A bibliometric analysis of scientific production in cancer molecular epidemiology

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Objectives: The main purpose of this research was to compare the scientific production in the field of cancer molecular epidemiology among countries and to evaluate the publication trend between 1995 and 2004. Methods: A bibliometric study was carried out searching the PubMed database with a combined search strategy based on the keywords listed in the medical subject headings and a free text search. Only articles from a representative subset of 92 journals—accounting for 80% of papers identified—were selected for the analysis, and the resulting 13 240 abstracts were manually checked according to a list of basic inclusion criteria. The study evaluated the number of publications and the impact factor (mean and sum), absolute and normalized by country population and gross domestic product. Results: A total of 3842 citations were finally selected for the analysis. Thirty-seven percent came from the European Union (UK, Germany, Italy, France and Sweden ranking at the top), 31.6% from USA and 9.7% from Japan. The highest mean impact factor was reported for Canada (6.3), USA (5.9), Finland (5.8) and UK (5.2). Finland, Sweden and Israel had the best ratio between scientific production and available resources. ‘Genetic polymorphism, glutathione transferase, breast neoplasm, risk factors, case–control studies and polymerase chain reaction’ were the most used keywords in each of the subgroups evaluated, although inclusion criteria may have privileged studies dealing with exogenous carcinogens. Conclusion: Cancer molecular epidemiology is an expanding area attracting an increasing interest. The identification of an operative definition is a necessary condition to give to this discipline a unique scientific identity.

Introduction

Scientists have long recognized the intrinsic limitations of the traditional epidemiological design to discern the causal link between risk factors and disease occurrence in this evolving society. The pressing need of developing new tools for etiologic research was the driving force that in 1982 moved Perera and Weinstein to propose an enhancement of the epidemiological approach through 'the incorporation of laboratory analytical techniques to elucidate the biochemical or molecular basis of disease etiology' (1). Since then, many studies have been conducted to investigate the distribution of diseases in human populations and their determinants, incorporating molecular biology techniques into the epidemiologic design (2–4).

In the last decades, molecular epidemiology has gained a well-established position in the field of cancer research, with a number of dedicated researchers and institutions all over the world. This increased popularity has resulted in a growing scientific production, whose impact in the field is still to be fully quantified. Bibliometric studies are systematically conducted to evaluate the amount and the evolution of the scientific production among countries in major biomedical fields (5–12), but are particularly useful for novel disciplines, whose impact on the larger field of biomedical research has yet to be fully evaluated.

Bibliometry surveys the scientific production of a scientist, a research unit, an institution or a country by taking into consideration the historical development of a discipline or by quantifying its role in the domain of science, or prospectively, identifying research fronts. To perform this evaluation, citation analysis is currently used.

Citation analysis is defined as the number of times an article is cited as a reference in other articles and is based on the general assumption that the number of citations reflects an article’s influence and notoriety and, hence, its quality. The databases most commonly used are those produced by the Thomson Scientific (formerly known as Thomson Institute for Scientific Information), which evaluates the papers published in >7500 peer-reviewed journals in the sciences and social sciences, and each year publishes an index (Journal Citation Reports) based on cited articles (13).

The main purpose of this paper is to provide a report on the scientific production in the field of cancer molecular epidemiology among countries. To this aim, the geographical distribution and the temporal trend of papers published between 1995 and 2004 have been investigated.

Basic information about published papers includes the list of those journals most often chosen by researchers in the field and further consideration was given to the impact factor (IF) of the journals where the papers were published. This parameter gives further information about the quality of the published material, especially if evaluated in the context of major socioeconomic variables, i.e. the source country population and its gross domestic product (GDP).

Finally, the evaluation of most frequently used keywords in cancer molecular epidemiology papers provided useful hints about the identification of main research trends and helped to interpret the perspective of evolution of this field.

Methods

Bibliographic search

The search for papers to be included in the analysis was performed using the PubMed database (National Library of Medicine, National Institutes of Health, Bethesda, MD—http://www.ncbi.nlm.nih.gov/sites/entrez).

The search strategy was built by (i) identifying, whenever possible, the keywords listed in the medical subject headings (MeSH) thesaurus (words appearing in the MeSH field [mesh]), i.e. the vocabulary of medical and scientific terms that are assigned to most PubMed documents by a team of trained experts (indexers) and (ii) performing, for search completeness, a free text search [words in title or abstract field (ti/ab)].

Our search covered the papers published during 1995–2004 and was performed on 30 June 2005. Because of the lack of specific keywords (MeSH terms) that could unequivocally identify cancer molecular epidemiology studies (14), the strategy adopted for this search was complex and included several keywords (MeSH terms) and also free text terms. The first group of keywords (MeSH terms) and free text terms refers to main concepts of molecular epidemiology such as ‘epidemiology, molecular’, ‘biological markers’, ‘biomarkers’, ‘polymorphism, genetic’, ‘genotype’, ‘susceptibility’, ‘microarray’. This selection is extended through the ‘OR’ operator to specific biomarker name (‘chromosome aberrations’, ‘micronucleus test’, ‘sister chromatid exchange’, ‘comet assay’, etc.) as additional concepts, in order to broaden the search. The second group includes the concept of cancer (“neoplasms”, “carcinogens”, “mutagens”, etc.) and of risk factors of environmental origin (“environmental pollution”, “occupational diseases”, “smoking”, etc.). This latter sector is strictly related to cancer, but rarely indexed with a cancer-related keyword. The third are the keywords (MeSH terms) necessary to restrict the search to human studies (“human”). The last two groups of keywords (MeSH terms) are designed to exclude clinically oriented studies (“diagnosis”, “therapy”, “prognosis”, “survival”, etc.) and non-research publications, such as reviews, letters, news, etc.
Keywords (MeSH terms) or free text terms related to epidemiological methods, e.g. case control, cohort, etc., have not been used since the result was too restrictive.

The study included all peer-reviewed papers with an abstract, and excluded reviews, news, congresses, case reports and letters to the editor (as identified in the publication type field (pt)).

The articles retrieved by our search strategy were manually reviewed before classifying them as a molecular epidemiology study of cancer. The basic inclusion criteria were the following: ‘all studies focused on cancer whose methodology clearly present an epidemiologic study design and the use of a molecular biology methods’. Papers lacking a clear definition of the epidemiological study and of the laboratory technique were excluded, as were studies unrelated to cancer. Results of the in vitro challenge assays were also excluded. Studies on cancer patients (without controls) or molecular/cellular characterization of samples from cancer patients were included in the study only if an evaluation of risk factors through interview, questionnaire, etc. was present. Studies based on clinical output (diagnosis, therapy, prognosis, survival) were excluded in order to better limit the field. This latter exclusion criteria contributed to remove from the analysis many studies in fields greatly contributing to cancer molecular epidemiology such as those on infections agents.

Journals selection
Since our search strategy produced a very high number of articles, we selected the source journals with the purpose of producing a representative sample of the international scientific production in the field of cancer molecular epidemiology. Retrieved articles were published in >1000 journals, but only 330 of them published >3 articles during the period considered. Out of these, 97 journals that published 80% of the articles (each publishing >15 articles in these 10 years) were chosen. Five journals without IF were eliminated. The bibliometric analysis has been performed on the remaining 92 journals listed in Table I that were considered representative of cancer molecular epidemiology literature and sufficient to outline a trend.

Countries
The European Community [European Union (EU)] was defined as the 15 official member states plus Norway, given its inclusion in the European economic area and in all calculations concerning the EU issued by the Statistical Office of the European Communities. Papers from England, Scotland, Northern Ireland and Wales were grouped under the heading UK. For non-European countries, only data from 19 countries with >10 entries during 1995–2004 were evaluated.

The first author’s country was considered as the country of origin of the article. Occasionally, it was necessary to manually identify the country source after consulting other bibliographic sources.

For each country, the number of publications and the mean impact factor (mIF) (sum of the IF divided by number of publications) were reported. To facilitate the comparability between countries, we eliminated the effects of the country size and the heterogeneous availability of resources. This was done by calculating the ratio between the scientific production of each country (expressed as the sum of the IF of all published papers) and the population size (number of inhabitants expressed in millions of inhabitants) or the national gross domestic product (expressed in current billion US dollars).

Demographic and economic data for each country were retrieved from the Statistical Office of the European Communities or other international statistical reviews (15–17) and represent an average figure of the period under analysis.

Keywords
Keywords were defined as MeSH terms assigned to PubMed documents by a team of trained experts (indexes). In the indexing process, a variable number of terms (~5–15) is assigned to each journal article to properly identify the content (18). The keywords (MeSH terms) used by PubMed experts to classify the 3842 articles selected for the study included as many as 3266 different terms. Of these, only 1792 (54.9%) were used more than twice. Keywords with similar meaning were assembled to produce a list of the most often used terms.

Results
A total of 13 240 citations were retrieved from the PubMed database applying the search strategy reported above, and all corresponding abstracts were manually reviewed. A total of 3842 papers (29%) met the inclusion criteria reported in the methods session and were further evaluated.

Number of papers
The total number of published papers in the field of cancer molecular epidemiology during the 10 years period 1995–2004 increased from 369 in the biennium 1995–1996 to a maximum of 1233 papers in the biennium 2001–2002. In the last period there was a decrease with 916 published papers (Table II). To provide a comparison with the general trend of publication in cancer literature, the number of papers extracted with an automatic search tool built by PubMed experts and called ‘cancer subset’ (19) was reported in the same table.

All European countries except Luxembourg were represented. The most productive countries were the UK (20.8% of total European
papers), Germany (16.1%) and Italy (13.8%) followed by France (9.4%), Sweden (9.0%) and Spain (6.5%). During the whole period, the EU published 1421 papers (37% of the total). In the same period, authors from USA produced 31.6% of the literature, Japan 9.7%, Taiwan and Australia 2.4% and South Korea and China 2.1%.

**Quality of papers**

The highest mean IFs were found for papers published by authors from Canada (6.3), USA (5.9), Australia (5.1), Hong Kong (5.1), Israel (5) and Taiwan (3.9). The overall performance of European papers was 3.7. Finland ranked first with a mean IF of 5.8 followed by the UK (5.2), The Netherlands (5.1), France and Sweden (4.4) and Spain (4.3). All other European countries had a mean IF between 4.2 and 1.7 (Table II). The global IF of all countries was 2.4.

**Scientific production vis-à-vis population and gross domestic product**

The ratio between the sum of IF and the resident population (expressed in millions of inhabitants), which describes the IF standardized by the size of the country, showed a mean value of 4.8 followed by the UK (5.2), The Netherlands (5.1), France and Sweden (4.4) and Spain (4.3). All other European countries had a mean IF between 4.2 and 1.7 (Table II). The global IF of all countries was 2.4.

**Research topics**

Table III gives the top 10 terms for each homogeneous groups of keywords (MeSH terms). In general, the most frequently used keywords were as follows: risk/risk factors (3192 times), genetic polymorphisms (2300), mutation (1793), genotype (1623), breast neoplasms (1506) and case–control studies (1432). Polymerase chain reaction (1113) was the most frequently used term among laboratory techniques, and glutathione transferase (911) among biomarkers.

**Discussion**

Our study shows that the two areas in the world with the highest scientific production in the field of cancer molecular epidemiology are Europe and USA. Taking into account the different size and availability of resources among countries, some areas of excellence emerge, such as Northern Europe and Israel. Among European countries, the analysis confirms the results observed in other biomedical disciplines, with the UK ranking first both in quantity and quality of scientific production. As a whole, the mean IF of cancer molecular...
epidemiology papers is higher than the corresponding value in oncology or other major fields of medicine, e.g. virology, rheumatology, ophthalmology, etc. (7–12).

During the first 8 years of the observation, the number of papers focused on cancer molecular epidemiology constantly increased all over the world. The decrease observed in the last biennium may be due (besides a possible decline of interest) to random variation in the process of abstracts manual selection (the total number of papers retrieved did not decrease accordingly) or to an incomplete collection of papers published in more recent years. However, despite this final discrepancy, most countries greatly increased their production during the years surveyed. Comparing the last biennium of the survey (2003–2004) to the first (1995–1996), the overall increase was 148%, which, if compared with the corresponding 17% of total cancer literature, provides a quantitative figure of the increasing interest for this field.

During the examined period, authors from all European countries published papers in cancer molecular epidemiology journals, with the exception of Luxembourg. Large countries, such as the UK, Germany, Italy and France published the highest number of papers. Among individual, non-EU countries (besides USA, that with the highest numbers of published papers (1216)), Japan (373), Taiwan (94) and Australia (91) were at the top.

Fig. 1. Scientific production in the field of cancer molecular epidemiology in all countries standardized by population and economic parameters. Bars represent the ratio between scientific production of each country (sIF, expressed as the sum of the publications IF) and population (Pop, number of inhabitants expressed in millions of inhabitants) or economic parameters (gross domestic product (GDP), expressed in current billion US dollars).


Table III. List of the keywords (MeSH terms) most frequently assigned by PubMed indexers to papers in the field of cancer molecular epidemiology

<table>
<thead>
<tr>
<th>Genetic phenomena and processes (27%)</th>
<th>Citations</th>
<th>Biomarkers (9%)</th>
<th>Citations</th>
<th>Neoplasms by sites (20%)</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphism, Genetic</td>
<td>2300</td>
<td>Glutathione transferase</td>
<td>911</td>
<td>Breast neoplasms</td>
<td>1506</td>
</tr>
<tr>
<td>Mutation</td>
<td>1793</td>
<td>p53 genes and protein</td>
<td>453</td>
<td>Lung neoplasms</td>
<td>1199</td>
</tr>
<tr>
<td>Genotype</td>
<td>1623</td>
<td>Brcal/Brca2 genes and protein</td>
<td>386</td>
<td>Colorectal neoplasms</td>
<td>617</td>
</tr>
<tr>
<td>Genetic predisposition to disease</td>
<td>1046</td>
<td>Cytochrome P-450</td>
<td>374</td>
<td>Prostate neoplasms</td>
<td>594</td>
</tr>
<tr>
<td>DNA damage and repair</td>
<td>605</td>
<td>Chromosome aberrations</td>
<td>204</td>
<td>Head and neck neoplasms</td>
<td>487</td>
</tr>
<tr>
<td>Heterozygote/homozygote</td>
<td>515</td>
<td>DNA adducts</td>
<td>170</td>
<td>Leukemia</td>
<td>339</td>
</tr>
<tr>
<td>Gene frequency</td>
<td>377</td>
<td>Arylamine N-acetyltransferase</td>
<td>143</td>
<td>Skin neoplasms and melanoma</td>
<td>337</td>
</tr>
<tr>
<td>Phenotype</td>
<td>321</td>
<td>Micronucleus tests</td>
<td>122</td>
<td>Liver neoplasms</td>
<td>315</td>
</tr>
<tr>
<td>Loss of heterozygosity</td>
<td>278</td>
<td>Sister chromatid exchange</td>
<td>103</td>
<td>Bladder neoplasms</td>
<td>291</td>
</tr>
<tr>
<td>Gene expression</td>
<td>211</td>
<td>Ras genes and protein</td>
<td>95</td>
<td>Ovarian neoplasms</td>
<td>244</td>
</tr>
</tbody>
</table>

Environment and public health (20%) | Citations | Epidemiologic methods (16%) | Citations | Laboratory techniques and procedures (8%) | Citations |
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Risk/risk factors</td>
<td>3192</td>
<td>Case-control studies</td>
<td>1432</td>
<td>Polymerase chain reaction</td>
<td>1113</td>
</tr>
<tr>
<td>Smoking</td>
<td>1107</td>
<td>Odds ratio</td>
<td>1003</td>
<td>DNA mutational analysis</td>
<td>341</td>
</tr>
<tr>
<td>Population</td>
<td>959</td>
<td>Comparative study</td>
<td>580</td>
<td>In situ hybridization, Fluorescence</td>
<td>218</td>
</tr>
<tr>
<td>Environmental exposure</td>
<td>403</td>
<td>Incidence</td>
<td>424</td>
<td>Sequence analysis</td>
<td>152</td>
</tr>
<tr>
<td>Occupational exposure/industry</td>
<td>417</td>
<td>Cohort studies</td>
<td>393</td>
<td>Amino acid substitution</td>
<td>124</td>
</tr>
<tr>
<td>Air pollution</td>
<td>263</td>
<td>Prevalence</td>
<td>325</td>
<td>Electrophoresis</td>
<td>117</td>
</tr>
<tr>
<td>Drinking/alcohol</td>
<td>203</td>
<td>Multivariate analysis</td>
<td>274</td>
<td>Chromosome mapping</td>
<td>102</td>
</tr>
<tr>
<td>Diet</td>
<td>191</td>
<td>Confidence intervals</td>
<td>192</td>
<td>Immunoblotting</td>
<td>92</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>188</td>
<td>Regression analysis</td>
<td>189</td>
<td>Flow cytometry</td>
<td>39</td>
</tr>
<tr>
<td>Public health</td>
<td>179</td>
<td>Reference values</td>
<td>148</td>
<td></td>
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</tr>
</tbody>
</table>

Nation rankings changed considerably when other end points were considered, such as the mean IF or the sum of IF adjusted by number of inhabitants or by GDP. The results of this survey extend to the field of cancer molecular epidemiology the common finding that small countries usually perform better than larger ones when the quality of the scientific production is considered (20). A better utilization of resources and a higher proportion of the GDP assigned to research are the most likely explanations (21–23).

The interpretation of the results of this bibliometric study should take into account a number of potential limitations. The most remarkable that may have affected the search strategy is the lack of standardized concepts to quantify the scientific production in the field of cancer molecular epidemiology. For example, it should be highlighted that some molecular epidemiology studies on biomarkers of infection, immunology, hormones, inflammation, etc. were not included in the analysis due to the lack of specific keywords in these fields. Furthermore, these biomarkers were commonly used in clinical studies, which were excluded from our study according to the search criteria. This potential bias, which is unlikely to occur differentially by country and calendar year, was addressed using an extensive choice of keywords and free text terms.

Another potential source of bias is the manual selection performed by three of the authors (D.U., R.P. and S.B.) of all candidate papers retrieved from the PubMed database (13 240!); despite the previous standardization among evaluators and the extensive quality controls, this procedure may have generated some discrepancy. Finally, the PubMed database is biased in favor of English-language journals; thus our survey may have penalized those countries that have a tradition of publishing in their own language journals. It is possible that some countries more than others, e.g. Japan and Russia, suffered particularly in this respect.

Problems were also encountered in the identification of main author address, i.e. the institutional and geographical affiliation. If the author’s address is reported inaccurately, a margin of error in data extraction is possible. Furthermore, this approach does not adequately reflect the contribution of various countries to international collaborative studies (e.g. large pooled analyses); however, the present analysis is based on large numbers, and international collaborative studies often entail a rotation of the first author.

An additional limitation of the study—which affects all bibliometric studies—is represented by the intrinsic inaccuracy in the measure used to describe the quality of scientific production. The IF of a journal is the average number of citations that a paper published in that journal receives in the 2 years following publication. Clearly, this index does not give score of the single paper, but is a journal average value, and may be severely conditioned by the ups and downs of scientific interests. This issue is currently the focus of a debate within research evaluators and funding agencies about the best methods for the allocation of resources (24–26). The use of the citation frequency to measure the impact of a published paper is the most accessible and suitable source of data for the evaluation of the scientific production. However, this approach is not flawless either, and ideally, an exhaustive survey would combine data of different bibliometric indicators.

A descriptive analysis comparing nations is an essential step in understanding science policies and a source of beneficial information that enables a country to define its position with respect to competitors. This in turn allows for better exploitation of opportunities arising in all scientific fields. These surveys offer a broad review of the existing data and help to gather impressions of scientific publication trends and the visibility of a country’s production.

A further consideration regards a problem that affects many biomedical disciplines. The analysis of keywords revealed a high heterogeneity of terms. In fact, only 22.2% of keywords are cited under the same definition that can unequivocally identify the boundaries of the discipline.

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