

A systemic review of human papillomavirus studies: global publication comparison and research trend analyses from 1993 to 2008

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Summary

The term "human papillomavirus" has been used as the keyword during searching titles, abstracts, and keywords based on the online version of Science Citation Index (SCI), Web of Science from 1993 to 2008. Twelve document types were found among the 14,943 papers published in 1,072 journals that were listed in 99 SCI subject categories. All the articles referring to human papillomavirus were assessed by using the following aspects: characteristics of publication output, distribution of output in journals, publication output of source country, source institute, and analysis of word clusters in title, author keywords, and keywords plus. The results have shown that the USA ranked first using five publication indicators including total, single country, international, first author, and corresponding author publications. China has had the sharpest rise of publications since 2004. The top four European countries in 2008 were France, Germany, the UK, and Italy, respectively. Trend studies with word cluster analysis were performed with regards to the areas of immunology, screening methodology, behavioral sciences, economics, and meta-analysis. All those areas have shown a sharp upward rise since 2004. In addition, hypermethylation-induced inactivation of the p16 gene in the early stages of oncogenesis has been getting more interest in recent years.

Key words: Human papillomavirus; Bibliometric; Research trend; Cervical cancer.

Introduction

Infection with the human papillomavirus (HPV) has been determined to be the main cause of cervical cancer [1, 2]. After HPV was identified on cervical swabs, the relationship between HPV and cervical cancer has been extensively and thoroughly explored. It was found that cervical cancer is mainly caused by HPV [3-5]. The HPV vaccine has since been developed and its clinical trial has indeed shown favorable results [6-8]. Following the discovery of the correlation between HPV and cervical cancer, numerous studies have been conducted on the subject, but nobody has yet looked at a global comparison of the research trends for such studies.

Bibliometry is the process of surveying the scientific achievements of a scientist and is well utilized in medical research. For example, this is accomplished by comparing the scientific production in the field of cancer molecular epidemiology among countries and by evaluating the publication trend [9]. However, there is a lack of global comparisons between performances and trends among HPV studies. This study explores HPV using the Science Citation Index (SCI) database since the first mention of HPV in 1975. Only studies from 1993 through 2008 were

used in the data collection in order to perform the global comparisons and trend analyses. Research performance has been analyzed and ranked across countries and institute publications. Research trends of prominent areas were assessed by words cluster analyses. These were obtained from a combination of author keywords, keywords plus, and words in title.

Methods

Documents used in this study were extracted from the online database of the Science Citation Index (SCI) retrieved from the ISI Web of Science, Philadelphia, USA. Journal Citation Reports (JCR) indexed 6,620 major journals with citation references across 173 scientific disciplines during the year of 2008. "Human papillomavirus" was used as a keyword in order to search titles, abstracts, and keywords from 1975 to 2008. Articles originating from England, Scotland, Northern Ireland, and Wales were reclassified as originating from the United Kingdom (UK). Articles from Hong Kong were not included in the ones from China. The reported impact factor (IF) of each journal was obtained from the 2008 JCR. Contributions of different institutes and countries were classified according to the affiliation of at least one of the authors to the publications. Collaboration type was determined by the addresses of the authors, where the term "single country publication" was assigned if the researchers' addresses were from the same country. The term "internationally collaborated publication" was given to those articles coauthored by researchers from multiple coun-

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tries. The term "single institute publication" was assigned if the researchers' addresses were from the same institute. The term "inter-institutionally collaborated publication" was assigned if authors were from different institutes.

All the articles referring to HPV from 1993 to 2008 were assessed using the following aspects: document types and language of publication, characteristics of publication outputs, distribution of outputs in journals, publication outputs of source country, source institute, and analysis of words in title, author keywords, and keywords plus.

Results and Discussion

Document type and language of publication

The distribution of document types identified by ISI was analyzed. From this study, 12 document types were found in the total of 14,943 publications during the 16-year study period. Articles (11,159) contained the most frequently used document type with 75% of all publications. They were followed by reviews (1,324; 8.9%) and the remainder having less significance, were proceedings papers (754), meeting abstracts (667), letters (401), editorial materials (388), notes (160), corrections (39), news items (25), additional corrections (18), reprints (6), and biographical items (2). Journal articles represented the majority of document types. Only 11,159 original articles were used for further analysis, whereas all others were discarded. Ninety-eight percent of all these journal articles were published in English. Several other languages were also used, including French (99), German (98), Spanish (40), Portuguese (7), Chinese (6), Polish (5), Korean (4), Turkish (2), Russian (2), and one in Italian, Romanian, and Serbian, respectively.

Publication output

The amount of SCI journal articles including the ones with "human papillomavirus" in the title only, since 1975, were counted and are displayed in Figure 1. The first paper on the "human papillomavirus DNA-physical map" was published in the *Proceedings of the National Academy of Sciences of the United States of America*, by Favre et al. from France. These authors also published HPV-related papers in the following years [10-12]. Figure 1 shows that there is an obvious increase in trends between 1984 and 1992. After plateau periods between 1992 and 2004, another sharp increase in trend was revealed. In the early 1980s, studies displayed great milestones in the detection of HPV in genital lesions [13] as well as, DNA sequence of HPV-6 [14,15] and HPV-11 and genome organization [14]. From the identification of the HPV on cervical swabs, the relationship of HPV type-16 and cervical cancer were clearly shown [16]. Physical characteristics of the virus, its DNA sequence and the prevalence of HPV-16 as well as the DNA sequence of HPV-18 were demonstrated [17]. In addition, there was progress in the study of HPV, demonstrating that the E6 protein of HPV-16 is capable of binding to the cellular p53 protein [3]. This confirmed the suspected role of genital HPV infections as the central etiologic factor [18] and

justified the need for invasive cervical cancer worldwide [2]. Furthermore, the efficacy, safety and immunogenicity of the HPV vaccine were proved [7] as were its long-term effects [8]. Above all, the authors of these findings have historically contributed to HPV research.

Publication patterns: subject categories and journals

Based on the classification of subject categories of JCR in 2008, the publication output data of HPV research is distributed in 99 SCI and 16 SSCI subject categories. Subject categories containing more than 700 HPV-related articles were statistically analyzed and are shown in Figure 2. The number of scientific articles per category exhibited consistently grew during the time period covered. This indicates that HPV research has developed steadily in various categories. Oncology was the most common category included in 141 journals in JCR 2008. In earlier years, characteristics of the lesions and risk of malignant conversion were associated with the type of HPV involved in epidermodysplasia verruciformis [12]. This was classified in the oncology category. HPV is associated with cervical lesions and its malignant changes was firstly reported in oncology papers. Moreover, prominent articles containing topics on the prevalence of HPV and its relationship to cervical cancer were also published in the area of oncology [2,18].

For 16 years, 11,159 articles were published in 1,072 different journals, including specialty journals and journals about other disciplines. Table 1 presents the 20 journals which contain more than 100 HPV-related articles. *Journal of Virology* listed HPV in the category of virology. It ranked first with 483 (4.3%) papers. The *International Journal of Cancer* listed it in the category of oncology, ranking second with 376 (3.4%) publications. The ten journals in Table 1 were listed under oncology followed by obstetrics and gynecology with five journals and virology with four journals. Twenty percent of the articles can be found in these seven core journals. According to JCR, the impact factor (IF) of *Cancer Research* reached 7.514, which was higher than in any other journal. In addition, five articles were published in the *CA-A Cancer Journal for Clinicians*, a journal which is ranked as the best of the 6,598 journals listed in SCI with an impact factor 74.575.

Publication performances: countries and institutes

The contribution provided by different countries/territories was estimated by focusing on the location of the affiliation of at least one author of the published papers. There were 37 articles without any author address information on the ISI Web of Science. Of all the articles with author addresses, 8,693 (78%) were single country publications and 2,429 (22%) were internationally collaborated publications. The top 30 countries/territories were ranked according to their number of total publications. This includes the number and percentage of total publications, single country publications, internationally collaborated publications, first author publications, and corresponding author's publications. Also considered were the country's collaboration percentage (%C) and the percent-

Table 1. — The top 20 most published journals on the topic of HPV.

Journal name	IF	TP (%)	Subject category	Position
Journal of Virology	5.308	483 (4.3)	Virology	3/27
International Journal of Cancer	4.734	423 (3.8)	Oncology	30/141
Gynecologic Oncology	2.919	376 (3.4)	Oncology	65/141
Oncogene	7.216	270 (2.4)	Obstetrics & Gynecology	12/61
			Biochemistry & Molecular Biology	
			Oncology	13/141
			Cell Biology	23/157
Virology	3.539	261 (2.3)	Genetics & Heredity	14/138
			Virology	8/27
			Cancer Research	12/141
			Oncology	28/141
British Journal of Cancer	4.846	209 (1.9)	Oncology	28/141
International Journal of Gynecological Cancer	1.932	186 (1.7)	Oncology	105/141
Journal of General Virology	3.092	181 (1.6)	Obstetrics & Gynecology	29/61
			Biotechnology & Applied Microbiology	34/144
Journal of Medical Virology	2.576	176 (1.6)	Virology	12/27
			Virology	14/27
Vaccine	3.298	168 (1.5)	Immunology	42/121
Cancer Epidemiology Biomarkers & Prevention	4.770	149 (1.3)	Research & Experimental Medicine	19/82
			Veterinary Sciences	1/134
Journal of Clinical Microbiology	3.945	148 (1.3)	Oncology	29/141
			Public, Environmental & Occupational Health	8/105
Journal of Biological Chemistry	5.520	129 (1.2)	Microbiology	18/91
Anticancer Research	1.390	127 (1.1)	Biochemistry & Molecular Biology	41/276
American Journal of Obstetrics and Gynecology	3.453	122 (1.1)	Oncology	119/141
European Journal of Gynaecological Oncology	0.641	114 (1.0)	Obstetrics & Gynecology	7/61
Cancer	5.238	114 (1.0)	Oncology	138/141
			Obstetrics & Gynecology	59/61
Sexually Transmitted Diseases	2.863	109 (1.0)	Infectious Diseases	19/141
Obstetrics and Gynecology	4.397	107 (1.0)	Obstetrics & Gynecology	20/51
			Obstetrics & Gynecology	2/61

IF: impact factor; TP: total published articles in the 16 years; %: percentage of all articles published in the years.

age of collaborated publications in total publications for each country (Table 2). Six of the G7 (seven major industrial countries of the world) countries ranked as the top six of the world publications. These were France, Germany, Italy, Japan, the UK, and the USA. Canada came in at number nine. The Netherlands (581; 7th) and Sweden (466; 8th) also ranked in the top ten. Moreover, the G7 had high productivity in independent papers (66%), first author publications (64%), and corresponding author publications (63%). Similar results were also found within medical research topics in terms of stem cell [19], asthma in children [20], and patent ductus arteriosus treatments [21]. The USA showed the greatest number of world publications (41%), followed distantly by other countries. It also had the most frequent partnered publications. This accounted for 54% of the internationally collaborated publications. However, compared to its total

publications, the USA presented a very low percentage (29%) of internationally collaborated publications with authors from other countries. Japan held 23% of the world publications, but only 5.7% of all internationally collaborated publications. Table 2 shows that 15 European countries, seven American countries, and seven Asian countries were ranked in the top 30 based on their publications. Only one country from Africa and one from Oceania were in the top 30; South Africa and Australia, respectively. When looking at the percentage of European articles that contained internationally collaborated content, the average was 51% with a range of 29% (Greece) to 68% (Switzerland) while American articles had an average of 60% and a range of 29% (USA) to 100% (Costa Rica). However, in Asian countries, a low average of 32% was found, with a range of 21% (South Korea) to 45% (China).

Fig. 1

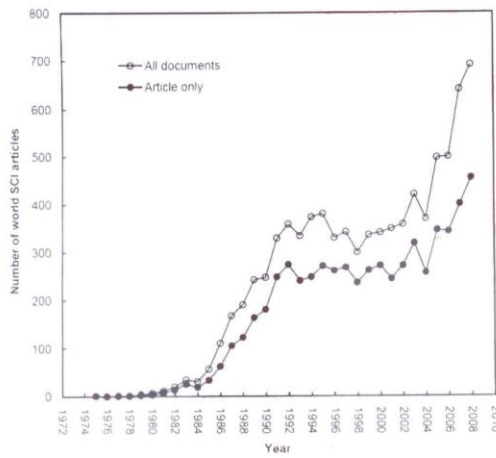


Fig. 2

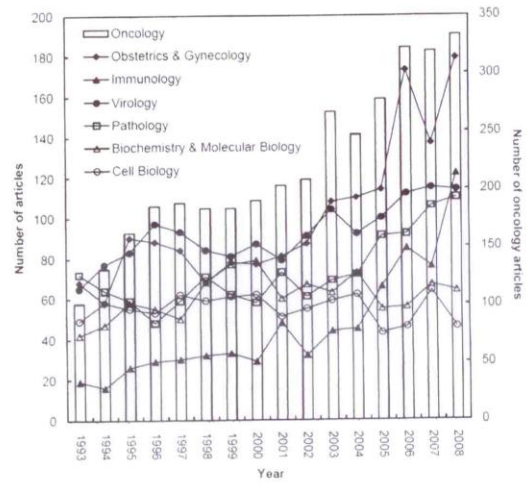


Fig. 3

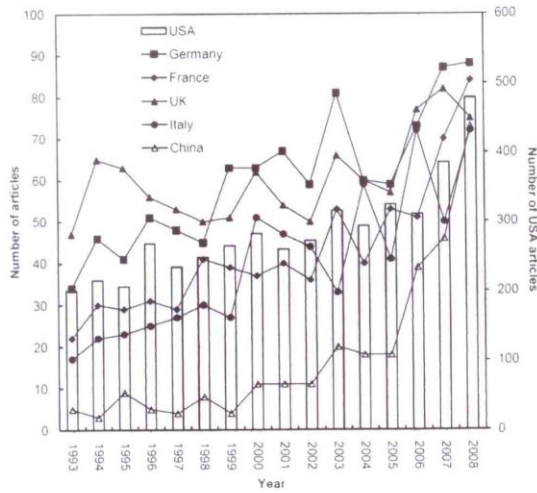


Fig. 4

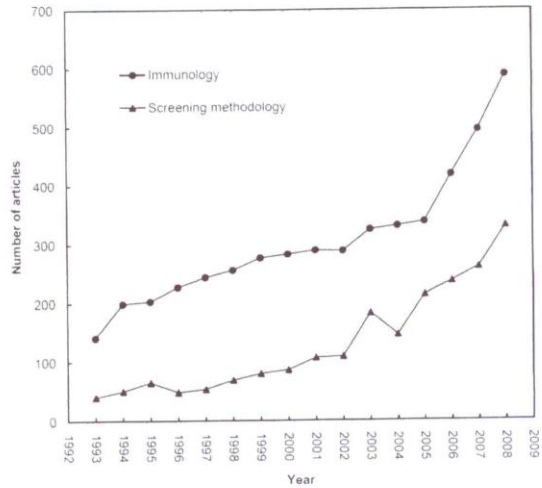


Fig. 5

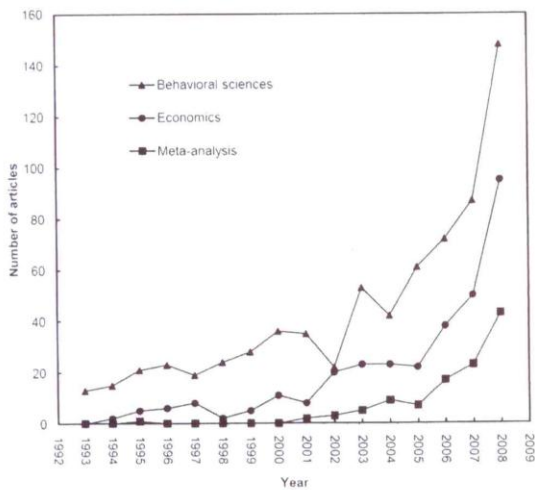


Figure 1. — Number of SCI papers referring to “human papillomavirus” in the title only (since the first paper was published in 1975).

Figure 2. — Growth trends of seven subject categories containing more than 700 publications.

Figure 3. — Publication growth of the top five countries compared to China.

Figure 4. — Trends between the research areas of immunology and screening methodology.

Figure 5. — Trends between the research areas of behavioral sciences, economics, and meta-analysis.

Table 2. — Top 30 most productive countries based on the number of articles published.

Country	TP	TPR (%)	SPR (%)	CPR (%)	FAR (%)	RPR (%)	% C
USA	4,571	1 (41)	1 (37)	1 (54)	1 (35)	1 (34)	29
UK	968	2 (8.7)	2 (6.4)	3 (17)	2 (6.7)	2 (6.3)	43
Germany	965	3 (8.7)	3 (6.0)	2 (18)	3 (6.3)	2 (6.3)	46
France	685	4 (6.2)	6 (3.9)	4 (14)	5 (4.4)	5 (4.6)	50
Italy	640	5 (5.8)	5 (4.5)	7 (10)	6 (4.3)	6 (4.4)	39
Japan	604	6 (5.4)	4 (5.4)	13 (5.7)	4 (4.8)	4 (4.8)	23
Netherlands	581	7 (5.2)	7 (3.3)	5 (12)	7 (3.5)	7 (3.4)	50
Sweden	466	8 (4.2)	9 (2.5)	6 (10)	8 (3.0)	8 (2.9)	54
Canada	410	9 (3.7)	11 (2.3)	8 (8.5)	9 (2.6)	9 (2.6)	50
Australia	335	10 (3.0)	12 (2.2)	12 (5.9)	10 (2.3)	10 (2.4)	43
Brazil	331	11 (3.0)	13 (2.0)	10 (6.5)	12 (2.1)	12 (2.3)	47
Taiwan	299	12 (2.7)	9 (2.5)	19 (3.5)	12 (2.1)	13 (2.2)	29
South Korea	287	13 (2.6)	8 (2.6)	25 (2.5)	11 (2.3)	10 (2.4)	21
China	285	14 (2.6)	14 (1.8)	14 (5.2)	14 (1.8)	14 (1.9)	45
Finland	283	15 (2.5)	17 (1.2)	9 (7.4)	15 (1.7)	15 (1.6)	63
Spain	257	16 (2.3)	16 (1.3)	11 (6.0)	16 (1.3)	16 (1.3)	56
Mexico	196	17 (1.8)	19 (1.1)	15 (4.3)	18 (1.2)	18 (1.2)	53
Belgium	184	18 (1.7)	18 (1.1)	17 (3.7)	18 (1.2)	18 (1.2)	49
India	172	19 (1.5)	15 (1.4)	26 (2.2)	17 (1.3)	17 (1.3)	31
Norway	157	20 (1.4)	25 (0.66)	16 (4.1)	24 (0.77)	22 (0.83)	64
Denmark	138	21 (1.2)	26 (0.61)	20 (3.5)	20 (0.81)	21 (0.84)	62
South Africa	122	22 (1.1)	23 (0.69)	24 (2.6)	25 (0.76)	25 (0.80)	51
Austria	121	23 (1.1)	24 (0.67)	23 (2.6)	23 (0.78)	20 (0.85)	52
Hong Kong	111	24 (1.0)	21 (0.83)	28 (1.6)	20 (0.81)	22 (0.83)	35
Switzerland	107	25 (1.0)	31 (0.39)	21 (3.0)	28 (0.57)	29 (0.55)	68
Greece	105	26 (0.94)	20 (0.86)	33 (1.2)	20 (0.81)	24 (0.81)	29
Poland	99	27 (0.89)	22 (0.75)	30 (1.4)	26 (0.64)	26 (0.69)	34
Costa Rica	87	28 (0.78)	N/A	18 (3.6)	50 (0.063)	47 (0.082)	100
Colombia	81	29 (0.73)	44 (0.10)	22 (3.0)	37 (0.22)	37 (0.23)	89
Argentina	79	30 (0.71)	30 (0.46)	28 (1.6)	30 (0.52)	30 (0.54)	49
Israel	79	30 (0.71)	28 (0.56)	33 (1.2)	27 (0.59)	28 (0.59)	38

TP: the number of total publications; % TPR: the share in total publications; SPR (%), CPR (%), FAR (%), RPR (%): the rank and percentage of single country publications, internationally collaborated publications, first author publications, corresponding author publications in total publications; %C: country collaboration percentage, the percentage of collaborated publications in total publications for each country; N/A: not applicable.

The data also shows that around 2005 China had a sudden sharp increase in publications. To illustrate this, a time series analysis was done comparing China to the top five publications producing countries (Figure 3). From 1993 until the end of the period covered, a fluctuating slight rise can be seen in the numbers of articles related to HPV research from Germany, France, and Italy. Germany had the greatest number of articles appearing in 2008. One can conclude that Germany had an observable but slightly increasing trend whereas, the UK, being at the top in 1993, remained steady. By contrast, with the lowest production of articles, China had a rapidly increasing trend after 2005. This phenomenon was also found in the field of oncology. The annual mean increase in publications is noticeable in Asian countries, especially in China (23%) [22]. The contribution of different institutes was estimated by the affiliation of at least one author of the published papers. Of articles with the author's address information on the ISI Web of Science, 11,122 were analyzed; 4,065 (37%) articles were independent publications and 7,057 (63%) were inter-institutionally collaborated publications. The top 30 institutes were ranked by their number of total publications. This includes the number and percentage of single institute publications and

inter-institutionally collaborated publications. Also considered were first author publications and corresponding author publications (Table 3). Most institutes listed in the table had a relatively high percentage of inter-institutionally collaborated publications (%C) from 57% (University of Alabama, USA) to 96% (International Agency for Research on Cancer, France) with an average of 76%.

Among the top 30 institutes, 18 (60%) originated from the USA, followed by the Netherlands, Finland, and Germany with two institutes and the others from France, Brazil, UK, Australia, Canada, and Sweden who all had one institute each. Leading the way was the USA's National Cancer Institute showing a large disparity with the others. It was followed by Harvard University, University of Texas, and Johns Hopkins University. The University of Texas had the most independent publications, seven times that of Johns Hopkins University.

Research emphasis: words in title, author keywords, and keywords plus

The length and number of key words per title were used to compare the complexity of titles between countries [23]. Distributions of words per title within different blocks were used to evaluate research trends [24]. Author

Table 3. — Top 30 most productive institutes based on the number of articles published.

Institute	TP	TPR (%)	SPR (%)	CPR (%)	FAR (%)	RPR (%)	%C
National Cancer Institute, USA	453	1 (4.1)	3 (1.5)	1 (5.5)	1 (2.1)	1 (2.2)	86
Harvard University, USA	283	2 (2.5)	3 (1.5)	3 (3.1)	4 (1.2)	4 (1.0)	78
University of Texas, USA	266	3 (2.4)	1 (2.4)	5 (2.4)	2 (1.6)	2 (1.4)	64
Johns Hopkins University, USA	259	4 (2.3)	49 (0.34)	2 (3.5)	6 (0.87)	6 (0.94)	95
Deutsch Krebsforschungszentrum, Germany	241	5 (2.2)	5 (1.5)	4 (2.6)	3 (1.3)	3 (1.2)	75
University of Washington, USA	193	6 (1.7)	13 (0.66)	6 (2.4)	9 (0.68)	13 (0.53)	86
University of California, San Francisco, USA	185	7 (1.7)	2 (1.6)	11 (1.7)	5 (1.1)	5 (1.0)	64
Karolinska Institute, Sweden	180	8 (1.6)	21 (0.54)	8 (2.2)	7 (0.72)	16 (0.47)	88
International Agency for Research on Cancer, France	173	9 (1.6)	113 (0.17)	6 (2.4)	10 (0.66)	7 (0.72)	96
McGill University, Canada	134	10 (1.2)	66 (0.27)	9 (1.7)	20 (0.50)	17 (0.46)	92
Albert Einstein College of Medicine, USA	133	11 (1.2)	57 (0.30)	10 (1.7)	51 (0.30)	43 (0.31)	91
Fred Hutchinson Cancer Research Center, USA	131	12 (1.2)	40 (0.39)	12 (1.6)	8 (0.69)	9 (0.67)	88
Johns Hopkins Medical Institute, USA	120	13 (1.1)	74 (0.25)	13 (1.6)	11 (0.61)	101 (0.17)	92
Centers for Disease Control and Prevention, USA	117	14 (1.1)	32 (0.44)	14 (1.4)	18 (0.52)	11 (0.57)	85
University of New Mexico, USA	106	15 (1.0)	25 (0.52)	15 (1.2)	28 (0.4)	22 (0.39)	80
Georgetown University, USA	105	16 (0.94)	21 (0.54)	16 (1.2)	21 (0.49)	38 (0.33)	79
Pennsylvania State University, USA	104	17 (0.94)	6 (1.1)	34 (0.86)	17 (0.54)	13 (0.53)	59
Leiden University, Netherlands	103	18 (0.93)	9 (0.84)	21 (1.0)	11 (0.61)	8 (0.70)	67
University of Alabama, USA	100	19 (0.90)	6 (1.1)	38 (0.81)	14 (0.58)	10 (0.58)	57
Indiana University, USA	95	20 (0.85)	27 (0.47)	17 (1.1)	13 (0.58)	15 (0.50)	80
University of Wisconsin, USA	95	20 (0.85)	12 (0.74)	28 (0.92)	14 (0.58)	17 (0.46)	68
University of Queensland, Australia	90	22 (0.81)	10 (0.81)	38 (0.81)	16 (0.55)	12 (0.54)	63
University of Cambridge, UK	90	22 (0.81)	19 (0.59)	26 (0.94)	24 (0.45)	43 (0.31)	73
Vrije University Amsterdam, Netherlands	89	24 (0.80)	52 (0.32)	17 (1.1)	58 (0.27)	41 (0.32)	85
University of Pittsburgh, USA	88	25 (0.79)	16 (0.64)	31 (0.88)	18 (0.52)	19 (0.43)	70
University of Cologne, Germany	83	26 (0.75)	21 (0.54)	34 (0.86)	28 (0.40)	28 (0.36)	73
University of Turku, Finland	82	27 (0.74)	88 (0.22)	19 (1.0)	37 (0.35)	31 (0.34)	89
University of California, Los Angeles, USA	81	28 (0.73)	11 (0.79)	51 (0.69)	23 (0.47)	31 (0.34)	60
University of Sao Paulo, Brazil	79	29 (0.71)	27 (0.47)	36 (0.85)	46 (0.31)	65 (0.25)	76
University of Helsinki, Finland	79	29 (0.71)	52 (0.32)	26 (0.94)	41 (0.33)	31 (0.34)	84

TP: the number of total publications; TPR (%): the rank and share in total publications; SPR (%), CPR (%), FAR (%), RPR (%): the rank and percentage of single institute publications, inter-institutionally collaborated publications, first author publications, corresponding author publications in total publications; %C: institute collaboration percentage, the percentage of collaborated publications in total publications for each institute.

keywords analysis provided the information on research trends. These could be found in recent years [25]. Analyzing the authors' keywords was much more frequently applied in the trends research [19,26]. Keywords and search terms were extracted from titles of papers cited in each new article in the database in ISI [27]. Each of them represents the authors' main ideas in a different fashion. When analyzing each word contained in titles, the phrase in source titles was segmented into single words. On the contrary, in the author keywords analysis, the exact words expressed by the authors were preserved. Also, the keywords plus, an independent supplement, revealed the contents in more detail. In order to analyze the historical development and trends of the research, the distribution of words in titles, author keywords, and keywords plus in different periods were analyzed as a whole. There were both similar and dissimilar trends in the statistical results within this study period. In order to overcome internal weaknesses we separated the process into three types of keywords analysis. We combined words in the title, author keywords, and keywords plus. Afterwards synonyms and phrases were combined into different categories in order to analyze the historical development of science and HPV programs more completely and precise-

ly more importantly, this was done in order to discover the directions of science in the future.

Table 4 lists the 30 most used author keywords with their ranks and percentages in various blocks. There are 9,577 author keywords appearing in 6,580 articles. Among them, 6,847 (71%) keywords appeared only once and 1,173 (12%) keywords appeared twice. The large number of once-only author keywords probably indicates a dim continuity in the research and a wide variety in research focuses [28]. Similar results were also reported in several research topics, for example aerosol [24] and stem cell research [19].

The study trends obtained from words in titles, author keywords and keywords plus can be differentiated into five *disciplines* including immunology, screening methodology, behavioral sciences, economics, and meta-analysis. First, immunology was comprised of p53, E6, E7, immunization, immune response, immunogenicity, vaccine, immunohistochemistry, vaccine efficacy, prophylactic vaccine, P16 protein, E5 oncoprotein, and herd immunity. Second, the screening methodology was composed of the following words: screen, HPV DNA testing, Pap smear, DNA chip, hypermethylation, and viral load. Similarly, Pap smear, sexually transmitted infection, cer-

Table 4. — Top 30 most frequently used author keywords during 1993-2008 divided into four 4-year periods.

Author keywords	93-08 TP	93-08 R (%)	93-96 R (%)	97-00 R (%)	01-04 R (%)	05-08 R (%)
human papillomavirus	1,881	1 (29)	1 (33)	1 (28)	1 (27)	1 (28)
HPV	1,022	2 (16)	3 (10)	2 (13)	3 (15)	3 (19)
cervical cancer	1,007	3 (15)	5 (7.5)	3 (10)	2 (17)	2 (20)
p53	418	4 (6.4)	3 (10)	4 (9.2)	4 (6.9)	6 (3.4)
polymerase chain reaction	319	5 (4.8)	2 (13)	5 (7.7)	11 (3.1)	22 (1.8)
cervical intraepithelial neoplasia	302	6 (4.6)	6 (5.5)	6 (5.2)	6 (4.2)	4 (4.3)
papillomavirus	278	7 (4.2)	7 (5.3)	7 (4.2)	5 (4.8)	5 (3.5)
PCR	211	8 (3.2)	7 (5.3)	9 (3.7)	13 (2.8)	13 (2.5)
squamous cell carcinoma	206	9 (3.1)	15 (2.2)	10 (3.6)	7 (3.7)	10 (2.9)
cervical carcinoma	197	10 (3.0)	10 (3.4)	11 (3.4)	12 (3)	12 (2.6)
human papillomavirus (HPV)	191	11 (2.9)	18 (1.8)	18 (2.0)	8 (3.6)	8 (3.2)
cervix	190	12 (2.9)	11 (3.3)	12 (3.2)	10 (3.3)	15 (2.3)
apoptosis	158	13 (2.4)	30 (1.2)	13 (2.9)	9 (3.5)	20 (1.9)
in situ hybridization	154	14 (2.3)	7 (5.3)	8 (3.8)	24 (1.5)	44 (1.1)
CIN	150	15 (2.3)	30 (1.2)	16 (2.4)	18 (2.0)	11 (2.8)
HIV	134	16 (2.0)	24 (1.5)	14 (2.8)	21 (1.8)	16 (2.1)
human papilloma virus	130	17 (2.0)	17 (1.9)	15 (2.6)	23 (1.6)	18 (2.0)
immunohistochemistry	127	18 (1.9)	13 (3.1)	18 (2.0)	22 (1.7)	27 (1.6)
screening	126	19 (1.9)	126 (0.42)	75 (0.65)	26 (1.4)	6 (3.4)
epidemiology	126	19 (1.9)	42 (0.93)	28 (1.3)	14 (2.7)	16 (2.1)
vaccine	117	21 (1.8)	76 (0.62)	44 (0.90)	52 (0.92)	9 (3.2)
cytology	112	22 (1.7)	16 (2.0)	56 (0.73)	33 (1.2)	14 (2.4)
E7	110	23 (1.7)	37 (1.0)	28 (1.3)	16 (2.0)	22 (1.8)
cancer	104	24 (1.6)	42 (0.93)	28 (1.3)	18 (2.0)	25 (1.7)
cervical neoplasia	104	24 (1.6)	18 (1.8)	17 (2.3)	27 (1.3)	31 (1.4)
E6	97	26 (1.5)	126 (0.42)	39 (1.1)	15 (2.2)	27 (1.6)
oral cancer	87	27 (1.3)	21 (1.7)	22 (1.7)	39 (1.1)	38 (1.2)
uterine cervix	85	28 (1.3)	30 (1.2)	18 (2.0)	24 (1.5)	56 (0.83)
colposcopy	81	29 (1.2)	26 (1.3)	28 (1.3)	39 (1.1)	34 (1.2)
cervix neoplasms	81	29 (1.2)	26 (1.3)	21 (1.8)	16 (2.0)	126 (0.41)

TP: the number of total publications; R (%): the rank and percentage of author keywords in total publications.

vical cancer prevention, and sexual behavior were referred to as behavioral sciences. Cost, decision analysis, and screen programming were considered as belonging to economics. Finally, due to the sharp rise of articles during the last four years, we were also interested in the topic of meta-analysis including systemic review.

The comparison of trends in immunology and screening methodology is shown in Figure 4. This revealed a sharp rise of articles from 2002 until the end of the period covered. Upward trends could be seen in the areas of behavioral sciences and economics from 2004 and meta-analysis from 2005 (Figure 5). These upward trends may be due to the study of efficacy, safety, and immunogenicity of the HPV vaccine studied in 2004 and its long-term effects discovered in 2006 [7,8]. Figures 4 and 5 demonstrate that five disciplines all showed an upward trend, firstly immunology and screening methodology, then behavioral sciences and economics, and finally meta-analysis.

The number of articles related to HPV shows an upward trend having two stages. Oncology was the most common category. The top three productive journals were *Journal of Virology*, *International Journal of Cancer* and *Gynecologic Oncology*. The top ten countries were the

seven major industrial countries (G7: the USA, the UK, Germany, France, Italy, Japan, and Canada), the Netherlands, Sweden, and Australia. The G7 produced almost two-thirds of single country publications. The American National Cancer Institute was the dominant institute in the total, inter-institutional, first author, and corresponding author publications. However, the University of Texas ranked first in single institute publications. In author keywords, p53, polymerase chain reaction, and apoptosis were popular. We artificially and innovatively analyzed the distribution and change of words in the title, author's keywords, and keywords plus. In doing so, we discovered five trends that were related to HPV and had increased in time series order. These were immunology, screening methodology, behavioral sciences, economics, and meta-analysis.

Conclusions

The result of this analysis by the bibliometric method can help researchers envision the panorama of HPV research. The results of the examination of the number of publications over time can exhibit the nation's performance. Once important findings are documented and pub-

lished, it is expected that there will be a rapid rising slope of publications. The achievement in cell biology, biochemistry and molecular biology can enhance the research in oncology, obstetrics and gynecology and immunology. The research trends can be traced to the trajectory of number of publications. Study trends could very well be effortlessly detected by words cluster analyses.

References

- [1] Schwarz E., Freese U.K., Gissmann L., Mayer W., Roggenbuck B., Stremmlau A., Hausen H.Z.: "Structure and transcription of human papillomavirus sequences in cervical-carcinoma cells". *Nature*, 1985, 314, 111.
- [2] Walboomers J.M.M., Jacobs M.V., Manos M.M., Bosch F.X., Kummer J.A., Shah K.V. *et al.*: "Human papillomavirus is a necessary cause of invasive cervical cancer worldwide". *J. Pathol.*, 1999, 189, 12.
- [3] Werness B.A., Levine A.J., Howley P.M.: "Association of human papillomavirus type-16 and type-18 E6 proteins with p53". *Science*, 1990, 248, 76.
- [4] Scheffner M., Huijbregtse J.M., Vierstra R.D., Howley P.M.: "The HPV-16 E6 and E6-AP complex functions as a Ubiquitin-protein Ligase in the Ubiquitination of p53". *Cell*, 1993, 80, 495.
- [5] Storey A., Thomas M., Kalita A., Harwood C., Gardiol D., Mantovani F. *et al.*: "Role of a p53 polymorphism in the development of human papillomavirus-associated cancer". *Nature*, 1998, 393, 229.
- [6] Koutsky L.A., Ault K.A., Wheeler C.M., Brown D.R., Barr E., Alvarez F.B. *et al.*: "A controlled trial of a human papillomavirus type 16 vaccine". *N. Engl. J. Med.*, 2002, 347, 1645.
- [7] Harper D.M., Franco E.L., Wheeler C., Ferris D.G., Jenkins D., Schuind A. *et al.*: "Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial". *Lancet*, 2004, 364, 1757.
- [8] Harper D.M., Franco E.L., Wheeler C.M., Moscicki A.B., Romonowski B., Roteli-Martins C.M. *et al.*: "Sustained efficacy up to 4-5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial". *Lancet*, 2006, 367, 1247.
- [9] Ugolini D., Puntoni R., Perera F.P., Schulte P.A., Bonassi S.: "A bibliometric analysis of scientific production in cancer molecular epidemiology". *Carcinogenesis*, 2007, 28, 1774.
- [10] Orth G., Favre M., Croissant O.: "Characterization of a new type of human papillomavirus that causes skin warts". *J. Virol.*, 1977, 24, 108.
- [11] Orth G., Breitburd F., Favre M.: "Evidence for antigenic determinants shared by the structural polypeptides of (shepe) rabbit papillomavirus and human papillomavirus type-1". *Virology*, 1978, 91, 243.
- [12] Orth G., Jablonska S., Jarzabekchorzelska M., Obalek S., Rzeza G., Favre M., Croissant O.: "Characteristics of the lesions and risk of malignant conversion associated with the type of human papillomavirus involved in epidermodysplasia verruciformis". *Cancer Res.*, 1979, 39, 1074.
- [13] Gissmann L., Devilliers E.M., Hausen H.Z.: "Analysis of human genital warts (condylomata-acuminata) and other genital tumors for human papillomavirus type-6 DNA". *Int. J. Cancer*, 1982, 29, 143.
- [14] Gissmann L., Wolnik L., Ikenberg H., Koldovsky U., Schnurch H.G., Zurhausen H.: "Human papillomavirus type-6 and type-11 DNA-sequences in genital and laryngeal papillomas and in some cervical cancers". *Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences*, 1983, 80, 560.
- [15] Schwarz E., Durst M., Demankowski C., Lattermann O., Zech R., Wolfspenger E. *et al.*: "DNA-sequence and genome organization of genital human papillomavirus type-6B". *Embo J.*, 1983, 2, 2341.
- [16] Wagner D., Ikenberg H., Boehm N., Gissmann L.: "Identification of human papillomavirus in cervical swabs by deoxyribonucleic acid insitu hybridization". *Obstet. Gynecol.*, 1984, 64, 767.
- [17] Durst M., Kleinheinz A., Hotz M., Gissmann L.: "The physical state of human papillomavirus type-16 DNA in benign and malignant genital tumors". *J. Gen. Virol.*, 1985, 66, 1515.
- [18] Bosch F.X., Manos M.M., Muñoz N., Sherman M., Jansen A.M., Peto J. *et al.*: "Prevalence of human papillomavirus in cervical-cancer: A worldwide perspective". *J. Natl. Cancer Inst.*, 1995, 87, 796.
- [19] Li L.L., Ding G.H., Feng N., Wang M.H., Ho Y.S.: "Global stem cell research trend: Bibliometric analysis as a tool for mapping of trends from 1991 to 2006". *Scientometrics*, 2009, 80, 41.
- [20] Chen S.R., Chiu W.T., Ho Y.S.: "Asthma in children: Mapping the literature by bibliometric analysis". *Revue Française d'Allergologie et d'Immunologie Clinique*, 2005, 45, 442.
- [21] Hsieh W.H., Chiu W.T., Lee Y.S., Ho Y.S.: "Bibliometric analysis of patent ductus arteriosus treatments". *Scientometrics*, 2004, 60, 205.
- [22] López-Illescas C., de Moya-Anegón F., Moed H.F.: "The actual citation impact of European oncological research". *Eur. J. Cancer*, 2008, 44, 228.
- [23] Rodríguez K., Moreira J.A.: "The growth and development of research in the field of ecology as measured by dissertation title analysis". *Scientometrics*, 1996, 35, 59.
- [24] Xie S.D., Zhang J., and Ho Y.S.: "Assessment of world aerosol research trends by bibliometric analysis". *Scientometrics*, 2008, 77, 113.
- [25] Chiu W.T., Ho Y.S.: "Bibliometric analysis of tsunami research". *Scientometrics*, 2007, 73, 3.
- [26] Ho Y.S.: "Bibliometric analysis of adsorption technology in environmental science". *J. Environ. Protect. Sci.*, 2007, 1, 1.
- [27] Garfield E.: "KeyWords Plus-ISIS breakthrough retrieval method. 1. Expanding your searching power on current-contents on diskette". *Curr. Contents*, 1990, 32, 5.
- [28] Chuang K.Y., Huang Y.L., Ho Y.S.: "A bibliometric and citation analysis of stroke-related research in Taiwan". *Scientometrics*, 2007, 72, 201.

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