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Lung cancer research and its citation on clinical practice guidelines

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ABSTRACT

Background: The impact of medical research is usually judged on the basis of citations in the serial literature. A better test of its utility is through its contribution to clinical practice guidelines (CPGs) on how to prevent, diagnose, and treat illness. This study aimed to compare the parameters of lung cancer research papers with those cited as references in lung cancer CPGs from 16 countries, and the Cochrane Collaboration. These comparisons were mainly based on bibliographic data compiled from the Web of Science (WoS).
Methodology: We examined 7357 references (of which 4491 were unique) cited in a total of 77 lung cancer CPGs, and compared them with 73,214 lung cancer papers published in the WoS between 2004 and 2018.
Results: References used by lung CPGs were much more clinical than the overall body of research papers on this cancer, and their authors predominantly came from smaller northern European countries. However, the leading institutions whose papers were cited the most on these CPGs were from the USA, notably the MD Anderson Cancer Center in Texas, the Memorial Sloan Kettering Cancer Center, New York, and the Mayo Clinic in Rochester, Minnesota. The types of research cited by the CPGs were primarily clinical trials, as well as three treatment modalities (chemotherapy, radiotherapy and surgery). Genetics, palliative care and quality of life were largely neglected. The median time gap between papers cited on a lung CPG and its publication was 3.5 years longer than for WoS citations.
Conclusions: Analysis of the references on CPGs allows an alternative means of research evaluation, and one that may be more appropriate for clinical research than citations in academic journals. Own-country references show the direct contribution of research to a country's health care, and other-country references show the esteem in which this research has been held internationally.

1. Introduction

1.1. The burden from the disease, and previous studies

Globally, lung cancer is one of the leading causes of, mostly avoidable, mortality and morbidity. According to the World Health Organization (WHO) it accounted for 16.2 % of the world total of Disability-Adjusted Life Years (DALYs) attributable to cancer in 2000, and 17.1 % in 2015 [1,2]. As the world becomes better off economically, and people live longer, cancer tends to increase and there is increased exposure to risk factors such as tobacco [3]. Lung cancer, which accounted for only 1.18 % of all DALYs in 2000, had increased its toll to 1.56 % in 2015, or by 32 %. The increase was lower in Europe (+11 %), but much higher in Asian countries (+50 %), and in Africa (+65 %). However, it was actually negative (-11 %) in Canada and the USA, probably because of aggressive measures to prevent smoking [4,5].

Although there is evidence [6,7] that research plays a major role in the improvement of the outcomes in non-communicable diseases and mental disorders, it appears that lung cancer does not attract the volume of research that its disease burden would warrant [8]. The reasons behind this are multi-factorial, not least because policy-makers view control of tobacco as their prime objective rather than research into lung cancer [9,10]. There are efforts by many governments to make cigarettes more expensive, to make them less attractive through packaging

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regulations, and to restrict where smoking can take place [11,12] although there is a considerable lack of enforcement in many countries [13]. An understanding of the impact of investment into lung cancer research is a crucial step to the redressing of the policy balance between the support for lung cancer research and the improvement of public health measures to control tobacco.

Lung cancer research, as determined by papers in the Web of Science (WoS, © Clarivate Analytics), has increased quite rapidly in terms of output in recent years [8], but this expansion is due almost entirely to China, which accounted for one third of the world total lung cancer research outputs in 2018. Most other countries have actually *reduced* their outputs of lung cancer research, relative to research on all cancer. Previous studies of cancer research have all demonstrated that lung cancer is relatively neglected within the cancer research portfolio compared with its share of the burden from all cancers [8]. The shortfall from parity is of the order of 38 % in India [14], 50 % in China [3] and 75 % or more in Europe [15]. In seeking to further understand and develop proof-of-principle of the impact of research into lung cancer and to provide alternate measures, we have examined the citation of research papers on a representative sample of lung clinical practice guidelines (CPGs). These are being developed and published in an increasing range of countries as a means to encourage evidence-based clinical practice.

1.2. Methods for research evaluation

The existing bibliometric tools for research evaluation mostly only take account of the impact of research on other researchers. Citations in the literature are the main currency employed, but there are now several others, collectively known as "Altmetrics", which include the numbers of social media interactions, reads and downloads of papers. Reads and downloads are also (since September 2015) counted in the WoS, both in the last 180 days (designated U1) and since 2013 (U2). Research evaluation can also be based on the ratings given by the F1000 group of reviewers [16] for papers in biology and in medicine. Citations among the reference lists of patents are another important way in which research can be seen to lead to innovation, especially for new pharmaceutical drugs. Research cited in this way tends to be very basic [17]. However, these ratings of "quality" give little indication of how influential papers are in terms of clinical practice – the prevention of illness, its diagnosis, and its treatment.

One measure of this has recently been developed in the form of the clinical impact® database [18] provided by Minso Solutions AB, which records the details of the references on CPGs. These are developed in many countries, initially in Europe and North America, but now in many other countries such as Australia, Brazil, China, India, Japan, Saudi Arabia and South Africa [19]. They are intended to guide clinical practice, and in some countries they may dictate, for example, which treatments (*e.g.*, pharmaceutical drugs) will be provided under the public health service because they are considered to be cost-effective [20–22]. An evaluation of 101 CPGs in oncology demonstrated heterogeneity in the underpinning evidence guiding clinical practice [23].

There are two features of these references that have been noted since the first papers that examined them as a potential means for the evaluation of clinical research [24,25]. One is that they are predominantly clinical observation (as opposed to basic research), with a concentration on methods of treatment (*e.g.,* chemotherapy, radiotherapy and surgery for cancer) rather than genetics. The second is that they over-cite research from the country of the CPG. [It has been demonstrated that most scientific papers over-cite ones from their own country [26]]. The relative emphasis on clinical work, and especially on clinical trials [19], is not surprising as the purpose of CPGs is to inform clinical practice in the country or region. However it does provide an alternative view of the utility of such research, which may be under-valued by conventional measures [27].

1.3. What this paper does

In this paper, we examined research papers cited in the evidence base of a selection of 77 CPGs from eight countries, and the Cochrane Collaboration library, that are covered in the clinical impact® database, and from seven further European countries that were processed by EP and GL at King's College London as part of an investigation into European research on five non-communicable diseases, of which cancer was one [15]. The list of countries and organisations is in Table 1, with their International Standards Organisation (ISO2) country codes.

The objective of the study was to seek the details of the cited papers in the WoS and in PubMed (the Public Library of Medicine published by the US National Library of Medicine) and analyse their parameters so as to reveal their characteristics, and how these compare with the larger set of lung cancer research publications in the WoS. The list of papers cited in CPGs contained many with multiple entries because they were cited on several different CPGs: it seemed to us appropriate to assign extra credit to these papers.

2. Methodology

2.1. Two sets of lung cancer research papers and means of analysis

This study uses two sets of references to research papers. The first set (CPGREF) consisted of references found in the 77 CPGs published between 2003 and 2018, where the references were published between 1955 and 2019. It was created from the lung cancer CPG references from two data sources: the clinical impact® database [18], and from a CPG reference database created at KCL [28]. The second set (WLCP) consisted of the world output of lung cancer research papers retrieved *via* the WoS, and published between 2004 and 2018.

The parameters for the analyses were :

1 the research level of the cited references on a scale from RL = 1.0 for clinical observation to RL = 4.0 for basic research;
2 the countries represented in their addresses based on fractional counts. For example a paper with one French and two German addresses would be categorised as FR = 0.33, DE = 0.67;
3 the leading institutions in terms of their contributions to the CPGREF papers from selected countries, based on fractional counts;
4 the domain or type of the research (*e.g.*, chemotherapy, surgery); and
5 the gap in years between the publication of the reference and that of the CPG.

2.2. The clinical impact® and the KCL databases

A description of the clinical impact® database and the process by which the references were extracted from the text of the CPGs was given by Eriksson et al. [19]. Details of the citing CPG included the country of origin, date, publisher and title. The cited references were identified by their PubMed identifiers (PMID. usually an 8-digit number) and/or their Digital Object Identifiers (DOIs). These were used to find the papers in

Table 1
List of countries whose Clinical Practice Guidelines in lung cancer were processed either in the clinical impact® database (ci®) or by King's College London (KCL) in order to list their references.

Country	*Code*	*Team*	*Country*	*Code*	*Team*
Canada	CA	ci®	Italy	IT	KCL
Cochrane Collaboration	CC	ci®	Netherlands	NL	KCL
Croatia	HR	KCL	Norway	NO	ci®
Finland	FI	ci®	Portugal	PT	KCL
France	FR	KCL	Spain	ES	KCL
Germany	DE	ci®	Sweden	SE	ci®
Greece	GR	KCL	United Kingdom	UK	ci®
Ireland	IE	ci®	United States	US	ci®

the WoS. Of those 5575 references, 5225 were identified in the WoS (94 %), and their bibliographic data were downloaded and transferred to an Excel spreadsheet by means of a MS Excel macro written by Philip Roe of Evaluametrics Ltd. Details of the other papers were obtained, either from PubMed or from Google Scholar. The CPGs from the KCL database, from the seven other European countries, had a total of 1796 references in the WoS. The CPGREF set thus had a total of 7371 cited references, including many with multiple entries because they were cited on two or more CPGs.

2.3. Description of analyses

We determined the research level (RL) of the papers in the two sets by means of a macro that counted the papers with either a "clinical" or a "basic" word in their title, or both [29]. These numbers gave a value between 1.0 and 4.0 for both the titles of the CPGREF papers (RLp) and for all the papers in the journals in which they were published (RL j), and similarly for the comparison cohort of lung cancer research papers (WLCP), see below.

We used another macro to identify papers in some 12 research domains or types (*e.g.*, surgery, radiotherapy) based on words in their titles, or sometimes, journal name strings [15]. Some papers were classified in more than one domain, but others could not be so classified. In addition, we identified papers that described clinical trials, and ones where the role of tobacco, or smoking, was also mentioned with title words.

In order to identify the leading institutions in terms of their contribution to the CPGREF set, we first counted the numbers of individual addresses for each paper. Because some institutions are described in different ways, we then sought significant words from the leading addresses. For example, one was MEM SLOAN KETTERING CANC CTR, NEW-YORK, NY 10021, USA, and we then used an MS Excel macro to count the occurrences of SLOAN KETTERING in the address field, as it was not always the first item in the address. We then divided these numbers by the number of addresses (D) to give the fractional counts of the Sloan Kettering Cancer Center on each paper, and then summed them over all the references in CPGREF. A similar procedure was used on the WLCP file, so that the presence of individual institutions in the two sets of papers could be compared.

2.4. The comparison cohort of lung cancer research papers

For the analysis a comparison set of papers covering the world output of lung cancer research papers (WLCP) was needed [8]. The file of lung cancer research papers was obtained from the WoS by application of a cancer "filter" that contained the names of 185 specialist cancer journals and 323 title words or phrases [30]. In addition, papers had to be either in a respiratory journal, such as *American Journal of Respiratory and Critical Care Medicine* or *Lancet Respiratory Medicine* or *Lung*, or contain a title word indicative of the respiratory system, such as *Lung* or *Trachea*. Papers were also taken if they were in lung cancer journals, such as *Clinical Lung Cancer* or *Lung Cancer,* or contained the title words *Lung-Cancer* or *NSCLC* or *SCLC*. The WLCP set was analysed similarly to the CPGREF set for the first four of the five parameters above. The parameters of the two sets, CPGREF and WLCP (their countries of origin and distribution between research domains), were compared in the corresponding years, so as to show whether there were significant differences between the two sets of papers.

The last analysis, of the gap between the publishing dates of the CPG and of its individual references, was calculated for different CPG countries, and for different research domains of the cited papers. A comparison was made with the corresponding gap between lung cancer papers in the WoS and their individual cited references. For this purpose, a simplified filter was used, based on the presence of the two title words, *cancer* and *lung*, and a sample of 500 papers from year 2017 was taken. These contained a total of 19,553 references whose dates could be determined.

2.5. Statistical analysis

This was concerned with the difference between the observed numbers of papers, and the numbers that would have been expected based on an assumed distribution. We used the chi-squared value for this difference, based on the Poisson distribution with one degree of freedom, and identified values that departed from those expected with probability < 5 % or < 0.5 %.

3. Results

3.1. Numbers of papers

There were 4491 individual papers cited on the CPGs, and the maximum number of CPG citations for a single paper was 23 for the following Canadian paper:

Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, Laupacis A. The Practice Guidelines Development Cycle - a Conceptual Tool for Practice Guidelines Development and Implementation. *J Clin Oncol*, 13(2), 1995, 502−512

Most of the CPGREF papers were cited on only one guideline, but 1286 were cited on two or more, 163 on five or more, and 27 on ten or more. The earliest cited paper was from 1955, and there were 12 in the 1960s, 41 in the 1970s, and 308 in the 1980s. For almost all comparisons between the CPGREF and WLCP sets, the differences described below are statistically significant with $p << 0.01$ % on the Poisson distribution with one degree of freedom.

3.2. Countries of the researchers

The next analysis was of the countries of the authors of the two sets of papers. This has changed over time: China contributed 33 % of the WLCP set in 2014−18, but only 5% in 2004−08. A comparison has therefore been made for two five-year periods, 2004−08 and 2009−13. [There were too few CPG references from 2014−18 to make an analysis useful.] The results are shown in Table 2. For example, in 2004−08, the US contribution to the CPGREF papers was 33.7 %, and its contribution to

Table 2
Percentage of world lung cancer papers (WLCP) by country; percentage of references found in CPGREF by country; and ratio between published papers and references in CPGREF, in two quinquennia, Q1 = 2004-08 and Q2 = 2009-13, fractional counts. *For ISO2 country codes, see* Table 1. *CN = China, JP = Japan, KR = (South) Korea; TW = Taiwan.*

Country	*WLCP Q1*	*WLCP Q2*	*CPGREF Q1*	*CPGREF Q2*	*Ratio Q1*	*Ratio Q2*
US	30.6	24.5	33.7	31.9	1.10	1.30
UK	3.92	3.07	7.51	8.57	1.92	2.79
IT	5.75	4.42	5.77	5.16	1.00	1.17
NL	2.39	2.06	5.8	4.84	2.43	2.36
CA	2.42	2.51	5.93	4.29	2.45	1.71
DE	4.93	3.64	5.59	4.12	1.13	1.13
ES	2.59	2.16	1.67	3.73	0.65	1.73
FR	4.91	3.48	3.77	3.32	0.77	0.95
SE	0.83	0.56	1.74	1.54	2.08	2.73
NO	0.52	0.41	1.13	0.967	2.15	2.38
GR	1.52	1.12	1.29	0.437	0.85	0.39
AT	0.47	0.43	0.332	0.294	0.71	0.69
IE	0.31	0.25	0.34	0.206	1.11	0.83
FI	0.33	0.23	0.128	0.189	0.39	0.81
HR	0.08	0.07	0.105	0.047	1.26	0.66
PT	0.15	0.36	0.055	0.019	0.36	0.05
CN	4.57	16.8	1.25	5.67	0.27	0.34
JP	15.7	12.6	8.85	7.83	0.56	0.62
KR	3.67	5.02	1.9	3.5	0.52	0.70
TW	2.93	3.58	0.74	0.95	0.25	0.27

WLCP was 30.6 %, so the ratio was 33.7/30.6 = 1.10. It was therefore slightly over-represented in the CPGREF compared with its contribution to lung cancer research in that quinquennium. Other countries, notably China, were under-represented.

The presence of a country's researchers among these CPG references has two separate effects. If they have contributed to the evidence base of CPGs from their *own country*, then they have been of potential benefit to their national health-care system. If they are cited in *other countries'* CPGs, then they have achieved international recognition, which is an indicator of research quality, as these references have all been selected because they represented good research, and were considered important for clinical practice. They are normally chosen as a result of a careful search for good evidence, on which clinical recommendations can be based, whereas citations in scientific papers are given for all sorts of reasons.

Accordingly, Table 3 shows the presence of individual countries' researchers both on *own* country CPGs and on *other* country CPGs, in the two quinquennia, as ratios of their percentage presence in lung cancer research in each time period. There was a total of 4487 CPGREFs from 2004−18 for which address data were available. Of these, for example, the US CPGs cited 148 references, and the other 4487−148 = 4339 references were cited on the CPGs from other countries (and international organisations). The US contribution to these 148 references was 66.3 papers, or 44.8 %. This compares with the US percentage presence in WLCP of 15,307/67,730 = 22.6 %, so the ratio is 44.8/22.6 = 1.98, or 2.0 to two significant figures. In the CPGs from other countries, the US fractional count presence was 1382 papers, or 31.8 % of 4339, so the ratio was 31.8/22.6 = 1.5. All the countries' research (except for that of Ireland) is over-cited in their own CPGs, as would be expected.. Their over-citation internationally is again mostly more than unity, except for Finland.

3.3. The leading research institutions in lung cancer

The leading institutions among those contributing to the CPGREF are listed in Table 4 for the time period from 2004−18. They are the Memorial Sloan Kettering Cancer Center in New York, the MD Anderson Cancer Center in Houston, Texas, and the Mayo Clinic in Rochester, Minnesota. The numbers are fractional counts, and are compared with the corresponding data for the WLCP from the same years. [For example, a paper with five addresses of which two were from the Memorial Sloan Kettering Cancer Center would count 0.4 of a paper to either total.] Both counts are also given as percentages of the total numbers of papers (4694 and 73,214, respectively), and the ratio between them, showing which institutions' papers are relatively the most cited in CPGs. However, there is a similar bias to that for countries, although most of the leading institutions are from countries that are well represented among the CPGs that were processed in the clinical impact® database or by KCL. There were five pharma companies with a strong presence among the CPG references, AstraZenneca plc, Eli Lilly Inc., F Hofmann La Roche s.a., Pfizer Inc., and Sanofi Aventis s.a. Their contributions are the sum of their explicit financial acknowledgements, and their presence among the addresses, without double counting, but with both elements being fractionated.

3.4. The different types of lung cancer research

The mean research level of the CPGREF papers was RLp = 1.23, and that of the journals in which they were published was RLj = 1.44, somewhat more basic. The corresponding values for the WLCP set were RLp = 2.03 and RL j= 2.06. So the CPG references were clearly much more clinical than those in the WLCP set, in keeping with earlier findings [24,25].

The next analysis was of the types of research, or research domains, in WLCP and in the CPGREF. The time period was the 15 years, 2004−18, and the results are in Fig. 1, and are given as percentages of the respective totals, 67,882 and 4694. The biggest differences are for clinical trials (CLIN) which are almost the largest contributor to the CPG references, and genetics (GENE), which are one of the least (compared with their contribution to lung cancer research), together with epidemiology (EPID). The three treatment modes, drug treatment (DRUG, including both conventional chemotherapy and targeted therapy), radiotherapy (RADI, 19 %) and surgery (SURG, 17 %) all contribute relatively much more to the CPG references than they do to lung cancer research. One third of the CPGREF set report research on drug treatment. Palliative care (PALL) and quality-of-life research (QUAL), which make tiny contributions to the WLCA papers, have a somewhat bigger, but still small, presence among the CPGREF papers, as does screening (SCRE). Few of either set make any reference to smoking or tobacco (TOBA) as a cause of lung cancer.

3.5. The time gap between CPGs, and research papers, and their references

The last analysis was of the gap in time between the year of CPG publication and those of their cited references. Overall, the mean gap was 9.8 years, but it varied between 15.5 years for Germany and 6.2 years for France, see Fig. 2. This was a larger gap than the corresponding one for prostate cancer, 8.2 years [19]. (The standard errors of the two means were 0.09 and 0.07 years, so the difference was statistically highly significant.) It was also larger for seven of the nine countries for which there were CPGs. There was also a variation in the rapidity with which research in different domains was incorporated in the CPG evidence. For surgery and epidemiology it was nearly 11 years, but for the relatively recently developed targeted chemotherapy it was only 4.6 years. A comparison with the dates of the references on a sample of lung cancer research papers (from year 2017) showed that the median gap between publication of a CPG and its references is 3.5 years longer than

Table 3
Presence of each country with lung cancer CPGs among its *own* CPG references (fractional counts) (Own CU or country), and among the CPG references from *other* countries (Other CU or country), for references that have addresses, and percentages of these references (Own %, Other %), and ratios to the percentage presence of the country in lung cancer research (WLCP) 2004-18. *For ISO2 country codes, see* Table 1.

ISO2	*WLCP*	*Own refs*	*Own CU*	*Own %*	*Ratio*	*Other refs*	*Other CU*	*Other %*	*Ratio*
US	22.6	148	66.3	44.8	2.0	4339	1382	31.8	1.5
UK	2.81	344	45.3	13.2	4.7	4143	300	7.2	2.6
IT	4.25	116	9.6	8.3	2.0	4371	232	5.3	1.2
NL	1.72	367	46.9	12.8	7.4	4120	185	4.5	2.6
CA	2.20	809	54.2	6.7	3.0	3678	172	4.7	2.1
DE	3.39	595	66.6	11.2	3.3	3892	157	4	1.2
FR	3.32	236	15.8	6.7	2.0	4251	145	3.4	1.0
ES	2.04	145	13	9	4.4	4342	110	2.5	1.2
SE	0.51	629	29	4.6	9.1	3858	41.3	1.1	2.2
NO	0.40	369	22.3	6	15	4118	29	0.7	1.8
IE	0.23	226	0.2	0.1	0.3	4261	11.8	0.3	1.2
FI	0.19	159	1	0.6	2.7	4328	5.5	0.1	0.7

Table 4
The leading research institutions and companies contributing to the references cited on the selected lung cancer CPGs (CPGREF), fractional counts, and the corresponding contributions to lung cancer research (WLCP), 2004-18. The percentages of the totals, and the ratio between them. Company contributions are the sum of explicit and implicit acknowledgements, but the former are only available for papers from 2009-18.

Address	*CPGs*	*WLCP*	*% CPGs*	*% WLCP*	*Ratio*
Memorial Sloan Kettering Cancer Center, New York, USA	86.7	469	1.93	0.64	3.0
Univ Texas, MD Anderson Cancer Center, Houston, TX 77030, USA	80.0	977	1.78	1.33	1.3
Mayo Clinic, Rochester, MN, USA	61.0	345	1.36	0.47	2.9
Vrije Univ Amsterdam, Netherlands	56.5	265	1.26	0.36	3.5
Harvard Univ, Beth Israel Deaconess Med Ctr, Boston, MA, USA	42.1	486	0.94	0.66	1.4
Duke Univ, Med Ctr, Durham, NC, USA	39.6	257	0.88	0.35	2.5
Massachusetts General Hospital, Boston, MA, USA	39.2	292	0.87	0.40	2.2
Washington Univ, St Louis, MO, USA	36.9	235	0.82	0.32	2.6
Univ Toronto, Toronto, Canada	32.0	236	0.71	0.32	2.2
National Cancer Center, Tokyo, Japan	31.7	386	0.71	0.53	1.3
Princess Margaret Hosp, Toronto, Canada	28.9	163	0.64	0.22	2.9
Sungkyunkwan Univ, School of Medicine, Seoul, South Korea	27.9	361	0.62	0.49	1.3
Univ Pittsburgh, School of Medicine, USA	27.6	320	0.62	0.44	1.4
Univ Health Network, Toronto, Canada	27.2	136	0.61	0.19	3.2
Univ North Carolina, Dept Med, Chapel Hill, NC, USA	26.6	174	0.59	0.24	2.5
Seoul National Univ, College of Medicine, Seoul, South-Korea	25.8	501	0.57	0.69	0.8
Univ Hospital, Freiburg, Germany	25.5	163	0.57	0.22	2.6
Dana Farber Cancer Institute, Boston, USA	24.4	222	0.54	0.30	1.8
Institut Gustave Roussy, Villejuif, France	22.4	182	0.50	0.25	2.0
Univ Chicago, Chicago, IL 60637, USA	21.9	176	0.49	0.24	2.0
Karolinska Institutet, Stockholm, Sweden	21.3	171	0.47	0.23	2.1
AstraZeneca plc, Macclesfield, England	39.7	255	0.88	0.38	2.3
Eli Lilly & Co, Inc., Indianapolis, USA	36.2	190	0.58	0.28	2.1
F Hofmann LaRoche s.a., Basel, Switzerland	32.8	258	0.73	0.38	1.9
Pfizer Inc., New York, NY, USA	22.8	153	0.51	0.22	2.3
Sanofi Aventis s.a., Paris, France	21.2	71	0.47	0.11	4.5

for WoS lung cancer research papers and their references.

4. Discussion

We have sought to evaluate countries' and research institutions' contributions to lung cancer research through their influence on CPGs from 15 countries and the Cochrane Collaboration. This is, of course, only one measure of the impact of the research papers, and has several limitations. First, only a rather small number of research papers are cited at all on CPGs, whereas the majority of research papers are cited at least once in the serial literature. Moreover, the likelihood of being cited varies greatly with the research domain. Second, some of the CPG references are not to lung cancer research papers. We found that some 78 % of them (that were published in the 15 years, 2004−18) were in our WLCP file. This percentage varied between 91 % for drug treatments and only 23 % for palliative care. Some 18 % of the papers not on lung cancer were on some other aspects of the lung. Only 1% were concerned with CPG development or their use.

As expected, important parameters for success were the conduct of clinical trials, research on the three main methods of treatment, and for the work to be patient-centred (*i.e.*, clinical) rather than basic research. The countries with the relatively greatest impact were the smaller ones in northern Europe. Research from the countries in East Asia had comparatively little influence on the set of CPGs that we examined, even though almost all of their papers (> 99 %) in the WoS were written in English. This may reflect both a bias against research outputs from this region, but also different approaches to patient management. The average time gap between CPG publications and their references was almost ten years, two years longer than for lung cancer research papers in the WoS, but the difference in the median time gaps was 3.5 years. This means that the evidence base of some of these CPGs was not very recent, particularly for Germany (Fig. 2); it was better for France and Spain, and for Canada and the USA. It is also notable that new evidence for pharmaceuticals was incorporated far more rapidly than, say, for surgery. This again may reflect relative biases for and against these modalities, but also may reflect the paucity of high-quality practice research emanating from the surgical community.

However, the numbers of papers from different countries are inevitably biased because some countries were not represented among the CPG publishers; there were varying numbers of CPGs from the different countries (17 from Canada, six each from France and Spain, but only one from many countries) and varying numbers of references from the individual CPGs (one CPG from Germany had 1272 references, but two others had only 2 references each). At the bottom of the table are four East Asian countries which did not have CPGs in our collection. All four were under-cited in the European and North American CPGs, but Japanese and South Korean lung cancer research had higher ratios of clinical impact than those of China and Taiwan.

The publications cited in CPGs are normally chosen, we assume, as a result of a careful search and systematic review for good evidence grading, on which clinical recommendations can be based, in contrast to citations in scientific papers which are not systematic. With traditional bibliometric measures appearing to under-estimate clinical research [27] and CPG citation analyses tending to favour clinical research as seen in this paper and others [19,24,25], this approach appears to be a valuable way to assess the impact of clinical lung cancer research, especially in view of the systematic process used to find and cite good evidence in the CPGs, and the influence of CPGs on health care practice.

The study has some limitations, notably that the selection of CPGs was not systematic, nor did we ascertain whether these were "actively" being utilised by the various lung cancer clinical communities. Some countries' lung cancer CPG collections had rather few references in total, usually because there was only one CPG. Not all their references were found in the WoS, but the shortfall (which only affected the analysis of addresses) was less than 5%. This is a rather new means for the evaluation of clinical research, and so the methodology for its deployment has not yet been fully validated.

The calculations of the leading pharmaceutical companies' contributions to the two databases, CPGREF and WLCP, are under-estimates because the majority of the attributions were based on explicit acknowledgements, which only appeared in the WoS after 2009. Papers from 2009−18 accounted for 82 % of the WLCP set from 2004−18, but only 51 % of the CPGREF set. There were therefore far fewer explicit acknowledgements to the five pharma companies in Table 4 than would have occurred if the time distributions of the two sets of papers had been similar.

5. Conclusions

- The analysis of the references on lung cancer CPGs shows which countries' and institutions' research has had most influence on clinical practice both in their own countries and internationally

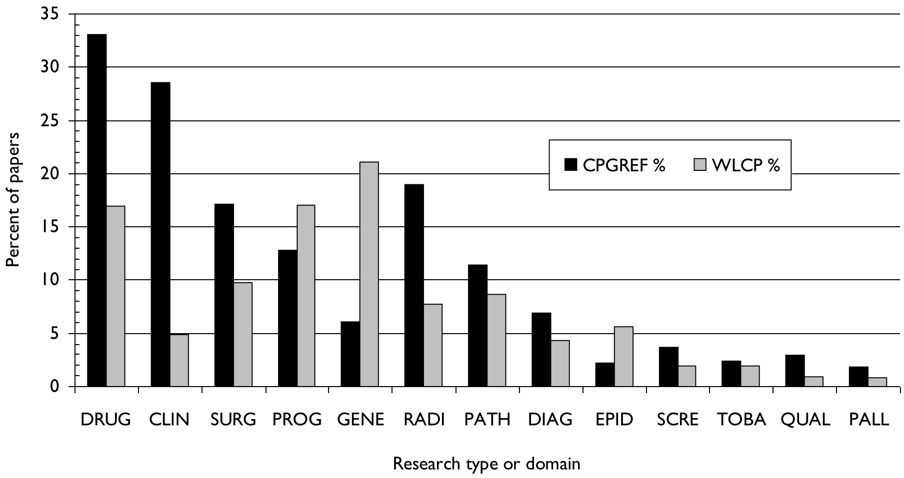

Fig. 1. Research domains of world lung cancer research papers (WLCP, grey columns) and of CPG references (CPGREF, black columns) in 2004-18, percentages. Domains are ranked by their mean contributions to the two sets of papers. *CLIN = clinical trials; DIAG = diagnosis; DRUG = chemotherapy (including targeted chemotherapy); EPID = epidemiology; GENE = genetics; PALL = palliative care; PATH = pathology; PROG = prognosis; QUAL = quality of life; RADI = radiotherapy; SCRE = screening; SURG = surgery;. TOBA = tobacco-related.*

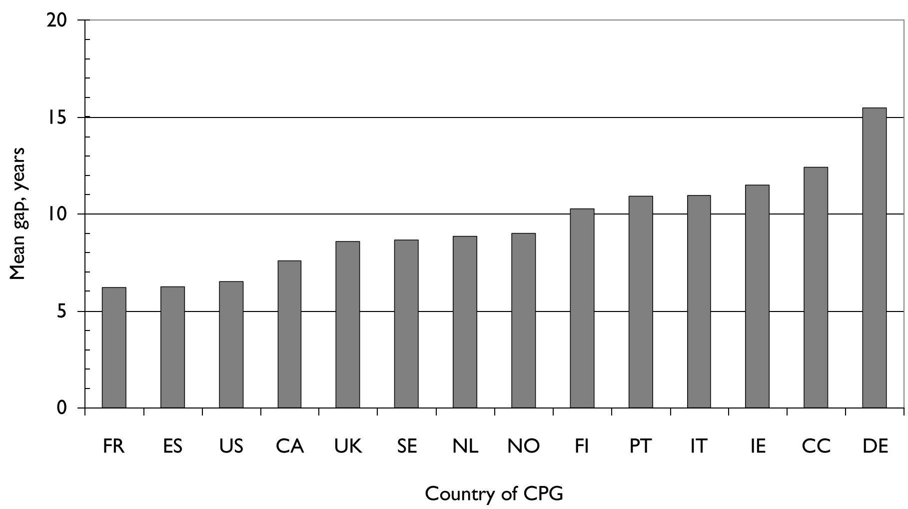

Fig. 2. Mean gap, years, between publication of a lung cancer CPG from a country and the references it cited. *Note: data for Austria, Greece and Croatia omitted, as they had too few references. For ISO2 codes, see* Table 1. *CC = Cochrane Collaboration.*

- Such research is very clinical (*i.e.*, patient-orientated), contains many clinical trials papers, and ones on the three main treatment methods (chemotherapy, radiotherapy, surgery)
- This method of research evaluation is more appropriate for clinical studies and trials, which tend to receive fewer journal citations than basic work, and may therefore be under-appreciated based on traditional bibliometric indicators.

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CRediT authorship contribution statement

Elena Pallari: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing. **Magnus Eriksson:** Software, Methodology, Data curation, Writing - review & editing. **Annika Billhult:** Software, Data curation. **Tommy Billhult:** Software, Data curation. **Ajay Aggarwal:** Validation, Writing - review & editing. **Grant Lewison:** Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Supervision, Project administration. **Richard Sullivan:** Funding acquisition, Supervision, Writing - review & editing.

Declaration of Competing Interest

EP, GL, AA and RS: no conflicts of interest to declare. ME, AB and TB are all shareholders in Minso Solutions AB, which contributed the data on the papers cited on the CPGs (see Table 1).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.01.024.

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