasive cervical cancer", "prevalence" and "population".

Analysis of keyword co-occurrence cluster

The keywords were clustered into four categories (Figure S1A). Cluster 1 included cervical intraepithelial neoplasia, HPV infection, intraepithelial neoplasia, liquid-based cytology, natural history, persistence, population, prevalence, risk factors, virus-like particles, women,

Table 2 Journals of the 100 most-cited articles

Journal	Document numbers	Total citations	Citation per document	Impact factor (year 2020)
NEW ENGLAND JOURNAL OF MEDICINE	14	20,168	1,440.6	91.245
JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE	9	11,443	1,271.4	13.506
LANCET	9	9,265	1,029.4	79.321
INTERNATIONAL JOURNAL OF CANCER	9	6,605	733.9	7.396
LANCET ONCOLOGY	5	5,255	1,051	41.316
VACCINE	5	3,956	791.2	3.641
JOURNAL OF VIROLOGY	5	3,135	627	5.103
CELL	3	6,070	2,023.3	41.582
NATURE	3	2,875	958.3	49.962
JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	3	2,587	862.3	56.272
BRITISH JOURNAL OF CANCER	3	2,426	808.7	7.64
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	3	1,776	592	11.205
JOURNAL OF CLINICAL ONCOLOGY	2	2,790	1,395	44.544
NATURE REVIEWS CANCER	2	1,712	856	60.716
EMBO JOURNAL	2	1,682	841	11.598
JOURNAL OF INFECTIOUS DISEASES	2	1,471	735.5	5.226
JOURNAL OF CLINICAL MICROBIOLOGY	2	1,114	557	5.948
JOURNAL OF PATHOLOGY	1	6,426	6,426	7.996
JOURNAL OF CLINICAL PATHOLOGY	1	2,509	2,509	2.493
SCIENCE	1	2,304	2,304	47.728
CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION	1	1,465	1,465	4.254
BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER	1	1,270	1,270	10.68
LANCET INFECTIOUS DISEASES	1	1,032	1,032	25.071
JOURNAL OF GENERAL VIROLOGY	1	986	986	3.891
OBSTETRICS AND GYNECOLOGY	1	870	870	7.661
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA-BIOLOGICAL SCIENCES	1	861	861	11.205
CLINICAL MICROBIOLOGY REVIEWS	1	843	843	26.132
AMERICAN JOURNAL OF EPIDEMIOLOGY	1	696	696	4.897
CLINICAL SCIENCE	1	694	694	6.124
MMWR RECOMMENDATIONS AND REPORTS	1	621	621	55.857
JOURNAL OF CLINICAL VIROLOGY	1	604	604	3.168
PREVENTIVE MEDICINE	1	592	592	4.018
CANCER	1	560	560	6.86
VIRUS RESEARCH	1	553	553	3.303
EPIDEMIOLOGIC REVIEWS	1	529	529	6.222
JAMA PEDIATRICS	1	525	525	16.193

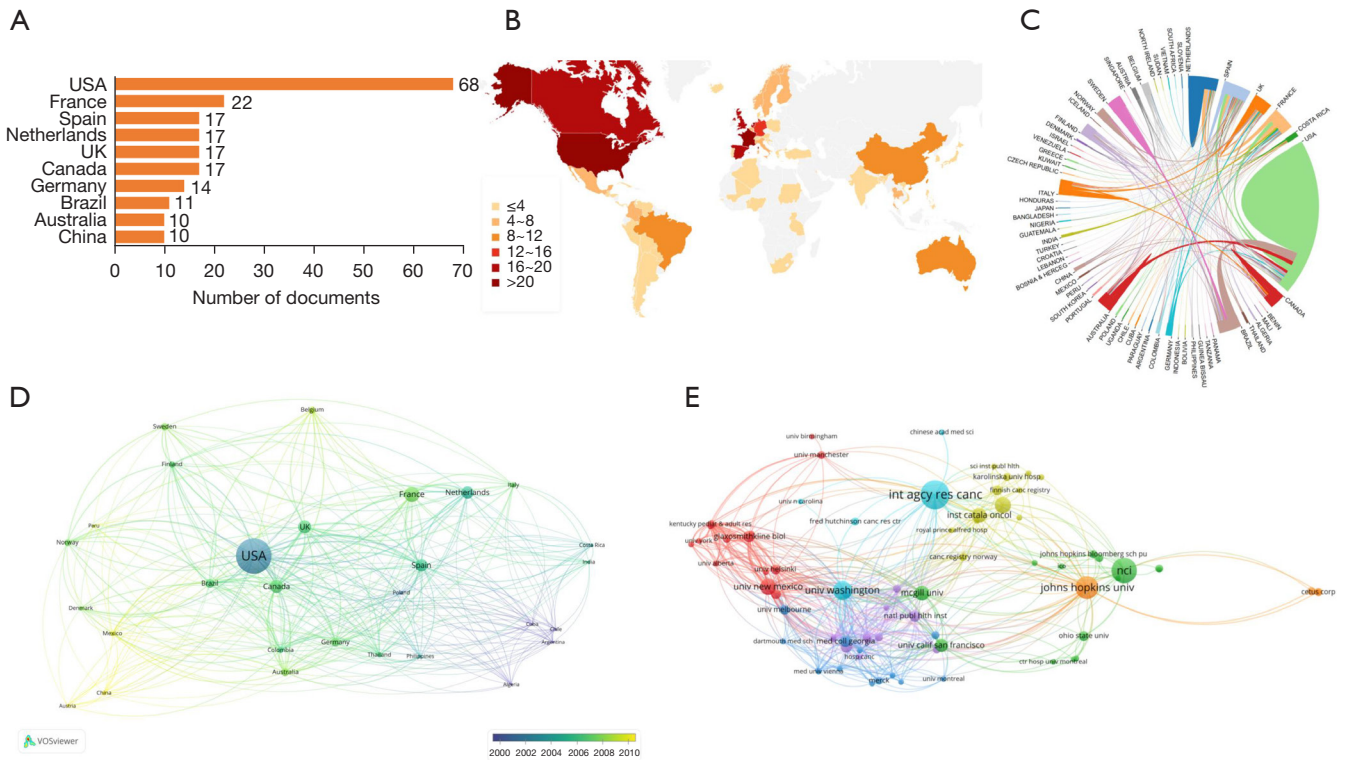

Figure 3 Country and institution distribution analysis of 100 top-cited articles in HPV. (A) Top 10 countries that contributed most articles. (B) Geographical distribution of all articles. The figure showed most articles came from two regions: North America and Western Europe. (C) Cooperation network between countries. (D) Overlay visualization of country co-authorship. (E) Institution co-authorship analysis map. HPV, human papillomavirus.

worldwide, and young women. Cluster 2 included association, cervical cancer, DNA, expression, head, HPV, identification, infection, oral cancer, sequences, squamous-cell carcinoma, and type-16. Cluster 3 included anal cancer, cervical cancer, epidemiology, HPV, lesions, meta-analysis, and risk. Cluster 4 included cancer, carcinoma, follow-up, neoplasia, particle vaccine, and united states. The keywords "women", "infection", "prevalence" appeared frequently and were strongly correlated with each other. The transition of keywords over time was visualized by overlay visualization (Figure S1B). Keywords such as DNA, identification, sequences, expression, carcinoma, cervical intraepithelial neoplasia appeared more frequently in earlier publications. Epidemiology, prevalence, risk were research hotspots, with an average time of 2004, followed by population, worldwide, virus-like particles, and natural history. Persistence, risk factors, follow-up were more prioritized keywords around 2008. Meta-analysis, liquid-based cytology, particle vaccines were more recent hot topics.

Since most articles were published before 2013, and only 7% of papers were published after 2013, we screened the 26,460 included articles by publication year and retrieved 13,646 articles published since 2013. Keywords were also analyzed in the same way. A total of 207 keywords appeared over 100 times and were clustered into five clusters (*Figure 6A*). The red cluster was associated with cancer prevention and vaccination, and the green cluster was mainly associated with cervical cancer screening, HPV detection, and HPV genotype. The blue cluster represented the diagnosis, therapy, and prognosis of HPV-related diseases. The yellow cluster represented the carcinogenesis mechanisms and immuno-therapy of HPV. The purple cluster represented the epidemiology and risk factors for HPV. In the overlay visualization, the color of the bubbles represented the average time of the occurrence of keywords. The yellow bubbles represented recent hotspots. "Vaccination", "cervical cancer screening", "head and neck cancer", "therapy" were the current focus (*Figure 6B*).

Table 3 Authors with at least five documents

Author	Number of documents
Bosch FX	13
Meijer CJLM	13
Munoz N	13
Franceschi S	11
Castellsague X	9
Howley PM	9
Clifford GM	8
De Sanjose S	8
Snijders PJF	8
Gillison ML	7
Koutsky LA	7
Wheeler CM	7
Shah KV	6
Barr E	5
Bruni L	5
Giuliano AR	5
Harper DM	5
Lehtinen M	5
Munger K	5
Westra WH	5

Discussion

HPV has been recognized as the etiology of cervical cancer for years. The research on HPV and HPV-related diseases is extensively proceeding. Through bibliometric analysis, we can understand the research trends and hotspots in a certain field, which often change rapidly. This is the first bibliometric analysis of the overall HPV research field. The other bibliometric study in the HPV field was published in 2021, focusing on the HPV vaccination (13). Our study aimed to reveal the current research hotspots and emerging trends of HPV research by evaluating the detailed information of the 100 most-cited articles closely related to HPV.

The most frequently cited papers tend to be those of high quality that represent the research interest. In this bibliometric analysis, 64% of the 100 most-cited articles were clinical studies and only 14 were laboratory research. Among the top ten articles with the most citations, two similar laboratory studies revealed the oncogenic mechanism of the E6 oncoprotein in 1990, which were published in *CELL* and *SCIENCE*, respectively (17,18). P53 is a tumor suppressor gene whose mutation may contribute to its oncogenic potential (19). In contrast, the E6 protein was shown to interact with p53, resulting in p53 ubiquitination and subsequent degradation (17). The study also identified different functions of E6 between low-risk and high-risk types. These two articles laid the foundation for subsequent studies, which further confirmed that E6-associated protein (E6-AP) also played an irreplaceable role in the ubiquitination of p53 (20,21). Further studies revealed that the structure of the E6/E6-AP/p53 complex and specific regions in E6-AP and the ubiquitination of E6 protein were critical for p53 degradation (22-24). Apart from the above-mentioned articles, there were seven clinical studies and one systematic review clarifying the correlation between HPV and cervical cancer, oropharyngeal cancer, head and neck cancer, ranking in the top ten.

Annual citations and total citations of highly cited papers reveal the development and status of research over the years. The annual summed citations reached the highest peak in 2007 as most articles were published in 2007, right after the approval of the HPV vaccine in 2006. Over 30% of the articles published in 2007 concentrated on the topic of vaccines. In 2010, two years after zur Hausen H won the Nobel prize in Physiology or Medicine for the discovery that HPV is the etiology of cervical cancer, the annual summed citations reached another peak (25). The top-cited publications showed a boom after 2002, but a decline after 2010. To find out the explanation for this phenomenon, we analyzed the correlation between citation and publication year. The citations of papers did not tend to change with the year of publication, which meant that the importance of the papers was always consistent. Nevertheless, the citation density was positively correlated with the time, which vigorously countered the recent collapse of HPV research. But it also suggested that researchers were paying more attention to recent findings, which could lead to bias and ignorance of the primary and first-hand evidence relevant to HPV.

The impact factor is calculated for each scientific journal based on the average citations annually, which is a standard for judging the quality of journals (26). However, it is still uncertain whether the top-cited articles in HPV are all published in journals with high impact factors. Therefore, the correlation between citation and impact factor was evaluated. Although positively correlated, the correlation

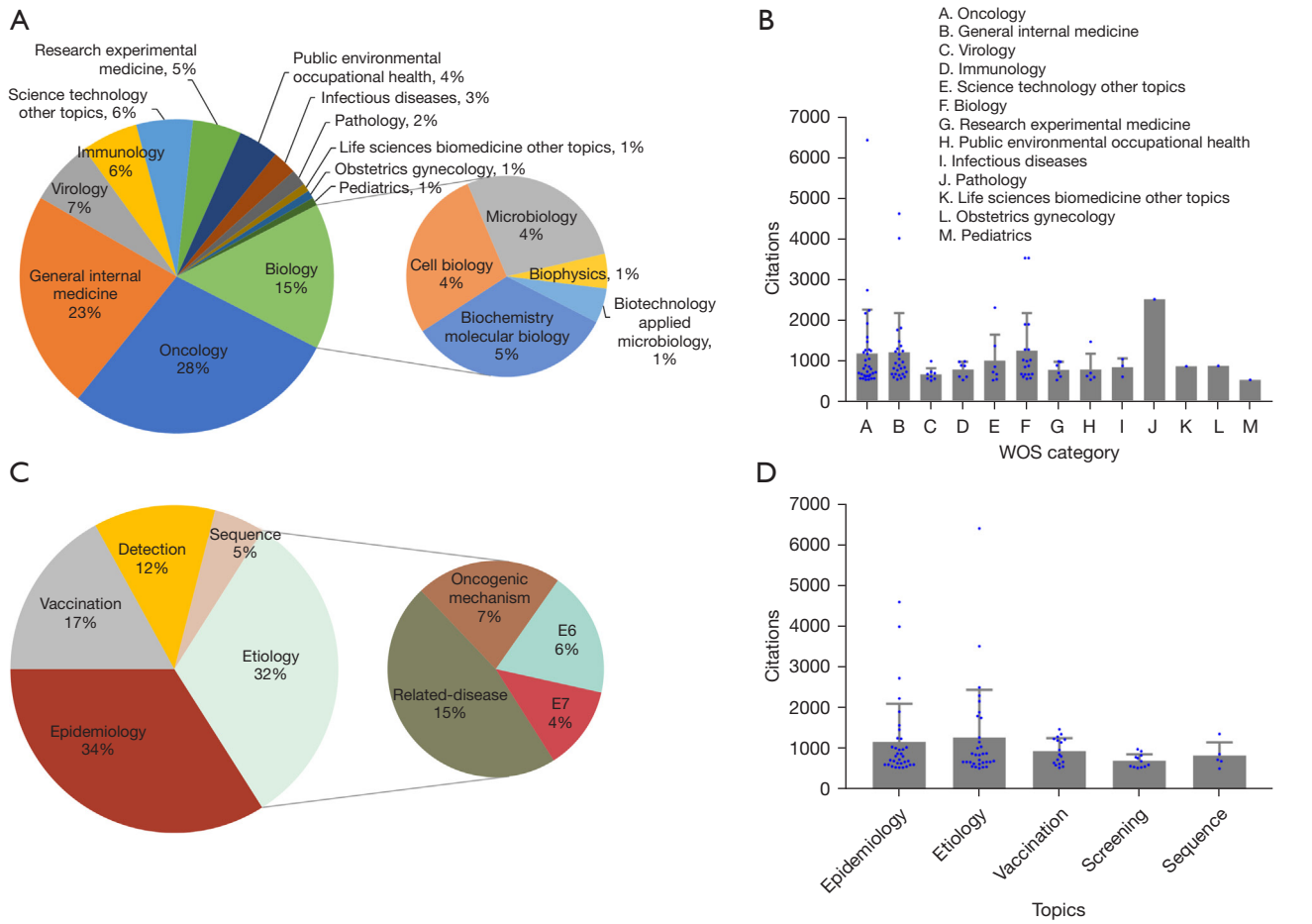

Figure 4 WOS category and topic distribution. (A) Oncology (n=28), general internal medicine (n=23) and biology (n=15) were the top 3 most common categories published. (B) Mean citation per article based on the WOS category. (C) Epidemiology (n=34), etiology (n=32) and vaccination (n=17) were the top 3 most common topics. (D) Mean citation per article based on the topic. WOS, Web of Science.

coefficient was rather small which was insufficient to show a positive correlation. Despite high impact factors, the average citation of *SCIENCE*, *CELL*, *LANCET*, and *NEW ENGLAND JORNAL OF MEDICINE* ranked behind some journals with lower impact factors. It indicated that despite authoritative journals being the best collections of high-quality articles, profound research can be collected in other journals, and the impact factor cannot fully represent the quality of each paper.

The USA, UK, Germany, and other European countries were the largest contributors to scientific research (27). However, the situation was slightly different in the HPV field. Some African and Asian countries, such as Brazil, China, Thailand, and Mexico also ranked in the top 20 countries of high-cited publications and played vital roles in HPV-related research. An increasing number of countries are participating in HPV research, manifesting that HPV has been recognized as a global issue and has attracted worldwide attention (28). Advances in HPV research provided opportunities for international collaboration, which prompted research outcomes more convincing. Cooperations between the research centers and hospitals were the most common and created links between clinical issues and biomedical research. The bridge between physicians and scientists was instructive to solve the clinical and health problem caused by HPV. Large research institutes remained the backbone of the HPV field, boosting the development of some regional research centers.

A majority of top-cited articles were research articles, which was consistent with the findings of most bibliometric studies (29,30). Irrelevant citations and article types indicated that the research articles and systematic reviews

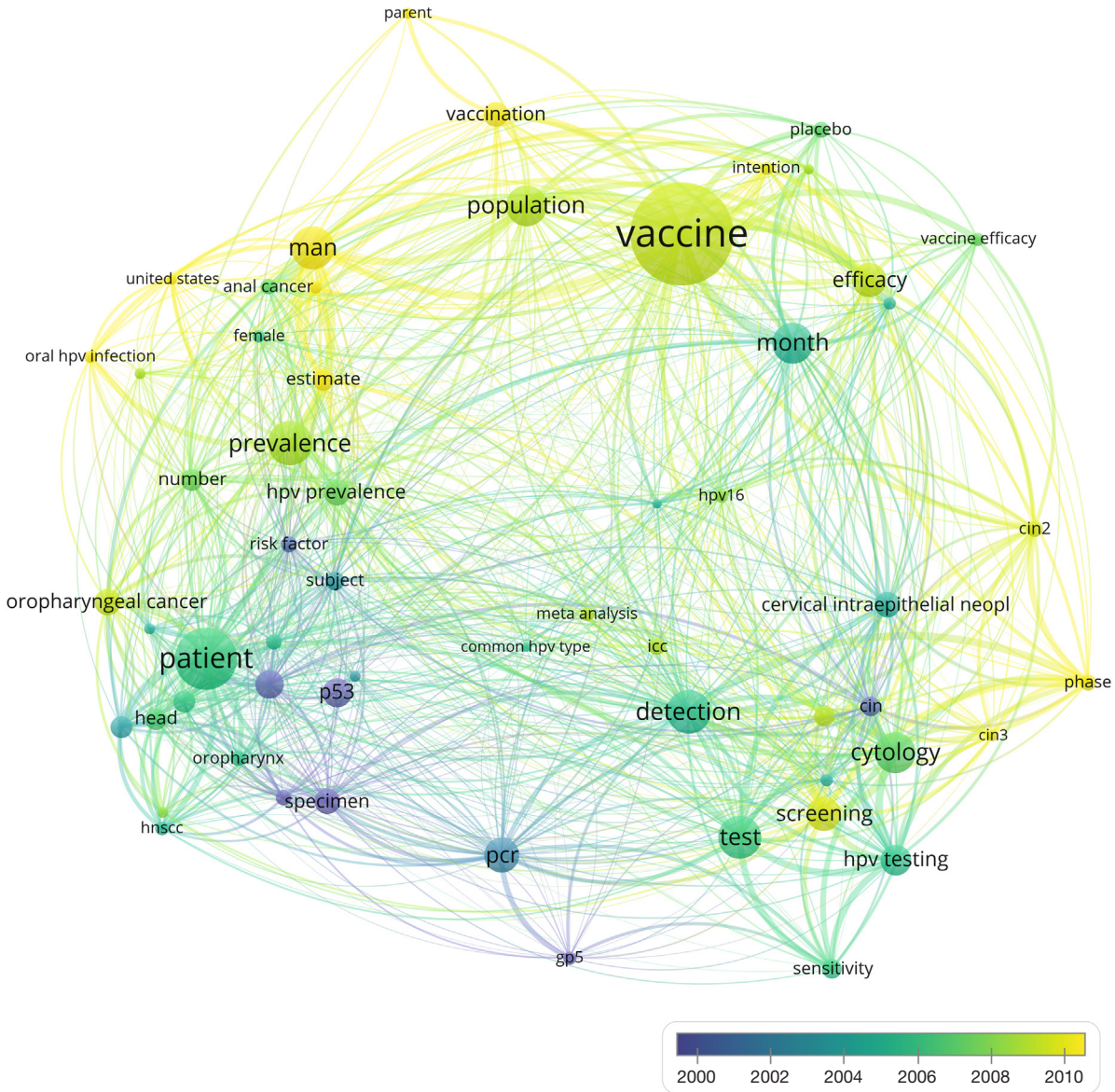

Figure 5 Overlay visualization of title and abstract of 100 top-cited articles in HPV. HPV, human papillomavirus.

were of equal importance. Most articles were categorized as "Oncology" in WOS, which was also a research hotspot in the field of public health. Furthermore, the carcinogenesis of HPV is of the greatest concern, explaining the decades-long focus on HPV-related diseases (31,32). As the WOS category cannot fully represent the research emphasis to a certain extent, we identified and analyzed the specific topic of each article. Research in the HPV field turned disproportionately to epidemiology and etiology. But the citations among the five topics were similar, suggesting comparable topic interest.

Title and abstract are the best condensing of the full text and represent the research trends and hotspots of the research. The trend in titles and abstracts in the HPV field was shifting from identification to screening and prevention. The research hotspots on HPV-related cancers also changed from cervical neoplasia to head and neck squamous cancer, oropharynx cancer, and anal cancer. Thereinto, more meticulous research detailed a specific phase of cervical intraepithelial neoplasia such as CIN2

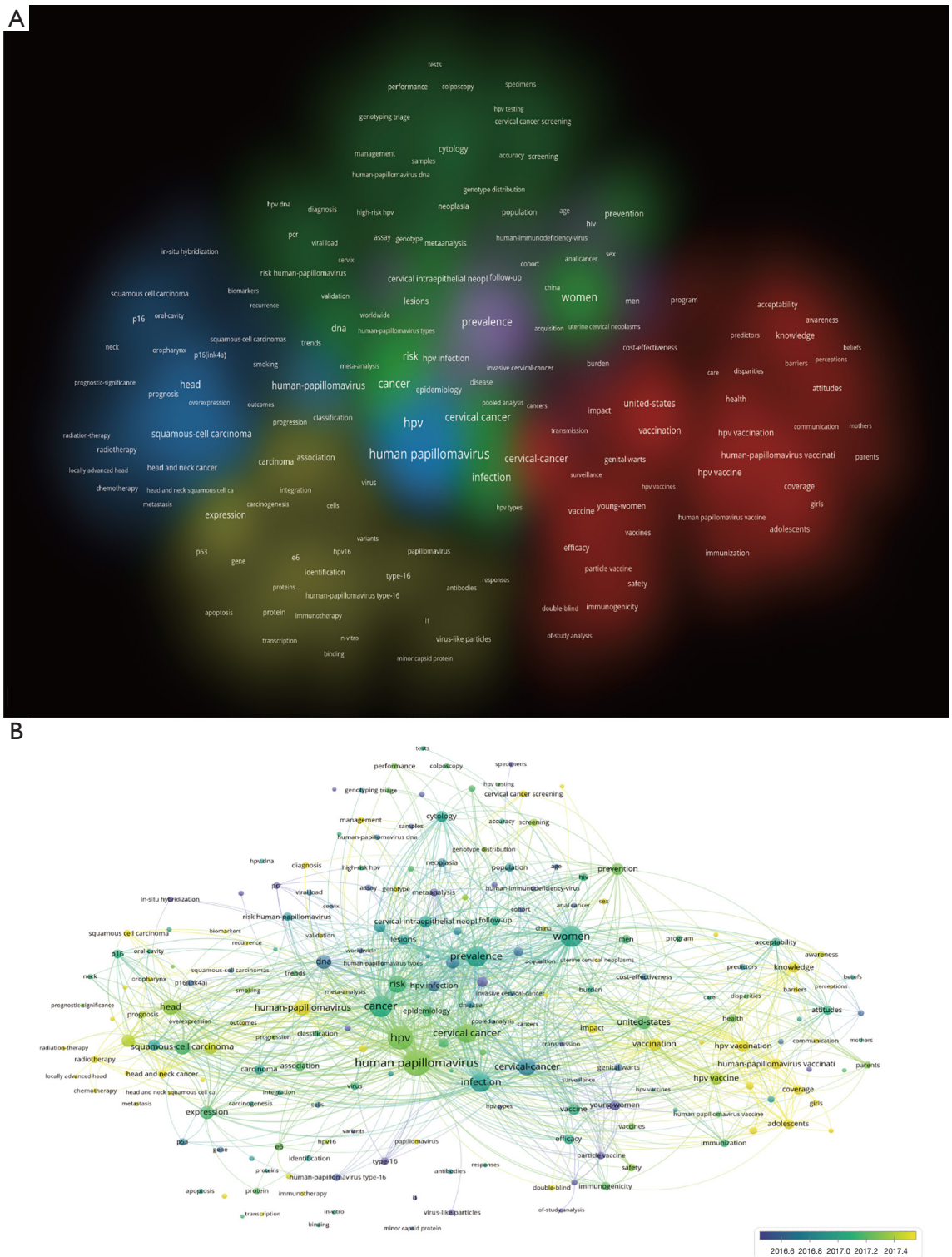

Figure 6 Network plot of keywords in HPV research since 2013. (A) Cluster visualization. (B) Overlay visualization. Of the 21,926 terms, 207 terms have occurred over 100 times. The size of the circles in the figure represents the occurrences of terms. HPV, human papillomavirus.

and CIN3 were conducted in recent years, highlighting the ability to identify and treat early precancerous lesions, rather than invasive cancer. Demographic changes from females to males also suggested a more in-depth study of HPV infections in the oral and anal regions. Recent studies put more emphasis on HPV vaccination, which marked a milestone in HPV oncogenic prevention. In our study, the titles and abstracts of those most cited articles overwhelmingly focused on the vaccine and its efficacy, vaccination intention, and population. On the topic of HPV vaccination, these top-cited articles were mostly randomized controlled trials published from 2002 to 2015. The efficacy of the HPV16 vaccine was first studied in 2002, followed by studies of bivalent, quadrivalent, and nonavalent vaccines. In addition to women, the efficacy of the HPV vaccine against anal infection and neoplasia for men was also published in 2011 (33), which was coherent with the recent studies on anal cancer. The recommendation, acceptability, and barriers of HPV vaccination were also hot topics (34-36), which were also identified in the previous bibliometric study (13).

The transition of keywords also revealed the progress of HPV-related research, which started from the identification of HPV, including obtaining its genome sequences. Then epidemiological and laboratory studies of HPV received extensive attention. In recent years, vaccination became a new research hotspot. The dynamic changes in keywords represented the natural research process of the virus, which has undergone the process of cognition, investigation, and prevention. The usage trends of keywords were correlated with that of the titles and abstracts. Articles published after 2012 had similar clusters to the top-cited articles. The epidemiology of HPV and cervical cancer remained the topic in the field of greatest interest in the field of HPV. The latest hotspot in HPV research was mainly HPV vaccination, which overlapped with the recent hotspot of the top-cited articles.

This is the first bibliometric study involving the most-cited articles in the entire HPV field. We visualized the citations, publication year, journal, authorship, country and institution, category and topic, title & abstract, and keywords co-occurrence of these articles. However, there were some limitations. Firstly, we only included articles written in English, which may omit some valuable research written in other languages. Secondly, some recently published articles were not yet read for lack of time, resulting in temporary low citations. This unavoidable bias raises the need for regular updates of bibliometric research.

Conclusions

This article provides a comprehensive summary of milestone publications in the HPV field. We summarized emerging trends in epidemiology, etiology, and HPV-related cancers that remained central to the field. Meanwhile, researches on HPV vaccination, screening, male, therapy, head and neck cancer are increasing. Given the increasing global burden of HPV-related cancers, interest in HPV will continue to grow. Comprehensive research on HPV will lead to greater progress in understanding, prevention, and treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-463/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

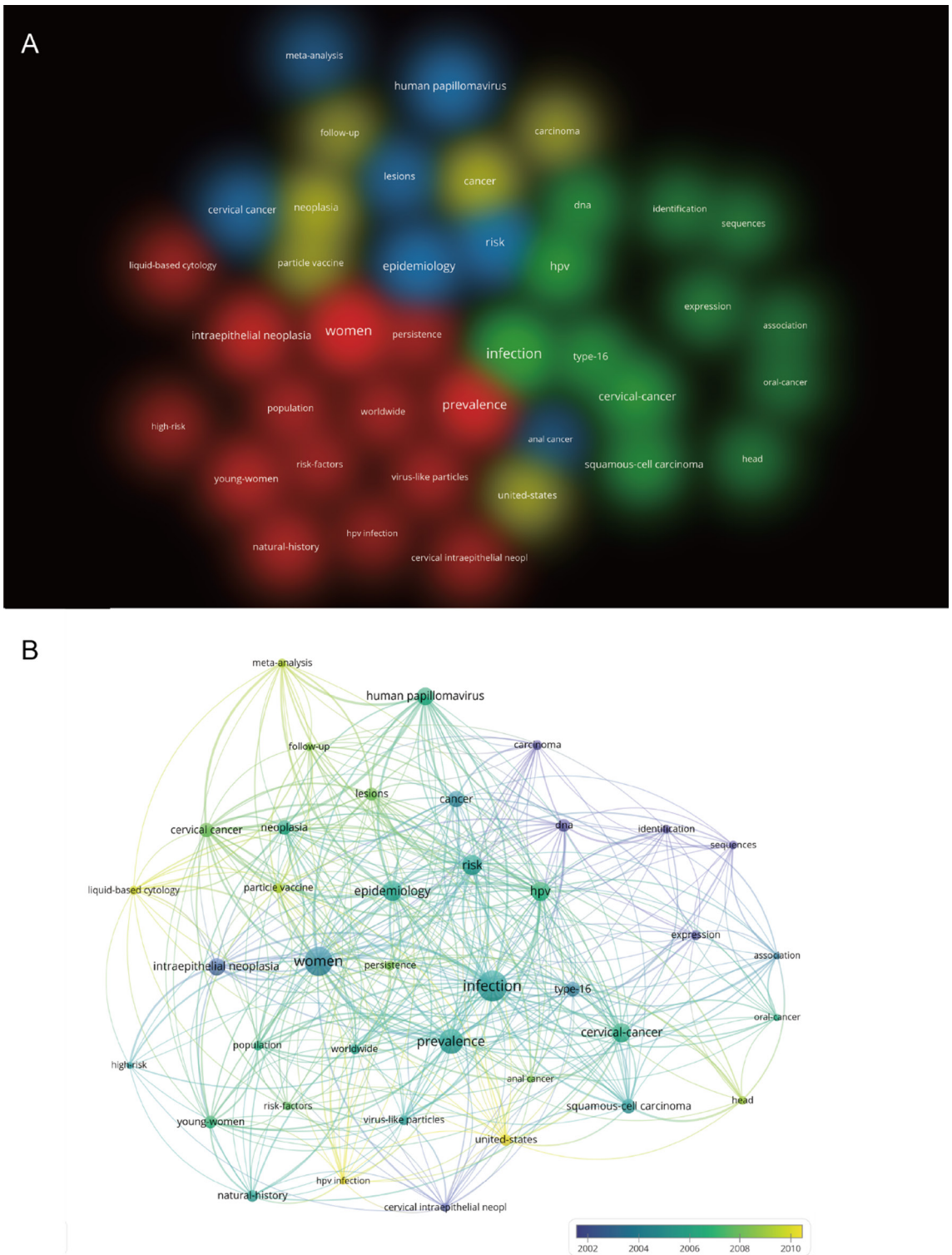

Figure S1 Network plot of keywords in HPV research of the 100 most-cited articles in human papillomavirus. (A) Cluster visualization. (B) Overlay visualization. The size of the circles in the figure represents the occurrences of terms. HPV, human papillomavirus.

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