ORIGINAL ARTICLE

The State of Lung Cancer Research: A Global Analysis

Ajay Aggarwal, MD, MSc,[a,*] Grant Lewison, PhD,[a,b] Saliha Idir, MSc,[c]
Matthew Peters, MD,[d] Carolyn Aldige,[e] Win Boerckel, MBA,[f] Peter Boyle, PhD,[g]
Edward L. Trimble, MD, MPH,[h] Philip Roe, PhD,[b] Tariq Sethi, MD, PhD,[i]
Jesme Fox, MD,[j] Richard Sullivan, MD, PhD[a]

[a]*Institute of Cancer Policy, Kings College London, London, United Kingdom*
[b]*Evaluametrics Ltd., London, United Kingdom*
[c]*Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia*
[d]*Oncology Europe, Africa, and Middle East Business Unit, Pfizer International Operations, Paris, France*
[e]*Prevent Cancer Foundation, Alexandria, Virginia*
[f]*Cancer Care, New York, New York*
[g]*International Prevention Research Institute, Lyon, France*
[h]*National Cancer Institute Center for Global Health, Bethesda, Maryland*
[i]*Department of Respiratory Medicine, Kings College London, London, United Kingdom*
[j]*Roy Castle Lung Cancer Foundation, Liverpool, United Kingdom*

Received 23 October 2015; revised 8 March 2016; accepted 8 March 2016
Available online - 21 March 2016

ABSTRACT

Introduction: Lung cancer is the leading cause of years of life lost because of cancer and is associated with the highest economic burden relative to other tumor types. Research remains at the cornerstone of achieving improved outcomes of lung cancer. We present the results of a comprehensive analysis of global lung cancer research between 2004 and 2013 (10 years).

Methods: The study used bibliometrics to undertake a quantitative analysis of research output in the 24 leading countries in cancer research internationally on the basis of articles and reviews in the Web of Science (WoS) database.

Results: A total of 32,161 lung cancer research articles from 2085 different journals were analyzed. Lung cancer research represented only 5.6% of overall cancer research in 2013, a 1.2% increase since 2004. The commitment to lung cancer research has fallen in most countries apart from China and shows no correlation with lung cancer burden. A review of key research types demonstrated that diagnostics, screening, and quality of life research represent 4.3%, 1.8%, and 0.3% of total lung cancer research, respectively. The leading research types were genetics (20%), systemic therapies (17%), and prognostic biomarkers (16%). Research output is increasingly basic science, with a decrease in clinical translational research output during this period.

Conclusions: Our findings have established that relative to the huge health, social, and economic burden associated with lung cancer, the level of world research output lags significantly behind that of research on other malignancies. Commitment to diagnostics, screening, and quality of life research is much lower than to basic science and medical research. The study findings are expected to provide the requisite knowledge to guide future cancer research programs in lung cancer.

*Corresponding author.

Drs. Aggarwal and Lewison contributed equally to this article.

Disclosure: Dr. Boyle was the scientific advisor to the commission for the development of the European Tobacco Directive and has been involved in radical legislation that banned smoking in bars, restaurants, and other public places. Dr. Sethi is vice president of the Respiratory, Inflammatory, and Autoimmune Diseases Translational Medicine Unit of AstraZeneca and a cofounder of Galecto Biotec. Dr. Lewison is a shareholder in GlaxoSmithKline, AstraZeneca, and Shire. Roy Castle Lung Cancer Foundation receives unrestricted grants for the work of the Global Lung Cancer Coalition from AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, GlaxoSmithKline, Lilly, Novartis, Pfizer, and Roche. The remaining authors declare no conflict of interest.

Address for correspondence: Ajay Aggarwal, MD, MSc, Institute of Cancer Policy, Kings College London, King's Health Partners Integrated Cancer Centre, Guy's Hospital Campus, Department of Research Oncology, Bermondsey Wing, London SE1 9RT, United Kingdom. E-mail: ajay.aggarwal@kcl.ac.uk

ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2016.03.010

Keywords: Research; Lung cancer; Bibliometrics; Health policy

Introduction

In 2013 it was estimated that there were 14.9 million incident cancer cases and 8.2 million deaths.[1] Of these cases, lung cancer remains the leading cause of cancer death globally in both high-income and low- and middle-income countries, accounting for 1.6 million cancer deaths annually (approximately 20% of total cancer deaths), with an estimated 1.8 million new cases annually worldwide.[2] Importantly, with the cigarette smoking habit established in lower-resource countries some years ago, the global burden of lung cancer will continue to grow for the coming decades.

It is not just the human cost that one needs to consider but the wider economic burden. A recent analysis of the costs associated with cancer care in the European Union demonstrated that relative to other cancers, lung cancer is associated with the highest economic costs (€18.8 billion or 15% of total cancer care costs) followed by breast cancer (12%) and colorectal cancer (10%).[3] These costs incorporate both the direct costs of managing the disease at all stages as well as the opportunity costs associated with the loss of productivity due to premature mortality and the indirect costs of informal care.

Although public health and policy efforts aim to reduce smoking initiation and increase cessation (especially in emerging economies),[4,5] for those in whom lung cancer has been diagnosed the outcomes remain poor. The mean age-standardized 5-year survival rate is 13.0% in Europe (varying from 9% to 14.8% across Europe)[6] and 16% in the United States.[7] The reasons are multiple and include the absence of a cost-effective screening tool, late stage at the time of diagnosis (65% of patients present with locally advanced or metastatic disease[8]), socioeconomic inequalities in health care access,[9,10] and the challenge in obtaining a histological diagnosis.[11] Furthermore, median survival time in advanced disease with standard chemotherapeutic regimens has not changed in the past two decades and remains at approximately 12 months.[12]

Cancer research is one of the most globally active domains of science, with more than $14 billion per annum in public and private expenditure.[13] Research is at the core of achieving improved outcomes from cancer, be it in defining country-specific epidemiology of the disease, understanding the pathogenesis of disease, identifying new targets for therapeutic agents, or directing policy to achieve affordable and equitable outcomes.[14] It is therefore important to understand from a public policy perspective how, why, and which particular research domains evolve and have an impact on outcomes.

In this article we present the results of a bibliometric analysis of global research on lung cancer between 2004 and 2013 (10 years) in the 24 leading countries in cancer research. This type of analysis is now used routinely to evaluate large numbers of scientific articles in a given research domain.[15,16] We examine the growth in output from these countries, their relative commitment to lung cancer research compared with all cancer research output, the main research types (e.g., genetics, chemotherapy), the amount of international collaboration as a function of the outputs of leading countries, and the impact of lung cancer research.

Methods

We performed a bibliometric analysis of research outputs during 2004 to 2013 on the basis of articles and reviews in the Web of Science (WoS) database. This analysis contains full bibliographic information about the articles, including all addresses and the numbers of citations received by each article. The WoS is considered the optimum database for undertaking this type of evaluation as the use of additional biomedical databases does not significantly increase the yield of relevant journals.

We identified the lung cancer articles by means of a specially developed algorithm formed by the intersection of two filters. Each filter consisted of lists of specialist journals for cancer (185 journals) and lung disease (11 journals), as well as specific title words relating to both subjects. All articles within the specialist cancer or lung disease journals were selected in addition to articles in nonspecialist journals that contained one or more of the title words. This approach had a precision or specificity of 0.95 and a recall or sensitivity of the same value, which is considered very high.[17]

This meant that articles in general medical journals were also covered, and the 32,162 articles were in as many as 2085 different journals. Nearly all of the articles were in English (31,000 or 96.4%), but others were in 18 different languages, led by French (554), Spanish (203), and German (168). A few were in Chinese, Japanese, or Korean. This double filter would be expected to have provided excellent coverage of lung cancer research, although some basic research articles might have been omitted if there was nothing in their titles to indicate that they were directly relevant to lung cancer.

The details of the selected articles from the 24 leading research-active countries internationally were downloaded. These countries accounted for approximately 97% of all lung cancer research articles published between 2004 and 2013. The countries included were as follows: Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, India, Italy, Japan, Netherlands, Norway, Poland, the Republic of Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, and the United States.

Counts of the numbers of publications per year were obtained on both integer and fractional count bases. As an example if an article had two addresses in Germany and one in France, it would be counted as one for each on an integer count basis but as 0.67 and 0.33, respectively, on a fractional count basis. The articles' addresses were parsed so as to show the fractional contribution of each of the 24 selected countries by means of a special macro. The intention was for the most part to base the analysis on fractional country counts of articles, which give a much better impression of the relative effort expended on the research than do integer counts.[18,19]

We had previously determined the numbers of publications in cancer research overall for each year and for each of the 24 selected countries on an integer count basis. These data were used to determine each country's relative commitment (RC) to lung cancer within oncology overall. For example, in 2004 to 2008, Austria published 101 lung cancer articles out of a total of 3197 for oncology (3.16%), whereas worldwide there were 12,508 lung cancer articles out of a total of 283,259 oncology articles (4.42%). So Austria's RC was only 3.16 of 4.42, or 0.715. Similar calculations were made for the second quinquennium (2009–2013) and for the other 23 countries.

We also investigated whether the relative commitment of the individual countries corresponded to their relative burden from lung cancer within the total for all cancers based on the Global Burden of Disease Study for 2010 (for the interactive tool used, see http://vizhub.healthdata.org/gbd-compare/). For this purpose, we obtained the percentages of disability-adjusted life years (DALYs) attributable to all cancers and to cancer of the "trachea, bronchus and lung" for the world and for the 24 selected countries. Worldwide, the latter represents 1.31% of all DALYs out of the 7.6% for all cancers, and it is by far the largest of the disease burdens for different cancers at 17.2%. We then compared these percentages, which varied from slightly more than 10% in India to slightly less than 30% in Turkey, with the RC values for the countries in 2009 to 2013.

Lung cancer research publications were also categorized by their research type, 12 of which were defined by means of subfilters based on title words and strings. These subfilters were all determined by R.S. and A.A. in collaboration with G.L. The research types used for analysis were as follows: chemotherapy, diagnosis, epidemiology, genetics, palliative care, pathology, biomarkers, quality of life (QoL), radiotherapy, screening, surgery, and targeted therapies. The categories were not mutually exclusive, and therefore, articles reviewing QoL in relation to radiotherapy studies would be included in both categories. Fractional counts of each country and research type were calculated, and the results were compared with the values for the world so as to show whether a country was overperforming or underperforming relative to the world average in each subject area.

The research level (RL) of a country's publications can be calculated in two ways: (1) from the titles of the individual articles and (2) from the journal in which the article was published in a given quinquennium. Articles are classified as clinical (RL = 1.0) or basic (RL = 4.0) depending on whether their titles contain one or more of a list of "clinical words" (e.g., *diagnosis, elderly*) or "basic words" (e.g., *activation, binding, chromosome*). These key words, which enable classification into basic and clinical research types, were developed and validated by G.L.[20] A macro was subsequently used to classify the words in the title of each article and mark the article as clinical, basic, or both. The journal RL was determined directly from the WoS for each 5-year period from 2000. It was possible to determine the journal RL for almost all the articles (32,096 of 32,162 [99.8%]). Some examples of journals frequently used for lung cancer research and their RLs for 2010 to 2013 are as follows: *Annals of Thoracic Surgery* (RL = 1.17), *Lung Cancer* (RL = 1.77), *PLoS One* (RL = 2.87), and *Cancer Research* (RL = 3.28).

The overall RL for each country was determined on the basis of fractional counts. For example, the fractional counts for Austria in 2004 to 2008 were 34.9 "clinical" articles, 8.2 "basic" articles, and 3.96 articles classified as "both." The article RL was then calculated as $(34.9 + 4 \times 8.2 - 2.5 \times 3.96)/(34.9 + 8.2 - 3.96) = 1.50$. The sum of Austrian fractional presences multiplied by the journal RL was 106.1, which when divided by the Austrian fractional total of 58.5 articles, gave a journal RL of 1.81. This means that Austrian lung cancer researchers were publishing clinical articles in rather more basic journals than the average.

Actual citation impact (ACI) is the number of citations received by an article in the 5 years beginning in the year of publication. It is created according to a validated algorithm based on actual citations of the article rather than by using the impact factor of the journals within which they are published. A 5-year window is used as it represents a compromise between the need for immediacy (i.e., citations to recent articles) and stability (i.e., inclusion of the peak year for citations, usually the second or third year after publication). It is best determined for a country on the basis of fractional counts, because many of the most cited articles are multinational. For this purpose, the articles were divided into two 3-year cohorts, 2004 to 2006 and 2007 to 2009. The fractional counts of a country's contributions were multiplied by the ACI counts for each article, these products were summed, and the total was divided by the sum of the country's fractional counts for the relevant years. The corresponding quotients for the world were 15.2 and 17.0 citations, respectively.

Another measure of citation impact is the number of a country's articles that receive enough citations to put them in the top 1%, 2%, 5% and 10% of the world's most cited lung cancer articles. For example, the number of articles with 137 or more citations (top 1%), 86 or more citations (top 2%), 50 or more citations (top 5%), and 33 or more citations (top 10%) in the 5 years after publication. These calculations were performed for all 6 years together (2004–2009); otherwise, for many countries the numbers would have been too small to analyze.

Results

Outputs of Individual Countries

Overall, world outputs have more than doubled during the decade. Figures 1(*A-D*) demonstrate that between 2004 and 2013 the fractional counts of lung cancer research articles from each of the 24 countries have largely increased year after year. China in particular has exhibited a marked rise in the volume of research output over this time. On the basis of integer counts of research publications, the United States, China, and Japan lead the way, with Brazil, Norway, and Austria among the least research-active countries (further detail in Supplementary Table 1). Using fractional counts, a similar relationship is observed, but in 2013 China overtook the United States to become the world leader on a fractional count (but not on an integer count) basis (see Supplementary Table 2 for further detail). For the entire 10-year period, the United States published more than twice as many research articles as Japan, the next ranked country.

RCs and the BoD

Lung cancer research accounted for 4.4% of all cancer research in 2004, and by 2013 that figure had increased to 5.6% in 2013. Apart from China, the RC of most other countries in fact declined between the two quinquennia, particularly in Belgium, Poland, France, Norway, Italy, Spain, Greece, and the Republic of Korea (Fig. 2). It appears from Figure 3 that there is little correlation between relative burden of disease (BoD) from lung cancer and RC to research in the subject area, except that Brazil and India both suffer less than average from lung cancer and do relatively little research; conversely, Turkey and Greece both suffer more than average and also do more research. Further detail is available in Supplementary Table 3.

The Types of Research Undertaken by the 24 Countries

The numbers of articles in each of the 12 types of research are shown in Figure 4. Of the 32,162 articles in the

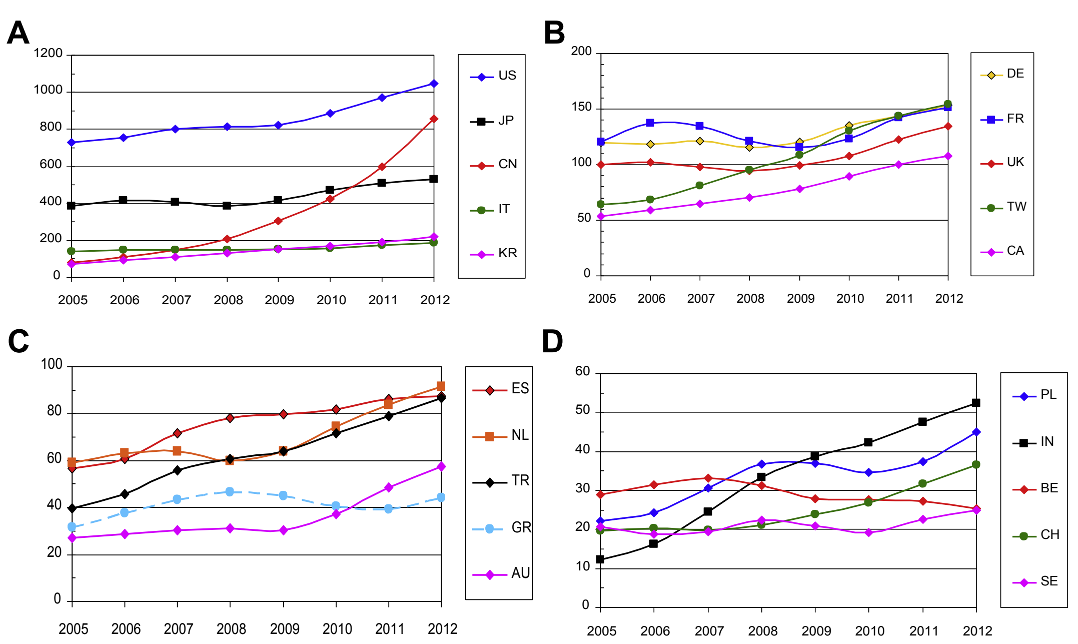

Figure 1. Fractional count annual outputs in lung cancer research (3-year running means) (*A*) for the United States, Japan, China, Italy, and South Korea, (*B*) for Germany, France, the United Kingdom, Taiwan and Canada, (*C*) for Spain, the Netherlands, Turkey, Greece and Australia, (*D*) and for Poland, India, Belgium, Switzerland and Sweden. Scale changes to *y* axis.

	2004–2008		2009–2013		2004–2008	2009–2013
	LUNCA	ONCOL	LUNCA	ONCOL	RC	RC
United States	4437	92928	5930	127679	1.08	0.91
Japan	2106	28170	2685	32826	1.69	1.61
China	706	13199	3725	48537	1.21	1.51
Italy	875	16660	1135	24777	1.19	0.90
Germany	823	22125	1080	29394	0.84	0.72
France	817	14288	945	20179	1.29	0.92
United Kingdom	712	19040	976	25605	0.85	0.75
Republic of Korea	511	7897	1112	17580	1.47	1.24
Canada	457	10585	811	16545	0.98	0.96
Taiwan	391	5018	778	9064	1.76	1.68
Spain	424	7215	646	11847	1.33	1.07
Netherlands	396	8235	649	12117	1.09	1.05
Turkey	259	4373	422	6750	1.34	1.23
Australia	202	6120	375	10697	0.75	0.69
Greece	235	3601	293	4686	1.48	1.23
Poland	208	2998	301	5445	1.57	1.08
Switzerland	181	4416	316	6748	0.93	0.92
Belgium	233	3832	244	5508	1.38	0.87
Sweden	174	5531	212	7318	0.71	0.57
India	114	4101	267	9204	0.63	0.57
Denmark	113	2592	194	4229	0.99	0.90
Austria	101	3197	166	4344	0.72	0.75
Norway	113	2236	146	3523	1.14	0.81
Brazil	68	3209	186	6575	0.48	0.56

Figure 2. Outputs of articles in lung cancer and all oncology research in two quinquennia and relative commitments to the subject area within cancer research. Cells tinted pale green indicate values greater than 1.41, those tinted yellow indicate values less than 0.71, and those tinted pink indicate values less than 0.50.

database, the largest research type (genetics) accounted for 20% of the articles, and the smallest (QoL) just 0.3%. Research on systemic therapies, which included articles in the chemotherapy (11.6%) and targeted agents (5.5%) categories, was the second largest research type (17.1%).

The different research types varied in how fast they expanded during the decade (further detail in Supplementary Table 4). Between the two quinquennia 2004 to 2008 and 2009 to 2013, genetics research remained dominant whereas research into targeted therapies, biomarkers, and diagnostics increased relative to that in other domains. Research into targeted therapies increased more than any other research category, with an almost parallel decrease in the percentage of research into chemotherapy drugs. With regard to screening and palliative care, although the volume of research nearly doubled in this time period, the relative contribution of research in these domains to overall lung cancer research remained the same.

Within each of the research types, we determined the fractional counts of articles from each of the 24 selected countries (further detail in Supplementary Table 5). As expected, the United States accounted for the highest volume published in each of the categories on the basis of fractional counts. However, fractional counts alone do not give us specific information on the predominant focus of lung cancer research in each individual country, as otherwise, countries producing the largest volume of research within a specific category would appear to have the greatest commitment.

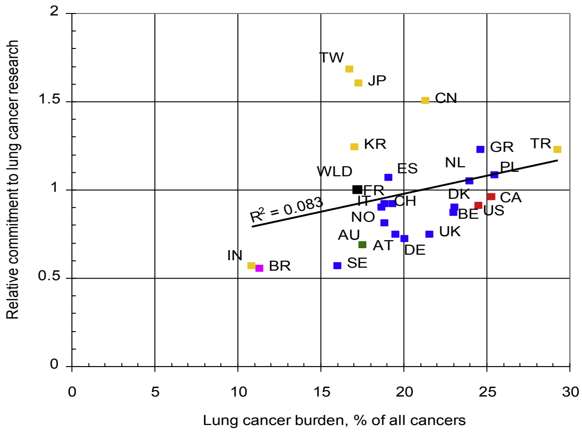

Figure 3. Correlation between lung cancer disease burden and the relative commitment to lung cancer research for 24 countries. Blue squares indicate European countries, red squares indicate North American countries, gold squares indicate Asian countries, pink square indicates Brazil, and green square indicates Australia.

The RC of the 24 countries to each research type is presented in Figure 5, which shows a markedly heterogeneous picture. For instance, the Netherlands has a strong commitment to radiotherapy and QoL research but little commitment in the way of genetics and epidemiological research. Norway on the other hand has a strong commitment to epidemiological and biomarker-based research, and the United Kingdom has a strong commitment to palliative care and QoL research.

ACIs

These are used as measures of the influence of the articles and of each country's senior scientists.

Table 1 shows the countries ordered by their mean ACI value and with the numbers of their articles (fractional counts) with enough citations to put them in the top 1%, top 2%, top 5%, or top 10% of articles on the basis of 5-year citation scores. The United States and Canada are the only countries with consistently superior performance at all four of these percentiles. High–research output countries such as China, Japan, France, and Germany rank in the lower half of the table. Of note, France is performing below the world average at all four percentiles. Conversely, Denmark, Switzerland, and the Netherlands appear to produce research with greater impact, despite the low volume of research relative to that of the other countries.

RL of Outputs

Charts showing the different values of RL for articles and for journals, and in the two quinquennia, 2004-2008 (1) and 2009-2013 (2), are presented in Supplementary Figures 1 through 3. The East Asian countries (China, the Republic of Korea, and Taiwan) are publishing relatively basic articles; this may be because their clinical articles are published in local journals not covered by the WoS. Within Europe, a few countries' publications are becoming more clinical (e.g., those of Denmark), but most outputs are becoming more basic (e.g., those of Italy, France, Spain, Greece, Switzerland, Sweden, and Austria).

International Collaboration

We estimated the extent of international collaboration as a proportion of all published articles from each individual country. We found that 17.2% (n = 5518) of all articles involved collaboration with investigators from two or more countries. Research from Norway, Austria, Switzerland, Belgium, and Sweden had the highest proportion of international contributors (see Supplementary Fig. 4 for more details). By comparison, relative to their research output, the East Asian countries

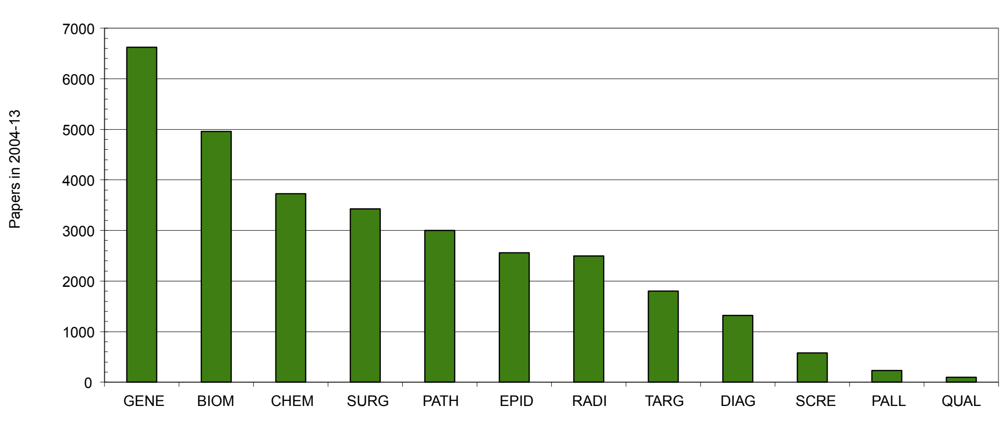

Figure 4. Numbers of each of the types of lung cancer research articles listed in the Methods section that were published in 2004 to 2013. GENE, genetics; BIOM, biomarkers; CHEM, chemotherapy; SURG, surgery; PATH, pathology; EPID, epidemiology; RADI, radiotherapy; TARG, targeted therapies; DIAG, diagnosis; SCRE, screening; PALL, palliative care; QUAL, quality of life.

	GENE	BIOM	CHEM	SURG	PATH	EPID	RADI	TARG	DIAG	SCRE	PALL	QUAL
United States	**0.88**	**0.92**	**0.88**	**0.85**	0.98	**1.31**	**1.15**	**1.14**	**0.94**	**1.71**	**1.28**	**1.64**
Japan	**1.10**	**1.15**	**1.14**	**1.85**	**1.24**	**0.52**	**0.84**	**1.35**	**0.88**	**0.54**	**0.45**	**0.39**
China	**1.65**	1.05	0.99	**0.56**	**0.83**	**1.18**	**0.57**	**0.80**	**0.80**	**0.26**	**0.19**	**0.35**
Italy	**0.75**	**0.84**	**1.41**	**1.33**	0.87	**0.74**	**0.59**	**1.43**	0.85	**1.48**	0.61	0.22
Republic of Korea	**1.37**	**1.20**	1.04	**0.82**	**1.25**	1.05	**0.72**	**1.28**	1.00	**0.44**	0.49	0.18
Germany	**0.80**	0.89	0.90	0.98	**1.35**	**0.70**	**1.34**	**0.81**	**1.58**	0.97	0.45	0.26
France	**0.55**	**0.75**	1.19	**1.24**	**0.64**	0.95	**1.21**	**0.89**	1.15	0.64	0.76	0.03
United Kingdom	**0.68**	1.06	**0.86**	1.02	0.93	0.92	**1.33**	**0.65**	1.28	1.15	**4.16**	**2.93**
Taiwan	**1.30**	1.08	**0.70**	**0.47**	**0.67**	**0.73**	**0.22**	**1.28**	**0.57**	**0.35**	1.59	1.92
Canada	**0.70**	1.03	0.91	0.82	**0.74**	**1.31**	**1.98**	**1.01**	0.80	**1.49**	**2.77**	**3.45**
Spain	0.90	**1.36**	1.12	0.94	1.19	0.88	**0.54**	**0.74**	1.06	0.74	0.31	0.05
Netherlands	**0.55**	0.95	0.91	0.82	0.87	**0.67**	**3.56**	**1.07**	0.83	**3.29**	1.77	**2.49**
Turkey	**0.80**	**1.23**	**0.97**	**1.92**	1.00	**0.59**	1.00	**0.09**	**1.58**	**0.00**	1.11	0.54
Greece	0.85	0.94	**2.28**	0.75	0.94	**0.32**	**0.50**	**0.67**	1.16	**0.10**	1.01	0.84
Australia	**0.60**	1.04	0.89	0.73	1.26	0.95	**1.72**	**0.56**	0.98	1.55	2.13	0.78
Poland	**1.34**	0.90	**0.78**	**1.90**	1.23	0.87	1.12	**0.46**	**1.76**	0.45	0.41	0.00
India	0.84	**0.48**	**0.83**	**0.09**	1.02	1.10	**0.58**	**0.11**	1.50	0.61	0.16	0.00
Belgium	**0.49**	1.03	**1.55**	**1.49**	1.14	**0.31**	**1.66**	**0.62**	0.54	1.14	1.33	0.41
Switzerland	0.78	0.95	1.12	1.20	0.93	0.62	0.96	**1.42**	1.18	0.62	0.15	0.00
Sweden	0.98	**1.40**	**0.87**	**0.42**	1.02	1.19	**1.71**	**0.11**	1.66	0.05	**4.43**	2.82
Denmark	1.04	1.05	**0.48**	0.75	1.25	**2.54**	**1.83**	**0.51**	1.44	**3.30**	1.43	1.74
Brazil	**0.59**	**0.62**	**0.93**	0.94	1.24	0.76	**0.22**	**0.32**	1.27	0.00	0.25	1.84
Norway	1.07	**2.28**	0.89	0.73	1.01	**2.02**	1.47	**0.27**	0.80	0.03	1.53	2.36
Austria	**0.57**	0.96	1.20	1.04	1.43	0.84	1.18	**0.55**	1.51	0.78	0.99	2.68

Figure 5. Relative commitment by each of 24 selected countries to different research types within lung cancer research, 2004 to 2013. Cells tinted pale green indicate values greater than 1.41, cells tinted pale yellow indicate values less than 0.71, and cells tinted pink indicate values less than 0.50 (as for Fig. 2). Values greater than 2.0 tinted dark green. Values statistically significant at $p < 0.05$ shown in bold. GENE, genetics; BIOM, biomarkers; CHEM, chemotherapy; SURG, surgery; PATH, pathology; EPID, epidemiology; RADI, radiotherapy; TARG, targeted therapies; DIAG, diagnosis; SCRE, screening; PALL, palliative care; QUAL, quality of life.

(Taiwan, India, the Republic of Korea, and Japan) and Turkey had the least amount of international collaboration. With regard to multinational studies, only 1.2% of articles (n = 397) had collaborators from five or more countries and 0.3% (n = 89) from 10 or more countries.

Discussion

Our results provide a comprehensive overview of lung cancer research in the 24 countries leading in research. Of concern is that despite a doubling of the volume of lung cancer research worldwide between 2004 and 2013, it still only accounts for a small proportion of the overall oncology research publication output (5.6%). In fact, the RC to lung cancer research compared with that to total oncology research output has fallen in most countries during this period, including in the United States, Italy, France, Spain, Taiwan, and the Republic of Korea (see Fig. 2). China is a notable exception. The surge in articles on lung cancer research emanating from there since 2008 (see Fig. 1) has meant that overall, there has been a 1.2% increase in the proportion of oncology research devoted to lung cancer in this period.

When research outputs are analyzed according to country-specific BoD, no correlation exists (see Fig. 3). Turkey, Poland, Canada, Greece, and the United States, despite having the highest country-specific burden of lung cancer, have all seen a decrease in their RC to lung cancer research between the two quinquennia (see Fig. 2). When compared with all 24 countries, Turkey and Greece publish relatively more research, which is in line with their increased BoD, but China, the Republic of Korea, and Taiwan appear to have relatively greater

Table 1. Citation Performance of 24 Selected Countries in Lung Cancer Research, Ranked by Mean ACI Value

Country	ACI	1%	2%	5%	10%	WS 1%	WS 2%	WS 5%	WS 10%
United States	23.2	74.2	165	401	764	160	177	171	160
Canada	21.4	5.7	8.9	31.6	48.9	151	117	165	125
Netherlands	19.8	2.3	5.4	26.7	58.3	63	74	146	157
Denmark	19.5	0.2	2.4	3.3	11.1	26	137	74	122
Switzerland	16.6	0.4	2.4	7.3	17.1	36	96	117	135
World	16.1	156	313	791	1608	100	100	100	100
Austria	15.2	0.6	2.5	4.9	6.8	86	172	134	91
United Kingdom	15.0	2.5	11.3	27.6	58.4	42	95	92	96
Belgium	14.9	0.8	4.4	10.4	17.3	44	125	116	95
Taiwan	14.9	3.5	6.1	15.0	35.3	76	66	64	74
Norway	14.8	0.4	0.7	3.4	8.0	46	44	84	96
Sweden	14.1	1.2	1.5	3.0	8.8	99	59	47	68
Italy	13.9	6.7	14.0	33.6	64.3	77	80	76	71
Australia	13.8	0.6	3.0	8.4	18.5	34	88	97	105
Germany	13.6	2.7	8.8	22.8	59.8	37	61	62	80
Japan	13.1	10.5	35.7	88.4	187.9	44	75	73	77
Spain	12.9	3.5	8.6	14.1	32.7	84	104	68	77
Republic of Korea	12.8	1.5	5.4	19.7	48.8	24	44	63	76
Brazil	12.4	0.5	0.7	0.7	0.8	65	44	17	10
China	11.1	3.4	7.1	20.4	49.0	38	40	45	54
Poland	10.5	1.1	2.2	3.8	7.2	65	62	43	40
France	9.6	1.7	6.1	18.6	44.0	23	41	50	58
Greece	9.5	0.9	1.9	5.6	14.2	37	41	47	58
India	8.5	0.3	0.5	0.5	2.0	24	19	7	14
Turkey	5.4	0.2	1.3	1.6	2.6	6	22	10	8

Note: Numbers of publications with ≥137 citations (top 1%), ≥86 citations (top 2%), ≥50 citations (top 5%), and ≥33 citations (top 10%) in 5 years after publication. World, refers to citation analysis of all worldwide lung cancer publications.
ACI, actual citation impact; WS, world scale value (ratio of percentages of a country's publications in the top x% (1%, 2%, 5% & 10%) relative to percentages of all worldwide publications in the top x% multiplied by 100).

commitment to lung cancer research compared with their lung cancer BoD (see Fig. 3).

Without further investigation, the reason for these trends can only be hypothesized. One explanation may be the extent to which certain cancers are covered by the media[21] and the subsequent impact this has on philanthropic, governmental, and industry funding of research. One study in the United States analyzing the content presented by media outlets, including television and print media, found that breast, colon, and brain cancers were all overrepresented relative to their incidence, whereas prostate and lung cancers were both underrepresented.[22] Similar findings have been seen in other countries, with lung cancer frequently underrepresented.[23,24] Coverage[25] tends to be influenced by "interested parties," be they academic, charity, or commercial, and often reflects the degree of celebrity endorsement and corporate sponsorship.[26] The consequent effect this has on research funding needs further evaluation and will be the subject of a separate article.

In the United Kingdom, despite the difference in relative burden compared with lung cancer, breast cancer and colorectal cancer received approximately 20% and 13% of Cancer Research UK's research funding in 2013 compared with 6% for lung cancer.[27] In the United States, National Cancer Institute funding for lung cancer research was $286 million in 2013, compared with $559 million and $238 million for breast and colorectal cancer, respectively.[28] From a public policy perspective, lung cancer research is competing with research into other cancer types for recognition and research funding, and not faring well.

The growth in cancer research in China is most likely a response to the rapidly increasing health burden associated with lung cancer. It is the most frequent cause of cancer-related mortality, having overtaken liver cancer, and there has been a fivefold increase in mortality rate over the past three decades.[29] This is due in part to the rapid demographic transition that China is undergoing, but also to growing tobacco consumption and air pollution.[30] As a result, the number of new lung cancer cases is expected to increase by 120,000 per year by 2020.[31]

Just as important as the volume of research is the distribution of research in the different types. Figure 4 highlights the inequity within lung cancer research, especially given the current challenges in the management of this disease. Late diagnosis[32,33] remains a key issue. Mechanisms for improving this include improved selection of at-risk patients from primary care for investigation,[34] the development of new innovative diagnostic tools (especially for indeterminate lung lesions), and cost-effective population-based screening.[35] Yet our analysis suggests that research on screening and diagnostics is not a priority relative to other research types. The United States, Japan, Netherlands, and Germany are currently leading the way in this research domain (see Fig. 5 and Supplementary Table 5).

Given the late stage of presentation of lung cancer for many patients and poor outcomes from current management, there is very limited research into palliative care strategies (see Fig. 4). This is despite published evidence of benefit from early palliative care input for individuals presenting with advanced disease.[36] Systemic therapies are predominantly used in the management of stage IV disease, and although they aim to achieve prolongation of survival, both effective palliation of symptoms and improvement in QOL remain core goals. Research into QOL and research into systemic therapies should therefore not be considered to be mutually exclusive, especially if we hope to achieve outcomes that are in line with patient preferences.[37] This is of equal importance for radical treatment, where dose escalation of radiotherapy[38] and multimodality therapy[39] are increasingly being examined in trials, but potentially at the cost of increased toxicities. The United Kingdom, Canada, and Sweden have demonstrated the greatest commitment to QOL and palliative care research (see Fig. 5).

The commitment to genetic, biomarker, and targeted therapy research is increasingly important in the era of personalized medicine, and our results show that research outputs have increased in these domains, with notable recent successes from targeted therapies.[40,41] Advances in these research types continue to be well publicized, as is evidenced by an analysis of cancer research reporting on the United Kingdom's British Broadcasting Corporation website, which found that cancer stories most frequently focused on new drug or vaccine developments (20%) and genetics research (9%).[25]

However, it is also important to ensure that research into surgery and radiotherapy continues apace as they will remain core modalities in the management of early and locally advanced lung cancer. For instance, stereotactic body radiotherapy using novel radiotherapy delivery techniques has increased the accuracy of treatment delivery, thus enabling radical treatment of men and women with early-stage lung cancer that was previously considered incurable because of comorbidities.[42] Furthermore, effective collaboration between practitioners of these research types is necessary to development of new paradigms of care (e.g., multimodality therapy with targeted agents) that have the potential to achieve significant gains in outcomes[43,44]

It is also important that this work be translated into clinically relevant outcomes for patients. We therefore analyzed the extent to which published lung cancer research was considered clinical (1.0) or basic (4.0) (see Supplementary Figs. 1 through 3). The results demonstrated that whereas East Asian countries such as China and Japan have consistently undertaken basic science research over the 10-year period, other countries, especially across Europe, were increasingly moving away from more clinically oriented research between the two quinquennia. What impact this will have in the long term and the driving force behind this are unknown, but a subsequent analysis will look into the main sources of funding for lung cancer research, be they public, industrial, or charitable, and the potential effect that this has had.[45] One potential factor is the rising costs associated with developing and supporting clinical trials, which have been exacerbated by difficulties in coordinating multiple institutions and recruiting patients.[46,47]

It is not just the type of research undertaken by each country that is relevant but the impact that this is likely to have on changing practice or encouraging further research work. As part of the analysis, we reviewed the ACI of published research from each country. When ranked (see Table 1), output from North America and Europe, in particular, the United States, Canada and the Netherlands, has the greatest influence. Conversely, countries such as China and Japan, which produce a high volume of lung cancer research, rank 15th and 19th in terms of their ACI. This may reduce the integration of research into clinical practice worldwide and potentially result in duplication of research work or greater inequity in clinical outcomes.

Although the number of major international clinical trials is increasing in general, our results demonstrate that they are not the major contributor to the lung cancer research oeuvre. For example, only 1.2% of articles had collaborators from five or more countries. In terms of individual countries, the level of international collaboration for China and Japan is low relative to their research output (Supplementary Fig. 4). Greater efforts are therefore needed to promote international collaboration with both these countries to assist in knowledge transfer.

There are several limitations of the present study. First, we have not provided a detailed analysis of the factors that have led to the observed trends and can only hypothesize potential reasons at this stage. Second, we have selected publications available in the WoS for analysis, and it is therefore likely that some research output in national language journals has not been included in this evaluation, which will affect our results for country-level outputs. Third, the quantity of research outputs may be affected by publication bias, with failure of up to 20% to 30% of trials to report their results.[48] This will have an impact on country-level integer and fractional counts, as well as on potential underrepresentation of clinical research outputs. Although our coding scheme for research types was made as explicit as possible, it is possible that some publications were miscategorized. Furthermore, we have not included every country publishing lung cancer research. However, it is envisaged that by reviewing the 24 leading research-active countries, we have provided public policy intelligence with respect to the major global patterns of lung cancer research and regional trends.

Conclusions

To conclude, our findings have established that despite the huge health, social, and economic burden associated with lung cancer, the level of international research output lags significantly behind that for other malignancies. Of even greater concern is the fact that the RC to lung cancer research is falling in most of the 24 leading research-active countries, which is likely to have an effect on the clinical outcomes that research is able to deliver. This comes at a time when real opportunities exist to better understand the disease: the drop in smoking rates in high-resource countries and the concomitant decline in the attributable fraction of DALYs from smoking provide an opportunity to better investigate other risk factors. In addition, the rapid rise in lung cancer in lower-resource countries, where smoking is just beginning to have an impact on health, should allow the coming lung cancer epidemic to be studied with modern technologies.

Greater efforts are required to prioritize lung cancer research as a whole, and in particular, research into key areas such as diagnosis and screening, which remain challenging for a disease that is associated with late diagnosis. We are also observing a gradual move away from clinical research toward basic science. It is important that translational research be encouraged so as to ensure that high-quality basic research leads to innovative developments and improves outcomes for a disease whose patients continue to have poor chances of survival.

Acknowlegments

This study was conducted by the Institute of Cancer Policy in partnership with and support from the Roy Castle Lung Cancer Foundation on behalf of the Global Lung Cancer Coalition of Advocacy Organisations and with funding from an unrestricted research grant from Pfizer.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.03.010.

References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1:505-527.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
3. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol*. 2013;14: 1165-1174.
4. Collin J. Tobacco control, global health policy and development: towards policy coherence in global governance. *Tob Control*. 2012;21:274-280.
5. Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. *N Engl J Med*. 2014;370:60-68.
6. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5—a population-based study. *Lancet Oncol*. 2014;15:23-34.
7. American Cancer Society. *Global Cancer Facts & Figures 2009*. Atlanta, GA: American Cancer Society; 2009.
8. Morgensztern D, Ng SH, Gao F, Govindan R. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. *J Thorac Oncol*. 2010;5:29-33.
9. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. *Lancet Oncol*. 2008;9:222-223.
10. Berglund A, Holmberg L, Tishelman C, Wagenius G, Eaker S, Lambe M. Social inequalities in non-small cell lung cancer management and survival: a population-based study in central Sweden. *Thorax*. 2010;65:327-333.
11. Navani N, Nankivell M, Lawrence DR, et al. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med*. 2015;3:282-289.
12. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-98.
13. Eckhouse S, Lewison G, Sullivan R. Trends in the global funding and activity of cancer research. *Mol Oncol*. 2008;2:20-32.
14. Chalkidou K, Marquez P, Dhillon PK, et al. Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries. *Lancet Oncol*. 2014;15:e119-e131.
15. Derrick GE, Pavone V. Democratising research evaluation: achieving greater public engagement with bibliometrics-informed peer review. *Science and Public Policy*. 2013;40:563-575.
16. Hood W, Wilson C. The literature of bibliometrics, scientometrics, and informetrics. *Scientometrics*. 2001;52: 291-314.

17. Lewison G. The definition of biomedical research subfields with title keywords and application to the analysis of research outputs. *Research Evaluation*. 1996;6:25–36.
18. Waltman L, van Eck NJ. Field-normalized citation impact indicators and the choice of an appropriate counting method. 2015. arXiv preprint arXiv:150104431.
19. Huffman MD, Baldridge A, Bloomfield GS, et al. Global cardiovascular research output, citations, and collaborations: a time-trend, bibliometric analysis (1999–2008). *PloS One*. 2013;8:e83440.
20. Lewison G, Paraje G. The classification of biomedical journals by research level. *Scientometrics*. 2004;60: 145–157.
21. Aggarwal A, Batura R, Sullivan R. The media and cancer: education or entertainment? An ethnographic study of European cancer journalists. *Ecancermedicalscience*. 2014;8:423.
22. Slater MD, Long M, Bettinghaus EP, Reineke JB. News coverage of cancer in the United States: a national sample of newspapers, television, and magazines. *J Health Commun*. 2008;13:523–537.
23. Konfortion J, Jack RH, Davies EA. Coverage of common cancer types in UK national newspapers: a content analysis. *BMJ Open*. 2014;4:e004677.
24. Williamson JML, Jones IH, Hocken DB. How does the media profile of cancer compare with prevalence? *Ann R Coll Surg Engl*. 2011;93:9–12.
25. Lewison G, Tootell S, Roe P, Sullivan R. How do the media report cancer research? A study of the UK's BBC website. *Br J Cancer*. 2008;99:569–576.
26. Len-Rios ME, Park S, Cameron GT, Duke DL, Kreuter M. Study asks if reporter's gender or audience predict for paper's cancer coverage. *Newspaper Research Journal*. 2008;29:91.
27. *Saving Lives through Research: Annual Report and Accounts 2012/2013*. London, United Kingdom: Cancer Research UK; 2014.
28. A snapshot of lung cancer. National Cancer Institute website. http://www.cancer.gov/research/progress/snapshots/lung. Posted November 5, 2014. Accessed September 14, 2015.
29. She J, Yang P, Hong Q, Bai C. Lung cancer in China: challenges and interventions. *Chest*. 2013;143:1117–1126.
30. Lin H-H, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. *Lancet*. 2008;372:1473–1483.
31. Chen W, Zheng R, Zeng H, Zhang S. Epidemiology of lung cancer in China. *Thorac Cancer*. 2015;6:209–215.
32. Torring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer*. 2013;49:2187–2198.
33. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax*. 2013;68:551–564.
34. O'Dowd EL, McKeever TM, Baldwin DR, et al. What characteristics of primary care and patients are associated with early death in patients with lung cancer in the UK? *Thorax*. 2015;70:161–168.
35. Field JK, Oudkerk M, Pedersen JH, Duffy SW. Prospects for population screening and diagnosis of lung cancer. *Lancet*. 2013;382:732–741.
36. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733–742.
37. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol*. 2010;28:1203–1208.
38. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16:187–199.
39. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374:379–386.
40. Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385–2394.
41. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
42. Louie AV, Palma DA, Dahele M, Rodrigues GB, Senan S. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights, and changing horizons. *Radiother Oncol*. 2015;114:138–147.
43. Provencio M, Sanchez A, Garrido P, Valcarcel F. New molecular targeted therapies integrated with radiation therapy in lung cancer. *Clin Lung Cancer*. 2010;11:91–97.
44. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. *Nat Rev Cancer*. 2011;11:239–253.
45. Eckhouse S, Lewison G, Sullivan R. Trends in the global funding and activity of cancer research. *Mol Oncol*. 2008;2:20–32.
46. Hawkes N. UK must improve its recruitment rate in clinical trials, report says. *BMJ*. 2012;345:e8104.
47. Collier R. Rapidly rising clinical trial costs worry researchers. *CMAJ*. 2009;180:277–278.
48. Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ*. 2013;347:f6104.