Scientific publications on hepatocellular carcinoma: a global survey of the literature with a special emphasis on China’s contributions

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Background: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver associated with a high morbidity and mortality. Scientific publications may be the most helpful method to distribute information and improve our understanding of HCC. A literature review aimed to systematically analyze the global distribution of scientific publications regarding HCC was performed.

Methods: The Web of Science database was searched to identify all papers regarding HCC from January, 1980 to December, 2016. The major categories included the publication years, regions, journals, research areas, organizations, and funding agencies.

Results: A total of 103,197 papers regarding HCC were identified. The number of papers gradually increased over years and peaked in 2016. USA, China, and Japan ranked as the top three countries in number of publications. In 2016, China ranked first as the country with the greatest number of publications. According to the number of papers published in 2016 by organization, Fudan University ranked first. According to the total number of papers by funding agency, the National Natural Science Foundation of China ranked first. Additionally, the three top research areas according to the total number of papers were gastroenterology/hepatology, oncology, and surgery; and the top three journals according to the total number of papers were Hepatology, Journal of Hepatology, and World Journal of Gastroenterology.

Conclusions: Our literature survey describes the global distribution of manuscripts in the field of HCC. Notably, Chinese researchers are now the leading publisher of manuscripts in the field.
Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy (1). It is estimated that HCC accounts for 70–90% of all liver cancers. HCC is the 6th most common cancer and the 2nd cause of malignancy-related death worldwide (2-5). Major etiologies of HCC include viral hepatitis B and C, alcoholic liver disease, nonalcoholic fatty liver disease, and autoimmune hepatitis. There are many therapeutic options to address HCC (6). Classical treatment options include liver transplantation, surgical resection, radiofrequency ablation, transarterial chemoembolization, as well as sorafenib (7-12). Novel treatment options have emerged in recent years, including radioembolization (13,14), thermotherapy (15), high-intensity focused ultrasound (16), radiotherapy (17), three-dimensional conformal radiation therapy, argon-helium cryotherapy system, traditional Chinese medicine (18), cytokine-induced killer cell therapy (19), regorafenib (20,21), and tivantinib (22,23), as well as others. Additionally, new modalities for the prognostic assessment of HCC and treatment selection have been proposed and/or employed in clinical practice (24-29).

Generally, current understanding of HCC has dramatically improved owing to a remarkable growth of scientific publications in this topic and rapid dissemination of associated knowledge. Herein, we have conducted a literature review to systematically analyze the distribution of scientific publications regarding HCC according to the publication years, regions, journals, research areas, organizations, and funding agencies by using the Web of Science database.

Methods

We searched published papers regarding HCC via the Web of Science database from January, 1980 to December, 2016. The search item was “hepatocellular carcinoma”. All publication types (reviews, case reports, comments, letters, and clinical or experimental studies) were included. We did not identify any duplicated publications among the different journals. We stratified the publications according to the specific categories originally established by the Web of Science, and we identified the publication year, countries/territories, journals, research areas, organizations, and funding agencies. We calculated the number of publications within the defined categories. All relevant data is reported in text and/or tables. Line charts are used to demonstrate the trends, while pie and line charts are used to express the proportions. Relevant statistical analyses were performed by using the SPSS 16.0 statistical software (Chicago, IL, USA) and Microsoft Excel 2010.

Results

Overall, 103,197 papers were identified in the query.

Publication year

The number of publications per year gradually increased over the period (Figure 1), the largest number being in 2016 (n=10,763). The increased trend in HCC publications was noted after 2007.

Countries/territories

The top 100 countries/territories of publication origin are summarized in Table S1 and Figure 2. The rank order of top 10 countries/territories of publication origin include USA (n=24,685), China (n=22,466), Japan (n=17,366), Italy (n=7,153), Germany (n=6,280), South Korea (n=5,632), Taiwan (n=5,285), France (n=5,213), England (n=3,484), and Spain (n=2,644), respectively.

Prior to 2003, Japan was the country of origin of the greatest number of publications, followed by USA. During the period of 2004–2012, USA was the greatest contributor of publications, followed by China and Japan. After 2013, China became the largest contributor of publications followed by USA. This trend continued with China leading the number of publications and in 2016 exceeding USA.
publications greater than 2-fold (Figure 3).

**Journals**

The top 100 journals according to the number of publications are summarized in Table S2. The top ten journals according to the number of publications included *Hepatology* (n=6,291), *Journal of Hepatology* (n=3,143), *World Journal of Gastroenterology* (n=2,214), *Gastroenterology* (n=1,950), *PLos One* (n=1,813), *Journal of Gastroenterology and Hepatology* (n=1,650), *Cancer Research* (n=1,424), *Hepatogastroenterology* (n=1,403), *Oncotarget* (n=1,090), and *Liver Transplantation* (n=1,046) (Figure 4).

Among the top five journals within the area of gastroenterology/hepatology according to the journal impact factor, the number of publications was listed as follows: *Gastroenterology* (n=1,950), *Gut* (n=504), *Nature Reviews Gastroenterology & Hepatology* (n=69), *Hepatology* (n=63), and *Hepatitis Reviews* (n=57).
(n=6,291), and Journal of Hepatology (n=3,143) (Figure 5).

Next, the top five journals within the area of oncology according to the journal impact factor, the number of publications was listed as follows: A Cancer Journal for Clinicians (n=0), Nature Reviews Cancer (n=40), The Lancet Oncology (n=0), Cancer Cell (n=40), and Journal of Clinical Oncology (n=930) (Figure 6).

Lastly, the top five journals within the area of general and internal medicine according to the journal impact factor, the number of publications was listed as follows: New England Journal of Medicine (n=111), Lancet (n=114), JAMA (n=0), British Medical Journal (n=32), and Annals of Internal Medicine.
The top 100 research areas are summarized in Table S3. The top ten research areas included gastroenterology/hepatology (n=29,931), oncology (n=24,609), surgery (n=10,474), radiology nuclear medical imaging (n=8,256), biochemistry molecular biology (n=7,385), cell biology (n=5,626), pharmacology pharmacy (n=5,070), research experimental medicine (n=4,868), pathology (n=4,459), and general internal medicine (n=3,642) (Figure 8).

**Organizations**

The top 100 organizations are summarized in Table S4. The top ten organizations included Assistance Publique Hopitaux Paris Aphp (n=2,299), Institut National De La Sante ET DE LA Recherche Medecale Inserm (n=2,225), University of California System (n=2,132), Fudan University (n=2,057), Harvard University (n=1,763), National Institutes of Health NIH USA (n=1,751), National Taiwan University (n=1,712), University of Tokyo (n=1,572), Sun Yat Sen University (n=1,505), and University of Hong Kong (n=1,470) (Figure 9). Notably, after 2012, researchers from the Fudan University ranked first among all organizations with respect to number of publications per year, followed by the National Taiwan University.

### Funding agencies

According to the number of publications supported by funding agencies, National Natural Science Foundation of China (n=7,779) supported the largest number of publications followed by National Institutes of Health (n=6,388), Health and Human Services (n=3,966), and National Cancer Institute (n=2,638).

**Discussion**

Currently, scientific publications are the reliable means of rapidly and widely disseminating relevant knowledge discovered by researchers worldwide. By analyzing the characteristics of scientific publications within a particular topic, researchers may obtain critical information such as: (I) the importance of the topic; (II) the contributions by different regions, institutions, and study teams; (III) the
most popular research areas at present and future. To the best of our knowledge, there are some similar papers which have explored the scientific publications in the field of Gastroenterology and Hepatology, such as primary biliary cirrhosis (30), portal vein thrombosis, and Budd-Chiari syndrome (31). In addition, there are manuscripts which have explored scientific publications according to the type of study (32) and journal distribution (33). In the present study, we have performed the first systematic analysis examining characteristics of scientific publications in the field of HCC.

We identified an abundance of manuscripts relating to HCC with a striking increase over recent years. Figure 1 demonstrates a drastically increased slope with regard to publication numbers over recent years. This finding is concordant with the increased global disease burden of HCC. Unfortunately, the increase in disease prevalence has not been accompanied by significant improvements in HCC outcomes despite developments of novel treatment modalities.
We also demonstrated the evolving distribution of HCC manuscripts worldwide. Until recently, USA had the largest number of HCC publications, closely followed by China. However, as shown in Figure 3, China has significantly surpassed all countries in the annual number of HCC manuscripts published after 2013. The following points should be noted: (I) only the Web of Science, in which nearly all indexed papers are published in English language, was employed; (II) manuscripts from the USA are published in English; (III) many Chinese researchers are more skilled at publishing in Chinese-language journals. Not surprisingly, China will rank first in total number of HCC manuscripts in the near future as evident by its swift increase in rate of publication. Indeed, this point could be confirmed by another two findings of our study: (I) the National Natural Science Foundation of China, the largest funding project in China, gives financial support to the largest number of publications among all funding agencies; (II) the Fudan University, one of the most prestigious Universities in China, has produced the largest annual number of HCC manuscripts in recent years. This phenomenon may be explained by the fact that China has the largest number of patients affected by HCC with an ever-growing incidence and perhaps due to more research funding having been provided by the Chinese government.

Based on the analysis regarding the number of publications according to journals and research areas, we found that a majority of papers were published in the field of digestive diseases and cancer. It should be noted that the Hepatology, the most impactful journal in the field of hepatology, had published 6,275 papers.

Our study has several limitations. First, we just analyzed the quantity of HCC papers according to the inherent categories established by the Web of Science. We did not evaluate the importance and quality of scientific publications or calculate the number of citations associated with each manuscript. Second, we limited the search to the Web of Science, rather than other databases. Last, we did not classify manuscripts according to the type of study.

In conclusion, we performed the first systematic analysis outlining world distribution of HCC manuscripts. It is clear over recent years that great attention has been focused on the study of HCC, with China contributing most to this great surge of dissemination of knowledge.

Acknowledgements

None.
**Table S2** The top 100 journals according to the number of papers

<table>
<thead>
<tr>
<th>Journal Title</th>
<th>Rank</th>
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<tbody>
<tr>
<td>Nature</td>
<td>1</td>
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<tr>
<td>Cell</td>
<td>2</td>
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<tr>
<td>Science</td>
<td>3</td>
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<tr>
<td>PNAS</td>
<td>4</td>
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<tr>
<td>EMBO Journal</td>
<td>5</td>
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<tr>
<td>N Engl J Med</td>
<td>6</td>
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<tr>
<td>Cancer Cell</td>
<td>7</td>
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<tr>
<td>Science Transl Med</td>
<td>8</td>
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<tr>
<td>J Clin Invest</td>
<td>9</td>
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<tr>
<td>Cancer Res</td>
<td>10</td>
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... (Remaining 91 journals listed)