Deliverable 4: An analysis of economic impact of childhood cancers based on systematic review of data to inform national and regional policymakers across the EU

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Abstract

Background: Every year, around 300,000 children are diagnosed with cancer. Although treatment of childhood cancer has seen significant progress, cancer is still an important cause of child mortality worldwide. In order to inform policy and planning, a better understanding of the economic burden of childhood cancer on healthcare systems and families is needed.

Objective: The aim of this study was to describe the economic burden (direct and indirect costs) of childhood cancers internationally.

Methods: Three academic databases and two web search engines were used to identify scientific as well as grey literature relevant to this review. Records were included if they were published in English between January 2006 and March 2016 and had elements of cost collection in a paediatric cancer population. Costs reported by the different studies were corrected for purchasing power parity and converted to US dollars.

Results: The systematic review yielded 25 publications. Cost estimates varied considerably between studies due to large differences in study design, perspective and types of costs included. Indirect costs were found to exceed direct costs. Total direct (medical and non-medical) costs of childhood cancer ranged up to more than 200,000 US dollars per case, and total indirect costs due to lost productivity can be more than 1 million dollars per patient.

Discussion: Childhood cancer is associated with a considerable economic burden. Efforts should be made to improve affordable access to cancer care, especially in resource-limited countries. Future research should focus on identifying targets for cost savings as well as on understanding the underlying reasons for differences in expenditures. In addition, standardised methods for cost estimates should be developed in order to facilitate interpretation and comparison of economic data on childhood cancer.

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List of Abbreviations

ALL	Acute lymphoblastic leukaemia
AYA	Adolescent and young adult
CNS	Central nervous system
COI	Cost of illness
EXPO-r-NET	European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment
HIC	High income countries
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
ICP	Institute of Cancer Policy
LMIC	Low- and middle income countries
NGO	Non-governmental organisation
WHO	World Health Organization

1. Introduction

1.1 The global burden of childhood cancer

Childhood cancer is an important global health issue, with recent incidence estimates by the International Agency for Research on Cancer (IARC) showing that global occurrence is higher than previously assessed. Every year, approximately 215,000 cancers are diagnosed in children aged 0-14 years and an additional 85,000 cancers occur in those aged 15-19 years (IARC, 2016).

In children, different types of cancer occur than in the adult population. The majority of paediatric cancers are caused by tumours that affect blood cells (leukaemia and lymphoma) while the second most common cancers in children are those of the central nervous system (IARC, 2016). Various types of cancer (e.g. neuroblastoma and retinoblastoma) occur only in children, whereas the most prevalent adult cancers are rarely found in children (IARC, 2016).

Management of childhood cancer has seen significant progress in the past decades, and the majority of patients can be cured if they receive proper treatment (Smith et al., 2010). However, cancer is still an important cause of child mortality worldwide, with estimates by the IARC at 80,000 deaths per year. Moreover, survival rates are around 80% in high-income countries (HICs) but are only 10% in some resource-limited countries (IARC, 2016). This difference is due to late detection and the presence of co-morbidities in low income countries, as well as to issues around affordability and access to proper treatment and care (Chirdan et al., 2009).

Treatment of childhood cancer usually involves hospital stays, various diagnostic tests, the use of chemotherapy and other pharmaceuticals, and in some instances radiotherapy or surgery (Barr et al., 2004). In addition, treatment entails numerous outpatient visits. Therefore, the costs of treating childhood cancer are high, both for the healthcare system and for parents of children diagnosed with cancer (Barr et al., 2004). In various low- and middle income countries (LMICs) where no national health insurance exists, treatment is paid for by families. These families often experience major financial problems due to the prohibitively high costs associated with childhood cancer, which may lead to abandonment of treatment (Arora et al., 2007). However, costs to families can also be significant in HICs, where health services are paid for by the government or through insurance schemes, since families often incur high out-of-pocket expenses (Tsimicalis et al., 2011).

Understanding the economic burden of childhood cancer around the world is essential for developing appropriate public health policy. When deciding on the allocation of healthcare resources, or when setting up financial support schemes for parents of children with cancer, it is crucial to have insight into the costs associated with childhood cancer. For the purpose of reviewing and quantifying these costs, valuable information can be obtained from “cost of illness” studies.

1.2 Cost of illness studies

Cost of illness (COI) studies are “descriptive analyses assessing the economic burden of health problems on the population overall” (Larg & Moss, 2011). It should be noted that these types of studies are not the same as economic evaluations (e.g. cost-effectiveness analyses), which evaluate the costs and effectiveness of a particular intervention. COI studies are useful tools to inform planning of healthcare services, but have also been criticised for lack of reliability (Larg & Moss, 2011). This debate has mostly

been focused on the large variation across studies (Akobundu et al., 2006). The economic burden of an illness can be measured in a number of different ways, with varying cost components, perspectives and approaches. For instance, some studies measure total healthcare expenditure while others only include the incremental costs incurred as a result of the illness (Akobundu et al., 2006). In addition, the term "cost" is not always clearly defined, with some researchers investigating actual costs incurred whereas others use data on hospital charges (list prices set by hospitals) to approximate costs. Hospital charges are generally more accessible than costs, but need to be converted using a hospital-specific cost-to-charge ratio in order to enable comparisons with cost data (Macario et al., 1995). The different types of costs, perspectives, and approaches used in COI studies are discussed in the following sections.

1.2.1 Types of costs: direct, indirect and psychosocial

The framework currently used in most COI studies was developed by Dorothy Rice (1967) and addresses the financial cost of illness using two categories: direct and indirect costs. A third category comprises psychosocial costs related to suffering and loss of quality of life (Larg & Moss, 2011). These "intangible" costs are often not included in COI studies because they are difficult to estimate and to quantify in monetary terms. Therefore, in the present study, the economic burden of childhood cancer is defined as the sum of all direct and indirect costs associated with cancer in children (Figure 1).

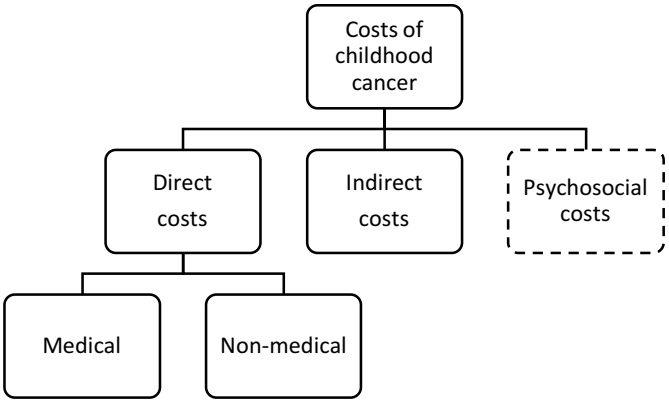

Figure 1 Conceptual framework: components of the economic burden of childhood cancer

In COI studies, direct costs of childhood cancer are those that involve an actual monetary transfer (Dagenais et al., 2008). Direct costs can be divided into medical and non-medical costs. Direct medical costs are those incurred for medical goods and services such as hospitalisation, medication, and diagnostic tests, etc. Non-medical costs are less often studied but include important components such as transportation or accommodation costs for out-patient visits, as well as other non-healthcare related resources.

Indirect costs are costs reflecting resources of economic value but without direct monetary exchange (Dagenais et al., 2008). These can be morbidity costs, which are related to productivity losses borne by the child with cancer or their family, and mortality costs, which account for lost production due to premature death. Morbidity and mortality costs are generally more difficult to measure than direct costs, since they are not directly measured but derived from productivity estimates (Larg & Moss, 2011). Productivity costs are often the only indirect costs measured in COI studies. However, in addition to productivity losses caused by their child's illness, parents of children with cancer also incur time costs related to caregiving and foregone leisure (Tsimicalis et al., 2011; Jo, 2014).

1.2.2 Perspectives

In addition to the different kinds of costs, COI studies also vary in the type of perspective taken (Jo, 2014). Measuring the costs of childhood cancer will give different estimates depending on whose costs are investigated: a study taking the family perspective may only measure non-medical costs incurred by parents, while another study assessing the costs borne by the healthcare system will only include medical costs. Table 1 summarises the various perspectives that can be taken in COI studies, and the types of costs investigated for each perspective (Jo, 2014). The societal perspective is the most comprehensive since it includes all costs. In this study, the family perspective is defined as the assessment of costs incurred by families, which are not only out-of-pocket costs but can also represent total treatment costs in countries where treatment is not reimbursed and families pay for everything.

. Costs included in cost of illness studies, by perspective (Source: Jo, 2014)

Perspective	Medical costs	Morbidity costs	Mortality costs	Transportation/ Nonmedical costs	Transfer payments
Societal	All costs	All costs	All costs	All costs	–
Health care system	All costs	–	–	–	–
Third-party payer	Covered costs	–	Covered costs	–	–
Business	Covered costs (self-insured)	Productivity losses (absenteeism)	Productivity losses	–	–
Government	Covered (Medical aid)	–	–	Criminal justice costs	Attributable to illness
Participants and families	Out-of-pocket costs	Wage losses/ Household production	Wage losses/ Household production	Out-of-pocket costs	Amount received

1.2.3 Approaches and data sources

There are two main epidemiological approaches that can be taken to determine the cost of illness (Larg & Moss, 2011). The most common is a prevalence-based approach, which is used to estimate the economic burden of a disease in a specific time frame, often a year. Studies using a prevalence-based approach are useful for policy makers because they give the economic burden over a certain period and because they often provide an overview of the cost components (Tarricone, 2006). The second approach is incidence-based, which estimates the lifetime costs of a disease, from diagnosis until cure or death. Thus, it gives the potential averted costs if new cases are prevented. These types of studies are most useful for analysing illness management and for designing preventive measures (Tarricone, 2006). Studies can also be differentiated based on the time of the study compared to the events of interest: they can be conducted retrospectively (previously recorded data is collected) or prospectively (subjects are followed up during the course of the study). Prevalence- and incidence-based studies can be both conducted in a retrospective or prospective manner.

Data sources used to measure COI also vary. Cost data can be obtained in a “top-down” manner using population level data obtained from administrative databases or through surveys (Larg & Moss, 2011). Alternatively, a “bottom-up” approach may be used to extrapolate costs from interviews, focus groups or cost diaries kept by families of children with cancer (Larg & Moss, 2011).

1.3 Research objective

Treatment of childhood cancer is costly and can pose a significant burden on the healthcare system and on families of children with cancer (Barr et al., 2004). Understanding this economic burden on society is crucial for informing policy and planning of healthcare and health-related services. Some authors have systematically reviewed certain issues around the costs of childhood cancer, specifically focusing on economic evaluations (e.g. cost-effectiveness studies) or on costs incurred by families (Russell et al., 2012; Tsimicalis et al., 2011). However, a systematic review providing a comprehensive overview of the economic burden of childhood cancer has not yet been performed.

Therefore, the aim of this study was to describe the economic impact of childhood cancers internationally, by conducting a systematic review of the literature. The following question guided the research: "What are the direct (medical and non-medical) and indirect costs associated with childhood cancer?" In addition to answering this question, issues regarding the comparability of costs are discussed in this report.

It is hoped that the results of this study can help guide future research and inform health policy in general and, specifically, that they can be used as a basis for studies in Europe through the Institute of Cancer Policy (ICP) and the European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment (EXPO-r-NET).

2. Methods

2.1 Eligibility criteria

This systematic review was conducted to identify publications that assess the economic burden (direct and indirect costs) of childhood cancer. Included in the review were studies that used monetary units to evaluate the economic aspects of cancer in children. In addition to publications from scientific databases, "grey literature" was included.

2.1.1 Grey literature

Grey literature is defined by the Institute of Medicine (2011) as including trial registries, conference abstracts, books, dissertations, monographs, and reports held by government agencies, academics, business, and industry. Benzies et al (2006) investigated the advantages and challenges of including grey literature in systematic reviews, and designed a decision aid for including grey literature. At least two of the items on this checklist list applied to our topic: there seemed to be a lack of consensus about the measurement of the cost of childhood cancer, and the volume of evidence was judged to be low. Following the recommendations by Benzies et al. (2006), it was therefore decided that the inclusion of grey literature would be valuable for the present study. Inclusion of grey literature could broaden the scope and provide a more comprehensive view of the literature (Benzies et al., 2006; Mahood et al., 2014). However, the disadvantages of including grey literature were also recognised. These included the additional time and effort require to locate grey literature, the vast number of grey literature sources, and the potential for data of lower quality (Mahood et al., 2014).

2.1.2 Inclusion and exclusion criteria

Inclusion criteria for scientific and grey literature were similar and include records published in English between January 2006 and March 2016 that have elements of cost collection in a paediatric cancer population (Table 2).

The publication date range of ten years was chosen because economic data becomes increasingly less comparable to the current situation as studies are older. Also, the potential value of cost estimates older than ten years does not outweigh the additional effort required to identify these studies. For these reasons, a time range of ten years is used in most systematic reviews on economic data (e.g. Dee et al., 2014; Gyllensvärd et al., 2014).

Studies included in this review were those investigating cancer in children. Following the methods used by the IARC in their upcoming International Incidence of Childhood Cancer, the population of interest in this study includes both children (0-14 years) and adolescents (15-19 years) (IARC, 2016b). The rationale presented by the IARC for including adolescents is that some cancer types peak in the (often neglected) age group 15-19 years, and that there is a need for a common strategy to treat children and adolescents (Bleyer et al., 2006). Studies investigating cancer in adults only were excluded from this review.

Economic evaluations of drugs or specific treatment protocols were excluded, as well as studies only reporting one type of cost (e.g. only transport costs). These types of studies were excluded because of the limited extent to which such data can be used to assess the overall cost of illness of childhood cancer. Systematic reviews were excluded, as were qualitative studies not reporting costs in monetary units.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• English language • Published between January 2006 – March 2016 • Publications (academic studies and grey literature) that assess the economic costs of childhood cancer	• Non-English language • Diseases other than childhood cancer • Adult population • Economic evaluations of specific treatments or drugs (e.g. cost-effectiveness studies) • Studies only investigating one type of cost • Systematic reviews • Studies without an element of cost collection

2.2 Data sources

Two types of data sources were used: academic databases and non-academic search engines. The Medical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medica database (EMBASE), and the Economic Literature Index (EconLit) were systematically searched to identify published scientific papers and conference abstracts. When the full text of an article was not available, the corresponding author was contacted to request the complete text. Authors of conference abstracts were contacted with the aim of providing context on the abstract and potentially identifying additional data or studies in progress. The database search was complemented with a search in Google and Bing, the two largest web search engines (in terms of market share in September 2015)[1] that differ from each other substantially with regard to their search algorithms. However, a limitation of using web search engines is related to the reproducibility of the results, because they sort results by popularity and filter them "on the basis of browser version, geographic location and previously entered search strings" (Mahood et al., 2014).

2.3 Search strategy

The main concepts of interest in this study were "costs" (or "economic(s)"), "child" and "cancer". Based on these concepts, a search strategy was developed using controlled terms from MeSH and Emtree thesauri as well as free terms. Boolean operators "AND" and "OR" were used to combine the concepts. Rare or very specific types of childhood cancers (e.g. gliomatosis) were not included in the final search strategy because they were found not to yield any additional results. The terms were searched for in titles and abstracts of database records. The full search strategy including limits is shown in Table 3. In addition to this database search, reference lists of records included in the review were screened to potentially identify additional publications.

The database search strategy was roughly similar to the web search query, although in creating the latter, some synonyms needed to be omitted due to the limit of 32 terms per search. Moreover, the search was focused on Microsoft Word and PDF documents, since relevant reports (such as policy reports from governments) would be published in these formats. Thus, the terms "filetype:pdf OR filetype:doc" were added to the search query. In Bing, publications from before 2006 were manually removed as this search engine does not have an option to select a date range. Only the first 100 results of the search engine search were retrieved and screened, as this is more efficient than screening all results and because data saturation is generally thought to be achieved at that point (e.g. in a WHO

[1] NetMarketShare (2015). *Search engine market share.* Retrieved March 30, 2016, from https://www.netmarketshare.com/search-engine-market-share.aspx?qprid=4

study by Ranson et al., 2010). A variety of previous studies conducted at the Institute of Cancer Policy have shown that search terms through web search engines like Google or Bing capture over 90% of relevant grey literature within the first 100 results (e.g. Aggarwal et al., 2014). However, limitations to including only the first 100 search records have been noted by some authors, who state that it is often unclear how the results are ordered and the small degree of screening my only constitute a small proportion of the volume of grey literature (Haddaway et al., 2015).

Table 2. Search strategy

#1	(Economics or economic or costs or "financial burden" or "cost of illness" or "health care costs" or "health expenditures").ti,ab
#2	(Cancer* or carcinoma* or oncolog* or tumo?r* or neoplas* or leuk?emia* or lymphoma* or sarcoma* or blastoma* or glioma* or glioblastoma* or medulloblastoma* or nephroblastoma* or hodgkin* or rhabdomyosarcoma* or retinoblastoma* or neuroblastoma* or osteosarcoma* or h?epatoblastoma).ti,ab
#3	(infant or infants or child or children or childhood or youth or adolescen* or teenage* or p?ediatric*).ti,ab
#4	1 and 2 and 3
#5	Limit to (English[lang])
#6	Limit to ("01/01/2006"[PDat]: "31/03/2016"[PDat])

2.4 Data extraction and synthesis

Retrieved literature was imported into Endnote to facilitate identification and removal of duplicates. Two-level screening of the literature was conducted. First, records were assessed for eligibility by title and abstract, based on inclusion and exclusion criteria. Second, the full text (if available) of the remaining records was screened to determine eligibility based on these predefined criteria. A data extraction form was developed to record the relevant data from each study. Extracted information included: publication details, study characteristics, participants, outcomes (direct and indirect costs), and comments made by the reviewers about relevant contextual aspects. Extracted study characteristics included the aspects of COI studies described in section 1.2, as these factors need to be taken into account when comparing results from different studies. Cost estimates were extracted and categorised based on the conceptual framework used in this study (Figure 1). The operationalisation of these cost concepts is depicted in Appendix I. It should be noted that the heterogeneity of childhood cancers might result in different treatment costs for different types of cancer. Also, there are significant differences in the international distribution of childhood cancers which may lead to different country-level cost estimates (IARC, 2016). Therefore, costs were extracted and reported separately for each type of childhood cancer.

In order to enable comparisons (even though other factors may complicate these), costs were corrected for purchasing power parity (PPP) by converting domestic currencies into dollars at an exchange rate that takes into account countries' purchasing power for the appropriate year(s). This correction was made using PPP conversion factors published online by the World Bank (retrieved April 13, 2016) which are based upon data from the International Comparison Program (ICP) as well as Eurostat and the Organisation for Economic Co-operation and Development (OECD). Lastly, reporting of the review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al. 2009).

3. Results

3.1 Study selection

The search strategy yielded 2,127 citations (Figure 2). Of these records, a total of 1,927 were identified through database searching while 200 were selected from the web search (the first 100 results from each search engine). After removal of duplicates, the remaining 1,666 studies were screened by title and abstract. This first level of screening resulted in 95 studies of which the full-text (if available) was reviewed for eligibility in the second level of screening.

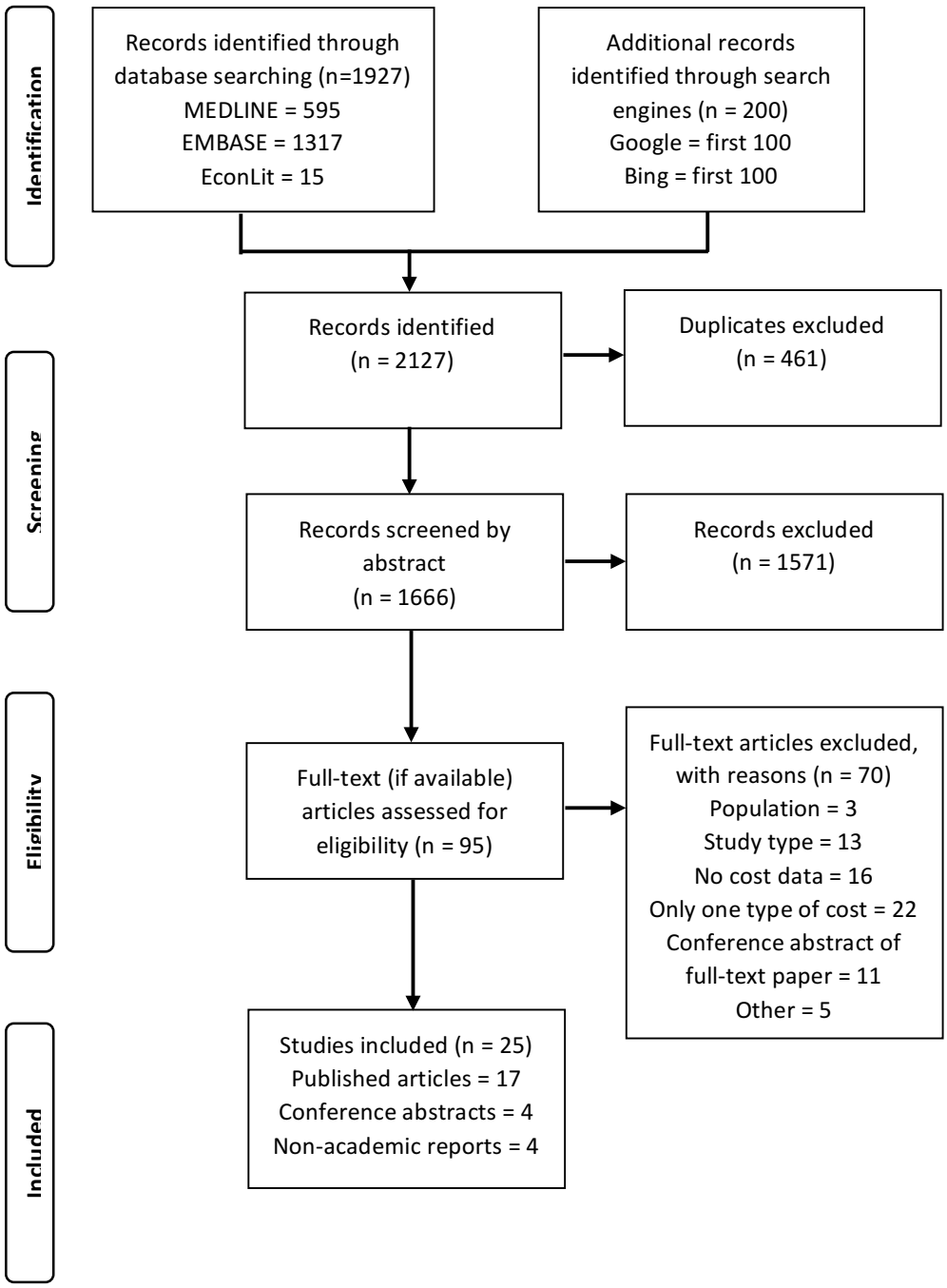

Figure 2. Flow chart of the study selection process

When reviewing conference abstracts, authors were contacted in order to ascertain whether the study met the inclusion criteria and, in some instances, to obtain additional data for extraction. Abstracts were excluded if the necessary information could not be obtained through personal communication.

In the second round of screening a total of 70 studies were excluded, mostly because they did not meet inclusion criteria for population, study type or reported costs. Studies were also excluded if they did not report mean or median costs but rather the number of patients or families incurring a certain cost. Several conference abstracts were excluded because the information contained in them was also available in published form. One report (Merrill et al., 2007) met the criteria for inclusion but was excluded because an updated version was identified (Anhang et al., 2012). Three reports on the environmentally attributable costs of children's diseases in US states were excluded because estimations for childhood cancer were based upon a study retrieved from the search (Trasande & Liu, 2011) and an older study of which the Trasande & Liu report is an update. Lastly, a study by Tsimicalis et al. (2013b) was excluded because the data reported there is also presented in their 2012 study retrieved in the search, with the only difference being that the 2013 paper provides a further breakdown of costs.

The two rounds of screening resulted in inclusion of 25 publications of which data was extracted. These were mostly academic papers (n=17), but also conference abstracts (n=4) and non-academic reports (n=4). During data extraction, reference lists of these studies were searched manually but no additional records were identified.

3.2 Characteristics of the selected studies

Table 4 summarises the most important aspects of the studies included in this review, based upon the characteristics of cost of illness studies as outlined in the introductory chapter of this report.

3.2.1 Country and setting

One third (n=8) of the studies originated from the US and two studies were conducted in Canada. Of the other studies, four were from European countries (of which one was an EU-wide analysis), five from Asia, three from Australia, two from Africa and one was from Central America. Of all studies, 10 were conducted at a single institution, whereas the others used data from patients treated at multiple hospitals or provided region- or country level estimates.

3.2.2. Cancer diagnosis

Of the 25 studies, 11 investigated costs for only one type of childhood cancer: six of these were about acute lymphoblastic leukaemia (ALL) while the other studies were on osteosarcoma, neuroblastoma, retinoblastoma, Hodgkin lymphoma and Wilms tumour. However, a small majority of publications (n=14) adopted a broader perspective and studied the costs of childhood cancer for more than one type or in general. Of these studies, four also reported costs specified for each type while ten did not differentiate per type.

3.2.3 Study population

The study population was not the same for all studies, with many studies (n=10) not explicitly stating the study population. Eight studies defined a paediatric population as 0-18 or 0-19 years of age, whereas two studies only included 0-14 year olds. Three studies differentiated between paediatric and adolescent and young adult (AYA) patients, of which one defined paediatric as 0-14 years and AYA as 15-17 years.

Table 3. Study characteristics

	Country	Setting	Study period	Diagnosis	Treatment phase	Population	Perspective	Study design	Cost measured	Source of cost data
Academic publications										
Audino et al. (2013)	USA	Multiple institutions	January 1, 2006– December 31, 2010	Bone sarcoma	Active disease	Paediatric and AYA (extracted: data for groups 0-14 years and 15-17 years)	Healthcare system	R/PB [?]	Direct M	Large administrative database of paediatric hospitals
Bartlett & Trasande (2014)	EU	Country-level estimates	2008	Brain/nervous system cancers; Hodgkin lymphoma; leukaemia; non-Hodgkin lymphoma	Various phases	Paediatric (0-14 years only)	Societal	R/IB	Direct M/NM, Indirect	Derived from Barr et al. (2004)
Ghatak et al. (2016)	India	Single institution	January 2013 - December 2013	Acute lymphoblastic leukaemia (ALL)	Induction phase (first month of therapy)	Paediatric	Family	P/PB	Direct M/NM	Cost diaries kept by families
Heath et al. (2006)	Australia	Single institution	Diagnosis in 2002	Leukaemia; solid tumour, non-CNS; brain tumour	12 months after diagnosis	Paediatric	Family	R/PB	Direct M/NM	Survey
Hendrickson & Rimar (2009)	USA	Single institution	October 1999-September 2004	Leukaemia and CNS tumours	First 3 years following diagnosis	Paediatric (0-19 years)	Healthcare system	R/PB	Direct M	Hospital database
Islam et al. (2015)	Bangladesh	Single institution	2010 - 2011	Acute lymphoblastic leukaemia (ALL)	Various phases	Paediatric	Family	P/PB	Direct M/NM	Receipts submitted by families
Ji et al. (2012)	China	Multiple institutions	October 2006 - February 2011	Retinoblastoma	First year of treatment	Paediatric	Family	R/PB	Direct M/NM	Patients' medical bills (M) / interviews with family members (NM)
Kanyamuhunga et al. (2015)	Rwanda	Single institution	January 2010 - December 2011	Wilms tumour	Various phases	Paediatric	Healthcare system	P/PB	Direct M	Survey / hospital tariffs
Kaul et al. 2016	USA	Single institution	January 1998 - December 2012	Acute lymphoblastic leukaemia (ALL)	Various phases	Paediatric and AYA (1-26 years)	Healthcare system	R/PB	Direct M	Hospital database

Liu et al. (2009)	China	Single institution	May 2005 - June 2006	Acute lymphoblastic leukaemia (ALL)	Various phases	Paediatric	Healthcare system	P/IB [?]	Direct M	Hospital database
Pagano et al. (2014)	Italy	Population based: Piedmont region	2000-2005	Hodgkin disease, Wilms tumour, retinoblastoma, gonadic tumours, all other tumours; non-Hodgkin lymphoma central, nervous system, neuroblastoma; malignant bone tumours, soft tissue sarcoma; leukaemia	The 3 years following diagnosis	Paediatric (0-19 years)	Societal (Family)	R/IB	Indirect	Administrative (regional) databases
Stefan & Stones (2008)	South Africa	Multiple institutions	1986-2006	Hodgkin lymphoma (HL)	Treatment for stage 2 disease, and two-year follow-up	Paediatric	Healthcare system	R/PB	Direct M	Hospital databases
Trasande & Liu (2011)	USA	Multiple institutions	2006-2008 (data merged and corrected for costs in 2008)	Not reported	Various phases	Paediatric (<20)	Healthcare system	R/IB	Direct M (incremental)	National databases
Tsimicalis et al. (2012)	Canada	Multiple institutions	November 2006 - March 2008	Leukaemia; lymphomas; CNS; renal tumours; malignant bone tumours; other	The three-month period following diagnosis	Paediatric (0-18 years)	Family	P/PB	Direct M/NM; Indirect	Records kept by parents
Tsimicalis et al. (2013)	Canada	Single institution	November 2006 - March 2009	Leukaemia; lymphomas; CNS; renal tumours; malignant bone tumours; other	The three-month period following diagnosis	Paediatric (0-18 years)	Family (Family Support Network)	P/PB	Direct NM; Indirect	Records kept by parents
Wang et al. (2008)	USA	Multiple institutions	1996 - 2004	Various types; see Table 2 in the article for breakdown	Various phases	Paediatric (<20 years)	Healthcare system	R/PB	Direct M	National survey on medical expenditures

Wedekind et al. (2016)	USA	Multiple institutions	April 2007 - March 2013	Acute lymphoblastic leukaemia (ALL)	The first 30 days following the initial day of admission	Admitted to paediatric hospitals (1-24 years old)	Healthcare system	R/PB	Direct M	Large administrative database of paediatric hospitals
Conference abstracts										
Ahuja et al. (2014)	India	Single institution	2014	ALL, Neuroblastoma, NHL, Bone sarcoma, Wilm's tumour	12 weeks following diagnosis	Paediatric (up to 19 years)	Family	P/PB	Direct M/NM	Records kept by parents/caregivers
Bustamante et al. (2014)	Guatemala	Single institution	2012	Not reported	The three-month period following diagnosis	Paediatric	Family	P/PB	Direct M/NM	Records kept by parents/caregivers
George & Buckle (2014)	England	Multiple institutions	April 2010 - September 2013	Neuroblastoma	Not specified	Paediatric	Healthcare system	R/PB	Direct M	National dataset
Mitra & Candrilli (2011)	USA	Multiple institutions	1997, 2000, 2003, 2006	Acute lymphoblastic leukaemia (ALL)	Not specified	Paediatric (up to 20 years)	Healthcare system	R/PB	Direct M	Nationwide paediatric hospital inpatient database
Non-academic reports										
Anhang et al. (2012)	USA	Multiple institutions	2009	Leukaemias; cancer of brain and nervous system; cancer of bone and connective tissue; other, primary; secondary malignancies; non-Hodgkin's ymphoma; cancer of kidney and renal pelvis; Hodgkin's disease; cancer of thyroid	Hospitili-zation	Paediatric (0-18 years)	Healthcare system	R/PB	Direct M	National database
Australian Institute of Health and Welfare (2013)	Australia	Multiple institutions	2008-2009	Leukaemia; brain; multiple myeloma; bone and connective tissue; non-hodgkin lymphoma; kidney; other	Various phases	Paediatric (0-14 years; AYAs 15-24 also reported but excluded here)	Healthcare system	R/PB	Direct M	National databases

Cancer Council NSW (2007)	Australia	New South Wales region	2005	Not specified	Various phases	Paediatric (0-14 years)	Societal	R/IB	Direct M/NM; Indirect	Databases and literature
Gravestock et al. (2011)	UK	Not reported	Not reported	Not specified	61% diagnosed for > a year, 42% active treatment	Paediatric	Family	R/PB	Direct NM	Survey; focus groups; interviews

IB = incidence-based; M = medical; NM = non-medical; NA = not applicable; P = prospective; PB = prevalence-based; R = retrospective.

The other two studies defined AYA patients as 15-24 or 15-26 years. From the former, only data for 0-14 year olds was extracted while this was not possible for the latter study (Kaul et al., 2016). Another study used a population of patients admitted to paediatric hospitals, whose ages ranged up to 24 years (Wedekind et al., 2016)

3.2.4 Study perspective

The majority of studies did not explicitly state the study perspective, but it could generally be derived from the data presented. A total of nine studies reported the costs for families of a child with cancer, usually from the parents' perspective, but in one study (Tsimicalis et al., 2013) costs were reported for the family support network (FSN) which included grandparents, other family members, partners of one of the parents, neighbours, and unspecified individuals. The other studies investigated costs from a healthcare system (n=13) or societal (n=3) perspective. One study stated to have adopted a societal perspective but only investigated indirect costs for families (Pagano et al., 2014).

3.2.5 Study design

Most studies were prevalence based, only a small number of publications assessed lifetime costs. The study design used in the majority of studies was retrospective and made use of (national) hospital databases or survey data. Publications reporting a prospective design were mostly conducted from a family perspective and involved parents recording costs. Several of these studies used a methodology developed by Tsimicalis et al. (2012) in which parents filled out cost diaries in the two weeks before and three months after diagnosis. In their study design, only four studies in total included sensitivity analyses to examine how sensitive their results were to certain parameters or underlying assumptions.

3.2.6 Types of cost reported

Of the included studies, 20 investigated direct costs, one indirect costs, and four both direct and indirect costs. Studies assessing direct costs included medical costs (n=13), non-medical costs (n=2), or both (n=9). Costs for separate components of direct and indirect costs were reported respectively in 16 and three publications. In some cases, it was unclear if the data represented hospital costs or charges, which complicated comparisons as these can give very different figures. One study (Trasande & Liu, 2011) reported direct costs as incremental costs.

3.3 Cost of childhood cancer

In the following sections, the costs of childhood cancer as found in the literature are reported. Direct and indirect costs associated with childhood cancer were extracted from the selected studies and corrected for PPP (Table 5). Results were categorised and sorted according to cancer type or group using International Classification of Childhood Cancer (ICCC) codes. The original uncorrected costs as provided in the publications (including standard deviations and ranges, when available) can be found in Appendix II.

3.3.1 Note on the comparability of reported cost figures

Before providing an overview of the results, some comments need to be made about the validity and comparability of the results. First, it should be noted that ranges between minimum and maximum reported costs were generally very large, which may be due to the occurrence of (severe) complications in some patients (Liu et al., 2009; Islam et al., 2015) or differences in insurance status or other demographic and socio-economic factors (Wang et al., 2008). Second, comparability of data is complicated by the

variation in methodology between studies. As noted in the previous section, researchers took different perspectives to study costs: some studies only measured out-of-pocket costs. However, medical out-of-pocket costs cannot be not compared to total direct medical costs, since in HIC healthcare is generally free at the point of care and parents only need to pay for over the counter medication or complementary treatments (Heath et al., 2006; Tsimicalis et al., 2012), and in LMIC government institutions or NGOs may provide some medication free of charge (Ahuja et al., 2014; Bustamante et al., 2014). Also, some researchers calculated costs per year, while others used a time frame of a month or several years, or used an incidence-based approach to calculate total (lifetime) costs. In addition, some studies reported costs per stay or total aggregate costs per country, rather than per patient. Lastly, it should be noted that the different types of cancer studied and the varying contexts (e.g. in terms of treatment availability and access to universal health coverage) limited the comparability of the results.

3.3.1 Direct versus indirect

The cost of childhood cancer includes both direct and indirect costs. However, most studies included in this review only reported direct costs or, if they did investigate indirect costs, they did not report mean loss of income in monetary units (e.g. Heath et al., 2006). Only four studies reported direct as well as indirect costs. In each of these studies, indirect costs exceeded direct costs. In Canadian research of families' direct and time costs, the latter accounted for more than 80% of total costs incurred by families (Tsimicalis et al., 2012; Tsimicalis et al., 2013). Moreover, lifetime productivity costs or lost productivity due to premature death were found to be much higher than direct healthcare system costs (Cancer Council NSW, 2007; Bartlett & Trasande, 2014).

3.3.2 Direct medical costs

Most researchers included direct medical costs in their analyses (Table 5). Several of these studies also reported costs for separate components. Although cost categories varied widely, the largest medical cost component was generally hospital care. When hospital care was differentiated into inpatient and outpatient care, the largest proportion of costs was attributed to inpatient care (Wang et al., 2008; Trasande & Liu, 2011; Australian Institute of Health and Welfare, 2013). A second major cost was associated with medication, mainly the cost of chemotherapy. In several studies, medication costs represented 30 to 50 percent of total medical costs (Liu et al., 2009; Ji et al., 2012; Audino et al., 2013; Islam et al., 2015; Kanyamuhunga et al., 2015).

Estimates of the direct medical costs of paediatric cancer varied widely, with total medical costs per patient ranging between around USD 4,000 to treat nephroblastoma in Rwanda (Kanyamuhunga et al. 2015) to almost 200,000 dollars for the treatment of high-risk neuroblastoma in the UK (George & Buckle, 2014). Variation in costs may be due to differences between cancer types. One US publication reported an average hospital cost of USD 40,400 per stay for all types combined, but ranging from USD 10,000 for thyroid cancer to USD 56,000 for leukaemia (Anhang et al., 2012). The most expensive types to treat were found to be leukaemia and cancers of the brain and nervous system (Cancer Council NSW, 2007; Anhang et al., 2012).

Cost estimates were also compared within and between countries. Within the US, where most studies were conducted, medical cost estimates were generally at similar levels. For instance, a study on leukaemia conducted in the USA (Hendrickson & Rimar, 2009) estimated total cost at a level similar to estimates in US reports on ALL (Mitra & Candrilli, 2011; Kaul et al., 2016). Cost estimates for ALL treatment in the USA only

Table 5. Direct and indirect costs of childhood cancer (corrected for purchasing power parity and converted to USD)

Type of cancer	Country	Description	Direct medical costs (US$)	Direct non-medical costs (US$)	Indirect costs (US$)	Study reference
Acute lymphoblastic leukaemia (ALL)	USA	Average per-patient first-year hospitalization costs in 2012	37,924	–	–	Kaul et al. (2016)
	USA	Mean costs for ALL-related stays in 2006	56,517	–	–	*Mitra & Candrilli (2011)*
	USA	Thirty-day median inpatient costs/charges (unclear) per patient	37,827.20	–	–	Wedekind et al. (2016)
	China	Average total expense per patient	24,016[a]	–	–	Liu et al. (2009)
	India	Median direct expenses during first month of therapy	1,882	745	–	Ghatak et al. (2016)
	Bangladesh	Basic treatment cost (paid by the family) (in 2010-2011)*	7,216	2,564	–	Islam et al. (2015)
Leukaemia (unspecified)	Australia	Total health system expenditure 2008-9	25.58m	–	–	*Australian Institute of Health and Welfare (2013)*
	Italy	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	11,790 (5 years at diagnosis); 11,384 (14 years at diagnosis)	Pagano et al. (2014)
	USA	Mean Actual Variable Direct Cost (AVDC) and Actual total cost in the first 3 years of treatment	46,877 (AVDC); 145,505 (total)	–	–	Hendrickson & Rimar (2009)
	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	55,700 (per stay); 3,200 (per day); 385.8m (total)	–	–	*Anhang et al. (2012)*
Multiple myeloma	Australia	Total health system expenditure 2008-9	8.05m	–	–	*Australian Institute of Health and Welfare (2013)*

Hodgkin lymphoma	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	28,400 (per stay); 3,200 (per day); 18.5m (total)	–	–	*Anhang et al. (2012)*
	South Africa	Average total cost of managing HL stage II for the first 2 years	13,034	–	–	Stefan & Stones (2008)
Non-Hodgkin lymphoma	Australia	Total health system expenditure 2008-9	3.08m	–	–	*Australian Institute of Health and Welfare (2013)*
	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	46,900 (per stay); 3,700 (per day); 48.1m (total)	–	–	*Anhang et al. (2012)*
CNS tumours	Australia	Total health system expenditure 2008-9	8.17m	–	–	*Australian Institute of Health and Welfare (2013)*
	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	39,600 (per stay); 3,600 (per day); 154.8m (total)	–	–	*Anhang et al. (2012)*
	USA	Mean Actual Variable Direct Cost (AVDC) and Actual total cost in the first 3 years	29,144 (AVDC); 76,416 (total)	–	–	Hendrickson & Rimar (2009)
CNS tumours and neuroblastoma	Italy	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	8,655 (5 years at diagnosis); 7,436 (14 years at diagnosis)	Pagano et al. (2014)
Neuroblastoma	England	Total costs per patient	188,845 [a] (HRNB patient) 104,813 [a] (newly diagnosed patient)	–	–	*George & Buckle (2014)*
Retinoblastoma	China	Direct costs incurred by patients during first year of treatment	12,266	4,576	–	Ji et al. (2012)
Renal tumours	Australia	Total health system expenditure 2008-9	2.43 mil	–	–	*Australian Institute of Health and Welfare (2013)*

	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	28,900 (per stay); 3,200 (per day); 26.8m (total)	–	–	*Anhang et al. (2012)*
	Rwanda	Direct total cost of treatment	4,145[a] (early stage) - 5,476[a] (advanced disease stage)	–	–	Kanyamuhunga et al. (2015)
Bone tumours	USA	Mean hospital charges	37,465 (0-14 years); 39,357 (15-17 years)	–	–	Audino et al. (2013)
Bone tumours and soft tissue sarcoma	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	28,700 (per stay); 3,700 (per day); 65.2mil (total)	–	–	*Anhang et al. (2012)*
	Italy	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	14,750 (14 years at diagnosis)	Pagano et al. (2014)
Thyroid cancers	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	10,100 (per stay); 4,100 (per day); 5.1m (total)	–	–	*Anhang et al. (2012)*
Other cancers	Australia	Total health system expenditure 2008-9	33.20m	–	–	*Australian Institute of Health and Welfare (2013)*
	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US	35,400 (per stay); 3,300 (per day); 66.4mil (total)	–	–	*Anhang et al. (2012)*
	Italy	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	3,657 (14 years at diagnosis)	Pagano et al. (2014)
Secondary malignancies	USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	23,000 (per stay); 3,300 (per day); 31.9mil (total)	–	–	*Anhang et al. (2012)*
Overall	Australia	Direct: lifetime health system costs per person and other financial costs ; Indirect: parents' annual loss in income, and children's' productivity costs (morbidity + mortality)	94,500[b] (lifetime health system costs per child);	1,318[b] (annual other (NM) financial costs per child); 7900[b] (lifetime costs of other financial costs)	8,021[b] (informal carer productivity loss) 325,800[b] (lifetime productivity costs for children)	*Cancer Council NSW (2007)*

Australia	Total health system expenditure 2008-9	84.81m	–	–	*Australian Institute of Health and Welfare (2013)*
Australia	Direct median out-of-pocket expenses during first 12 months of treatment	746 (total M and NM) [c]		–	Heath et al. (2006)
Canada	Mean (median) total direct and time 3-month costs incurred per Family Support Network	–	603 (median 127)	3,852 (median 2,294)	Tsimicalis et al. (2013)
Canada	Mean (median) total direct and time 3-month costs incurred per family	4,500 (median 2895) (total M and NM) [c]		18,903 (median 19,116)	Tsimicalis et al. (2012)
Austria	Direct: costs per case; Indirect: lost productivity per death due to premature death	128,166[b] (total M and NM)		1,089,198[b]	Bartlett & Trasande (2014)
Belgium		119,957		1,019,437	
Bulgaria		38,776		329,535	
Cyprus		89,057		756,837	
Czech Republic		80,183		681,423	
Denmark		122,905		1,044,490	
Estonia		71,642		608,836	
Finland		116,662		991,43	
France		111,083		944,023	
Germany		113,049		960,725	
Greece		100,229		851,779	
Hungary		64,083		544,599	
Ireland		149,86		1,273,558	
Italy		101,877		865,783	
Latvia		58,172		494,366	
Lithuania		54,877		466,359	
Luxembourg		265,539		2,256,637	
Malta		76,238		647,892	
Netherlands		126,851		1,078,021	

Poland		53,244		452,484	
Portugal		71,642		608,836	
Romania		36,479		310.007	
Slovakia		65,066		55,295	
Slovenia		89,722;		762,49	
Spain		110,751		941,197	
Sweden		121,273		1,030,614	
UK		116,012		985,906	
Italy	Overall median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	9,143	Pagano et al. (2014)
UK	Average extra expenses	–	524 (per month) 6,286 (per year)	–	*Gravestock et al. (2011)*
USA	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	40,400 (per stay); 3,900 (per day); 859.8m(total)	–	–	*Anhang et al. (2012)*
USA	Total annual incremental direct cost per case	138,446	–	–	Trasande & Liu (2011)
USA	Mean annual total health expenditures per patient	3,541.03	–	–	Wang et al. (2008)
Guatemala	Mean direct costs per family	294 (total M and NM) [c]		–	*Bustamante et al. (2014)*
India	Two-week median costs prior to diagnosis; Median weekly costs 12 weeks following diagnosis.	386 (2 weeks prior to diagnosis); 133 (weekly, following diagnosis) (total M and NM) [c]		–	*Ahuja et al. (2014)*

All costs converted to US dollars and corrected for purchasing power parity (PPP); References to conference abstracts and non-academic publications set in *italics*; m = million; * Cost of treatment provided here is the "basic" cost, as only this cost was divided into medical and non-medical. The actual average cost was higher at USD (PPP corrected) 13,435 [a] Costs reported in US dollars: converted back into LCU using historical exchange rates before PPP correction; [b] PPP correction already applied in original article. [c] Only out-of-pocket expenses included in the study.

deviated in a study by Wedekind et al. (2016), in which they were much higher, potentially because the study was based on hospital charges. When looking at medical costs for all types combined, a study by Wang et al. (2008) reported annual health expenditures of around USD 3,000, which is very low compared to another study estimating incremental costs of childhood cancer at around USD 140,000 annually (Trasande & Liu, 2011). However, the former publication reported very large ranges between minimum and maximum expenditures (Wang et al., 2008). Publications reporting overall total health system expenditure on childhood cancer in HIC gave relatively similar figures in Australia (USD 85 million) and in the US (USD 860 million), when taking into account population size (Anhang et al., 2012; Australian Institute of Health and Welfare, 2013). However, between European countries, fairly large differences in direct costs were apparent (Bartlett & Trasande, 2014). It should be noted that this study did not provide figures for the separate medical and non-medical costs but only reported total direct costs, which were estimated based on literature (Barr et al., 2004).

Studies conducted in HIC and LMIC showed striking differences in costs, even after correcting for purchasing power. For instance, treatment costs for ALL are much lower in Bangladesh and China as compared to the US. However, in Bangladesh treatment is paid in full by families due to the lack of national health insurance. In a country where many people are very poor, ALL treatment is often non-affordable which leads to high rates of treatment refusal and abandonment (Islam et al., 2015). Similar results were found in Shanghai, China, where ALL treatment costs per patient were also lower than in HIC (Liu et al., 2009). In this study, local Shanghai children received government support whereas treatment of non-local patients, who constituted the majority of the study population, was paid for by families (Liu et al., 2009). Another study from China investigated direct costs incurred by families of children with retinoblastoma (Ji et al. 2012). The average income in China is approximately 30% of the costs for retinoblastoma as estimated in that study, and Chinese children are not covered by national health insurance programmes, which means that treatment costs can pose a substantial burden upon families (Ji et al. 2012). In Rwanda, treating renal tumours is significantly cheaper than in the US, but late presentation and poor compliance led to higher costs, which were already very high for the Rwandese population even though some patients with Community Health Insurance received financial support (Anhang et al., 2012; Kanyamuhunga et al. 2015). Similarly, treatment for Hodgkin lymphoma was found to be more expensive in the US (Anhang et al., 2012) than in South Africa (Stefan and Stones., 2008), although it may still be unaffordable for South Africans.

3.3.3 Direct non-medical costs

Direct non-medical costs are often not included in studies investigating the costs of childhood cancer (Table 5). Only a handful of studies included total medical as well as non-medical costs (Cancer Council NSW, 2007; Ji et al., 2012; Islam et al., 2015; Ghatak et al., 2016). In three of these publications, non-medical costs constituted between 25 and 30 percent of total direct costs (Ji et al., 2012; Islam et al., 2015; Ghatak et al., 2016). In studies only reporting out-of-pocket costs, non-medical costs constituted a large proportion of total out-of-pocket costs (Tsimicalis et al., 2012; Tsimicalis et al., 2013; Ahuja et al., 2014; Bustamante et al., 2014). Generally, cost of travel to the hospital was the largest cost component, followed by costs for food, accommodation and communication. Tsimicalis et al. (2012; 2013) also reported costs associated with formal care: paying someone to do household work or provide childcare. In a study conducted by a cancer charity for children in the UK (CLIC Sargent), non-medical costs also included additional spending to keep the child occupied, such as toys or games (Gravestock et al., 2011).

In most studies, non-medical costs were found to add up to several thousand dollars each year, thereby posing a significant burden upon families. One study conducted in an Australian hospital reported lower annual out-of-pocket costs when compared to the other studies (Heath et al., 2006). However, this might be due to the exclusion of families from overseas, non-English speaking parents, and those caring for very ill or terminal patients, since these groups may have the highest expenses (Heath et al., 2006). In studies conducted in Guatemala and India, non-medical costs were lower than in the same type of study conducted in Canada, which may be due to the fact that families received support from the government or NGOs, for instance in the form of accommodation and meals free of cost (source: personal communication). However, in spite of this support the combination of medical and non-medical costs associated with their child's cancer might still be prohibitively high for families in LMIC. For instance, in a study conducted in India the monthly expenses were seven times the monthly per capita income, even though seventy percent of patients received partial financial support for medication (Ghatak et al., 2016).

3.3.4 Indirect costs

Indirect costs were addressed in a small number of publications, and only three of these described the separate cost components that made up indirect costs. A publication on cancer costs in the Australian State of New South Wales provided estimates (based on literature) of cost components associated with loss of income due to care for a child with active cancer. In this report, the largest cost was associated with closing or suspending a business, followed by costs associated with a reduction in paid hours. In addition to loss of income, a study conducted in Canada also included time costs based on the time spent doing unpaid activities. These costs constituted the largest part (73%) of indirect costs for parents of a child with cancer (Tsimicalis et al. 2012). The family support network incurred mostly indirect costs related to foregone leisure time (Tsimicalis et al., 2013).

Two studies assessed cancer costs from a societal perspective and included both total direct and indirect costs. One of these studied costs for a region in Australia (Cancer Council NSW, 2007) and the other for countries in the European Union (Bartlett & Trasande, 2014). The latter based the cost estimates on literature (Barr et al., 2004), and used them to study costs of environmental diseases. This article provided the indirect societal cost for children with cancer, which was defined as lost productivity due to premature death, for 27 European countries (Bartlett & Trasande, 2014). Costs varied widely across European countries, with lower costs reported in Eastern European nations (Bartlett & Trasande, 2014). This study only reported indirect costs for children in terms of loss of productivity due to premature death, while the Australian study described productivity costs for parents and caregivers as well as total lifetime productivity costs for children (Cancer Council NSW, 2007). Productivity costs for children (USD 325,800) were higher than for caregivers (USD 8,021 annually). One study only reported indirect costs of childhood cancer (Pagano et al., 2014). In this study conducted in the Piedmont region of Italy, the overall opportunity cost for one of the caregivers (USD 9,143) was similar to the estimate from the Australian study. In the Canadian study by Tsimicalis et al. (2012), time costs for caregivers where higher: around USD 19,000 for two caregivers combined, in the first three months after diagnosis.

4. Discussion

The purpose of this study was to identify and evaluate the current evidence regarding the economic burden of childhood cancer. The economic burden was defined as the sum of all direct (medical and non-medial) and indirect costs associate with cancer in children. In the following sections, the main findings of this study are discussed, as well as strengths and limitations and suggestions for future research.

4.1 Main findings of this review

A total of 25 publications (scientific as well as grey literature) were identified in this review and provided valuable information on the magnitude of the economic burden of cancer in children. Studies assessing the cost of childhood cancer have been performed in several countries, mostly in the United States. A small majority of the reviewed studies assessed the cost of illness for all types of childhood cancer combined while several others specifically investigated one type, which was mostly acute lymphoblastic leukaemia (ALL). Despite differences in methodology that limited comparability (discussed in section 4.1.2), it was apparent that the costs of childhood cancer are significant.

4.1.1 Childhood cancer is associated with a substantial economic burden

The economic burden of childhood cancer was found to be substantial, with total direct cost estimates ranging up to more than USD 100,000 per case (above USD 200,000 even, in some countries), and indirect productivity costs adding up over a million US dollars per patient (Cancer Council NSW, 2007; Bartlett & Trasande, 2014). Indirect costs far exceeded direct costs, which is common in COI studies (Dagenais et al., 2008; Bahadori et al., 2009).

The majority of publications reviewed for this study were focused on direct medical costs. Separate cost components of medical expenses were provided by some authors, with inpatient, outpatient and medication costs most often reported as cost drivers. Medical costs generally accounted for the largest proportion of direct costs and were very high, with ranges up to around USD 190,000 for high risk neuroblastoma (George & Buckle, 2014). The reported costs are considerably higher than those associated with adult cancer: in Australia lifetime treatment costs were USD 94,500 per child compared to USD 29,900 per person of working age, and hospital stays for cancer in the US cost about 2.5 times more for children than for adults (Cancer Council NSW, 2007; Anhang et al., 2012; Anhang et al., 2012b). In these studies, the reason given for higher expenses among children was the difference in types of cancer being treated, with blood cancers (leukaemias and lymphomas) and CNS tumours having high treatment costs per patient. This may be due to more intensive treatment for childhood cancers, and the longer periods of hospitalisation associated with leukaemia and lymphoma (Anhang et al., 2012). The high medical costs associated with childhood cancer can pose a substantial burden upon the healthcare systems of HIC and LMIC, as well as upon families in countries where there is no universal health coverage (e.g. Islam et al., 2015). Although treatment costs were found to be significantly lower in LMIC, in some countries families pay for treatment themselves, which can lead to relatively high rates of refusal or abandonment of treatment (Arora et al., 2007).

Non-medical costs were only taken into account by a minority of authors, even though they can pose a considerable financial burden upon families of children with cancer, both in LMIC and HIC. Families were found to incur several thousand dollars in non-medical costs each year, which mostly comprised travel costs. This is in line with results from a questionnaire study conducted by Eiser and Upton (2007) in which

travel was the largest cost reported by parents of a child with cancer. Non-medical expenses can be a considerable source of financial hardship and stress for families, although the extent may vary due to differences in geographical, socio-economic and health care use factors (Heath et al., 2006; Tsimicalis et al., 2011; Fluchel et al., 2014; Warner et al., 2014).

Indirect costs associated with childhood cancer are a neglected area of study, with only a handful of study reporting some type of indirect cost. The highest indirect costs reported in studies are productivity-related and due to morbidity or mortality among children with cancer. Survivors of childhood cancer often experience adverse health and quality of life outcomes, which can have a considerable impact on their earnings (Guy et al., 2014; Phillips et al., 2015). However, these morbidity costs were only investigated in one of the reviewed studies and were not reported separately from mortality costs (Cancer Council NSW, 2007). Mortality costs of childhood cancer were found to range up to 1 million US dollars per death in Europe, which is more than four times higher than for adult cancers (Bartlett & Trasande, 2014; Hanly & Sharp, 2014). This difference is mostly caused by the difference between children and adults in average years of life lost from cancer (Hankey, 1992). Indirect costs for caregivers were found to be close to USD 10,000 annually, and are related to loss of income and extra time spent caring for the child. A reduction of paid hours or loss of a job due to their child's illness can be devastating for parents already struggling to afford care or pay for non-medical expenses. In addition to parents and caregivers, childhood cancer can also pose a financial burden on other family members and friends (Tsimicalis et al., 2013).

4.1.2. Large variation between studies

The studies included in this review reported widely varying cost estimates. As described in the previous section, costs can vary depending on the type of childhood cancer studied. The context in which the study took place (several studies were restricted to a single institution) and the healthcare system in a country can also affect cost estimates of childhood cancer. Cost estimates may also vary for different years (Lipscomb et al., 2004). Moreover, the discrepancies in costs across studies can be attributed to methodological differences which severely limited comparisons. This heterogeneity in reporting has been noted before, for instance in a systematic review on the economic burden of head and neck cancer by Wissinger et al. (2014), who stated that "truly comparable cost data were sparse in the literature" (see also: Cooper, 2000; Dagenais et al., 2008). The methodological differences encountered during the current review are described briefly in the following section.

Among the studies reviewed, only two publications adopted the societal approach and included all direct and indirect costs. Although estimates from a narrower perspective can be valuable, these do not take into account all costs. For instance, they may look only at out-of-pocket expenses incurred by families. Direct medical costs were included in most studies but non-medical and indirect costs were often not taken into account. Several studies were not explicit about the types of costs included and how they were calculated, and the separate components of costs were not always reported. Also, in some instances it was unclear if the data represented hospital costs or charges, which complicated comparisons. Generally, the use of hospital costs, not charges, is recommended (Barr et al., 2004). Characteristics of the study population were also often not stated clearly, and differences in age groups included may have produced different cost estimates. Prevalence of certain cancer types is different in children 0-14 years than in adolescents (IARC, 2016), and different age groups may also incur different types of costs. For instance, a study examining osteosarcoma treatment costs for children 0-14 years old and 15-17 years old noted a

difference in medication costs between these groups, which the authors attributed to the greater burden of chronic pain in older patients (Audino et al., 2013). Also, most studies reported mean costs while some only provided median costs, which limited comparability. Although the mean is a useful measure for calculations, some authors have stated that the median may provide a better description of actual costs (Cooper, 2000). Lastly, although uncertainties in costs estimates of COI studies can be understood through the conducting of sensitivity analyses, in only four studies such analyses were performed (Cancer Council NSW, 2007; Trasande & Liu, 2011; Bartlett & Trasande, 2014; Pagano et al., 2014).

4.2 Limitations of the study

This study was the first to systematically assess the economic burden of childhood cancer. However, the review was not without limitations. Although efforts were made to enhance comparability, by correcting for purchasing power parities to adjust for price differentials between countries, there was large methodological variation between studies, as discussed in the previous section. These discrepancies between studies limited the interpretation of results and prevented the calculation of pooled results from studies to provide average costs.

Other potential limitations were associated with the design of the review itself. Data sources used were both scientific databases and grey literature sources, in order to enhance the comprehensiveness of the review (Benzies et al., 2006; Mahood et al., 2014). Since several valuable sources were identified through the grey literature search, this can be seen as a strength of the study. However, it should be noted that there are also limitations associated with this strategy, especially related to the small proportion of grey literature that is identified when only looking at the first 100 results, and the potential for retrieving data of lower quality (Mahood et al., 2014; Haddaway et al., 2015). In addition, some authorities such as the Agency for Healthcare Research and Quality (AHRQ) have advised against the inclusion of conference abstracts, "given the variable evidence of concordance between conference abstracts and their subsequent full-text publications" (Balshem et al., 2013). This limitation is recognised, and in order to mitigate the limitations associated with including conference abstracts, authors were contacted in order to provide context on the data, if they were willing to do so.

In addition, inclusion and exclusion criteria used in this study were comprehensive but may still have excluded potentially useful studies. Economic evaluations were excluded, while some studies evaluating treatment protocols for childhood cancer may include cost data useful for the current study. However, generally such studies only investigate the cost of a specific treatment strategy and do not provide data on the overall economic burden. In addition, qualitative studies were excluded that, for instance, only provided the percentage of families experiencing financial hardship (e.g. Limburg et al., 2007). Although such studies could have provided additional information, they did not report costs in monetary units and would thus have further limited comparability. Lastly, potentially useful data from studies older than ten years was not included. However, the current value of this data would be questionable (Dee et al., 2014).

4.3 Suggestions for further research and action

Although methodological variations between studies were large, this review has shown that the economic burden of childhood cancer is high. In the following sections, the policy implications of this finding are discussed and suggestions for future research are made.

4.3.1 Reducing costs and improving access to healthcare

Expenditures on childhood cancer vary between countries, which may reflect issues in access to screening, diagnostics and treatment, as well as the political priority of cancer in children (Aggarwal et al., 2014b). Issues related to affordability and restricted access to treatment and care are often found in resource-limited settings and, especially in combination with late presentation of cancer and the presence of co-morbidities such as malnutrition, may hamper effective treatment (Chirdan et al., 2009). Poorer healthcare provision in developing countries means that patients may need to make long and expensive journeys in order to receive optimal treatment, or even that certain treatments are not available at all. For instance, in a study on Wilms' tumour included in this review, it was reported that patients did not receive radiotherapy as this is not available in Rwanda (Kanyamuhunga et al., 2015). It is known that around eighty percent of people in Africa do not have access to the treatment and care needed for cancer (Barton et al., 2006). However, according to Sullivan et al. (2013), there is reason to be optimistic and the "policy myth that developing countries cannot afford to treat children with cancer needs to be debunked". Appropriate treatment can produce high cure rates (especially for some types of childhood cancer such as Burkitt's lymphoma), thereby resulting in many potential life-years saved and thus in a cost-effective investment (Sullivan et al., 2013). It should be noted that in addition to differences in healthcare systems between LMIC and HIC, outcomes also vary between populations of different socio-economic class, even in high-income countries (Sullivan et al., 2013). A study conducted in Indonesia showed that almost fifty percent of parents from deprived areas refused or abandoned their child's treatment, while this was only 2% in affluent areas (Mostert et al., 2006).

Reducing inequalities and improving affordable access to care requires a further understanding of the underlying reasons for high costs and differences in expenditures. In future research and policy-making, a focus on the drivers of costs could help identify potential targets for cost savings. Relatively simple interventions could make a large difference in costs. For instance, improvement of hospital hygiene conditions and hygiene education for parents may result in significantly lower occurrence of chemotherapy-related complications, which can be a large cost component (Liu et al., 2009). Efforts should also be made to investigate how to reduce costs of medication, which were found to be important cost drivers of childhood cancer treatment in several studies. Although access and affordability of pharmaceuticals is a complex issue, the costs of cancer medicines on the WHO Essential Medicines Lists remain higher than expected and could potentially be reduced (Cameron et al., 2009). Especially in developing countries where families cannot afford treatment, access to appropriate health services should be improved. This can be done through the provision of financial support from non-governmental organisations, or through the development of so-called "twinning" programmes in which cancer centres from different regions cooperate and share best practices (Sullivan et al., 2013). In the long term, however, sector and system reforms are needed to make childhood care affordable to families in developing countries (Sullivan et al., 2013). In HIC where treatment is available at no cost to families, the potentially substantial out-of-pocket costs should be further investigated, as well as the question as to what would be a fair burden on families (Tsimicalis et al., 2011).

4.3.1 Development of standardised costing methods

This study has found that there are major variations in the measurement of childhood cancer costs, which means that their results should be interpreted with caution. Because COI studies on childhood cancer are valuable tools for informing policymakers, it is essential that these studies adequately measure the

economic burden. Therefore, it is recommended that guidelines are developed to standardise the methodology for COI studies on childhood cancer. The establishment of such guidelines is beyond the scope of this review, but a few suggestions can be made. First, if studies aim to provide an overview of the COI, it is important that all types of cost are reported, direct (both medical and non-medical) as well as indirect. Thus, the societal perspective is recommended (Barr et al., 2004). In all studies, the types of costs included should be clearly stated as well as who pays for them. Ideally, costs are reported as mean and median. In this review, psychosocial costs were not taken into account as these are not generally reported in monetary units. However, future research that provides insight into how to quantify such intangible costs would be valuable. Second, it would be valuable if the definition of costs was uniform, using a predefined set of cost categories. An example of such an overview of cost categories can be found in a review by Tsimicalis et al. (2011), although this specific study was only focused on costs for families. Third, it is important that study characteristics such as data sources used and the study population are clearly stated as these can have an influence on outcomes (Cooper, 2000). Fourth, sensitivity analyses should be performed to test the assumptions underlying the analyses (Cooper, 2000). Last, the appropriate time range (e.g. annual) of cost estimates of childhood cancer should be investigated and implemented in studies in order to enable comparisons.

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Supplementary Material

Appendix I – Concept operationalisation

Table S1. Operationalisation of the types of costs related to childhood cancer, based upon the framework by Rice (1967).

Type of cost	Definition[a]	Examples
Direct	Costs that involve an actual monetary exchange	
Medical	Direct costs related to healthcare	Inpatient care Outpatient care Hospital care Room and board Emergency room visits Home health care Physician services Diagnostic tests Chemotherapy Other medication Drug administration Surgery Radiotherapy Focal therapy Blood products Medical devices Medical supplies Complementary and alternative medicine (CAM)
Non-medical	Direct costs related to goods and services consumed because of the illness but not considered healthcare related	Transport Accommodation Communication Food Formal care Clothes Toiletries Gifts
Indirect	Costs reflecting the economic value of consequences for which there is no direct monetary exchange	Production lost due to premature death Productivity losses due to morbidity Parents' loss of income Foregone leisure time Time costs of providing care

[a] Dagenais et al., 2008

Appendix II – Costs as originally reported

Table S2.Direct and indirect costs as originally reported in the selected studies

				Total direct costs			Total indirect costs			
Type of cancer	Country	Currency	Description	Mean / median	SD	Range	Mean / median	SD	Range	Study reference
Acute lymphoblastic leukaemia (ALL)	USA	USD (adjusted to 2013 inflation)	Average per-patient first-year hospitalization costs in 2012	37,924	–	–	–	–	–	Kaul et al. (2016)
	USA	USD (2010)	Mean costs for ALL-related stays in 2006	56,517	–	–	–	–	–	*Mitra & Candrilli (2011)*
	USA	USD	Thirty-day median inpatient costs/charges (unclear) per patient	37,827.20	–	–	–	–	–	Wedekind et al. (2016)
	China	USD (CNY not reported)	Average total expense per patient	11,022.07	6955.28	5,597.04– 49,848	–	–	–	Liu et al. (2009)
	India	INR (2013)	Median direct M/NM expenses during first month of therapy	43,934 (M: 31,471; NM: 12,463)	–	M: 23,749–46,623; NM: 8541–17,625 (IQR)	–	–	–	Ghatak et al. (2016)
	Bangladesh	BDT (2010-2011)	Mean total treatment cost to the family	311,028	–	226,400 (basic cost) - 537,040	–	–	–	Islam et al. (2015)
Leukaemia (unspecified)	Australia	AUD?	Total health system expenditure 2008-9	36.83 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*

	Italy	EUR (2005)	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	–	10,257 (5 years at diagnosis); 9,904 (14 years at diagnosis)	–	9,581–10,689 (5 years); 9,386–10,611 (14 years) (95% CI)	Pagano et al. (2014)
	USA	USD (adjusted to 2007 inflation)	Mean Actual Variable Direct Cost (AVDC) and Actual total cost	46,877 (AVDC); 145,505 (total)	61,907 (AVDC); 130,979 (total)	–	–	–	–	Hendrickson & Rimar (2009)
	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	55,700 (per stay); 3,200 (per day); 385.8m (total)	–	–	–	–	–	*Anhang et al. (2012)*
Multiple myeloma	Australia	AUD?	Total health system expenditure 2008-9	11.59 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*
Hodgkin lymphoma	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	28,400 (per stay); 3,200 (per day); 18.5m (total)	–	–	–	–	–	*Anhang et al. (2012)*
	South Africa	ZAR (2008)	Average total cost of managing HL stage II for the first 2 years	53,178.20	–	–	–	–	–	Stefan & Stones (2008)
Non-Hodgkin lymphoma	Australia	AUD?	Total health system expenditure 2008-9	4.43 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*
	USA	USD	Mean hospital cost and total aggregate costs for US	46,900 (per stay); 3,700 (per day); 48.1m (total)	–	–	–	–	–	*Anhang et al. (2012)*

CNS tumours	Australia	AUD?	Total health system expenditure 2008-9	11.76 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*
	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	39,600 (per stay); 3,600 (per day); 154.8m (total)	–	–	–	–	–	*Anhang et al. (2012)*
	USA	USD (adjusted to 2007 inflation)	Mean Actual Variable Direct Cost (AVDC) and Actual total cost	29,144 (AVDC); 76,416 (total)	58,855 (AVDC); 155,053 (total)	–	–	–	–	Hendrickson & Rimar (2009)
CNS tumours and neuroblastoma	Italy	EUR (2005)	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	–	7,530 (5 years at diagnosis); 6,469 (14 years at diagnosis)	–	5,991–8,166 (5 years at diagnosis, CI); 4,771–7,848 (14 years at diagnosis, CI)	Pagano et al. (2014)
Neuroblastoma	England	GBP	Total costs per patient	130,303 (HRNB patient) 72,321 (newly diagnosed patient)	–	–	–	–	–	*George & Buckle (2014)*
Retinoblastoma	China	USD (CNY not reported)	Direct M/NM costs incurred by patients during first year of treatment	9,422 (M: 6,862; NM: 2,560)	3,709 (M: 3,463; NM: 1,348)	5,060-22,180 (range) (M: 3,290-18,907; NM: 78-7,741)	–	–	–	Ji et al. (2012)
Renal tumours	Australia	AUD?	Total health system expenditure 2008-9	3.50 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*

	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US	28,900 (per stay); 3,200 (per day); 26.8m (total)	–	–	–	–	–	*Anhang et al. (2012)*
	Rwanda	USD (RWF (2011) not reported)	Direct total cost of treatment	–	–	1,831.2 (early stage) - 2,418.7 (advanced disease stage)	–	–	–	Kanyamuhunga et al. (2015)
Bone tumours	USA	USD	Mean hospital charges	37,465 (0-14 years); 39,357 (15-17 years)	–	–	–	–	–	Audino et al. (2013)
Bone tumours and soft tissue sarcoma	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	28,700 (per stay); 3,700 (per day); 65.2m (total)	–	–	–	–	–	*Anhang et al. (2012)*
	Italy	EUR (2005)	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	–	12,833 (14 years at diagnosis)	–	11,029–16,468 (95% CI)	Pagano et al. (2014)
Thyroid cancers	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	10,100 (per stay); 4,100 (per day); 5.1m (total)	–	–	–	–	–	*Anhang et al. (2012)*
Other cancers	Australia	AUD?	Total health system expenditure 2008-9	47.81 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*

	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	35,400 (per stay); 3,300 (per day); 66.4m (total)	–	–	–	–	–	*Anhang et al. (2012)*
	Italy	EUR (2005)	Median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	–	3,182 (14 years at diagnosis)	–	2,386–3,500 (CI)	Pagano et al. (2014)
Secondary malignancies	USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	23,000 (per stay); 3,300 (per day); 31.9m (total)	–	–	–	–	–	*Anhang et al. (2012)*
Overall	Australia	USD (from 2003 AUD, PPP corrected)	Direct: lifetime health system costs per person and (lifetime) other financial costs (NM); Indirect: parents' annual loss in income per child with active cancer, and lifetime productivity costs for children	94,500 (lifetime health system costs per child); 1,318 (annual other (NM) financial costs per child); 7900 (lifetime costs of other financial costs)	–	–	8,021 (informal carer productivity loss) 325,800 (lifetime productivity costs for children)	–	–	*Cancer Council NSW (2007)*
	Australia	AUD?	Total health system expenditure 2008-9	122.13 million	–	–	–	–	–	*Australian Institute of Health and Welfare (2013)*

	Australia	AUD	Direct: median out-of-pocket expenses during first 12 months of treatment; Indirect: income lost	1000	–	–	–	–	Income lost (77% of families): 500-50,000	Heath et al. (2006)
	Canada	CAD	Mean (median) total direct and time 3-month costs incurred per Family Support Network	730 (median 154)	1520	0-10,315	4661 (median 2776)	5497	0-29,061	Tsimicalis et al. (2013)
	Canada	CAD (2007)	Mean (median) total direct and time 3-month costs incurred per family	5,446 (median 3503)	6659	754-51,906	22,873 (median 23,130)	9594	1259-49,236	Tsimicalis et al. (2012)
	Austria	USD (2008) (corrected for inflation and PPP)	Direct: costs per case; Indirect: lost productivity due to premature death	128,166	–	–	1,089,198	–	–	Bartlett & Trasande (2014)
	Belgium			119,957			1,019,437			
	Bulgaria			38,776			329,535			
	Cyprus			89,057			756,837			
	Czech Republic			80,183			681,423			
	Denmark			122,905			1,044,490			
	Estonia			71,642			608,836			
	Finland			116,662			991,43			
	France			111,083			944,023			
	Germany			113,049			960,725			
	Greece			100,229			851,779			
	Hungary			64,083			544,599			
	Ireland			149,86			1,273,558			
	Italy			101,877			865,783			
	Latvia			58,172			494,366			
	Lithuania			54,877			466,359			
	Luxembourg			265,539			2,256,637			

Malta			76,238			647,892			
Netherlands			126,851			1,078,021			
Poland			53,244			452,484			
Portugal			71,642			608,836			
Romania			36,479			310.007			
Slovakia			65,066			55,295			
Slovenia			89,722;			762,49			
Spain			110,751			941,197			
Sweden			121,273			1,030,614			
UK			116,012			985,906			
Italy	EUR (2005)	Overall median opportunity cost of caregiving by one of the parents after 3 years of follow-up	–	–	–	7,954	–	–	Pagano et al. (2014)
UK	GBP (2011?)	Average extra expenses	367 (per month) 4,400 (per year)	–	–	–	–	–	*Gravestock et al. (2011)*
USA	USD	Mean hospital cost (daily and per stay) and total aggregate costs for US in millions	40,400 (per stay); 3,900 (per day); 859.8 million (Total aggregate costs for US)	–	–	–	–	–	*Anhang et al. (2012)*
USA	USD (2008)	Total annual incremental direct cost per case	138,446	–	–	–	–	–	Trasande & Liu (2011)
USA	USD (2004)	Mean annual total health expenditures per patient	3,541.03	SEM: 439.63	0-134,751.00	–	–	–	Wang et al. (2008)

	Guatemala	GTQ (2013)	Mean direct costs per family	1,073	–	–	–	–	–	*Bustamante et al. (2014)*
	India	INR (2014?)	Two-week median costs prior to diagnosis; Median weekly costs 12 weeks following diagnosis	6,565 (2 weeks prior to diagnosis); 2,263 (weekly, following diagnosis)	–	438-20,076; 1071-7102 Rs/week	–	–	–	*Ahuja et al. (2014)*

For this analysis cancer research was defined by means of a complex filter originally devised in consultation with Cancer Research UK and recently updated with the aid of our Spanish partners in the project, the Escuela Andaluza de Salud Publica, S.A.. It consisted of long lists of specialist oncology journals and title words, including the various types of cancer, genes that increase individuals' chance of having particular cancers, and drugs used exclusively for the treatment of cancer. The filter was modified several times in order to improve its precision, p, and recall, r, and the final version had p = 0.95 and r = 0.98. Childhood cancer research filters were as previously described

These were applied to the Web of Science (WoS) and articles and reviews in 31 European countries, see Table 1, were identified and downloaded to files from both the SCI and the SSCI. Five-year citation scores were also obtained for the papers from 2002-09. The details of the papers were transferred to an Excel spreadsheet by means of special macros for analysis, and the downloaded citation files were transformed by another macro so that the paper citation scores could be calculated and then transferred to the papers in the original spreadsheet, which contained details of 282,055 papers.

Table 1. List of 31 countries used to limit the ONCOL papers whose details were obtained.

ISO	Country	ISO	Country	ISO	Country	ISO	Country
AT	Austria	EE	Estonia	IS	Iceland	PL	Poland
BE	Belgium	ES	Spain	IT	Italy	PT	Portugal
BG	Bulgaria	FI	Finland	LT	Lithuania	RO	Romania
CH	Switzerland	FR	France	LU	Luxembourg	SE	Sweden
CY	Cyprus	GR	Greece	LV	Latvia	SI	Slovenia
CZ	Czech Rep.	HR	Croatia	MT	Malta	SK	Slovakia
DE	Germany	HU	Hungary	NL	Netherlands	UK	United Kingdom
DK	Denmark	IE	Ireland	NO	Norway		

The spreadsheet was annotated with 31 additional columns each of which contained the product of the paper's citation score, ACI, with the fractional presence of each country

among its addresses. The sum of these products, divided by the fractional count of the country for the relevant years (in the first instance, the eight years 2002-09), then gave the country's citation score on a fractional count basis, which is more appropriate than the score based on integer counts. These individual country scores could then be compared with the ACI values for the world. These were obtained for each year's ONCOL publications directly from the WoS, although the sets of papers needed to be divided into sub-sets, based on journal initial letters, in order that each one should have no more than 10,000 papers, as this is the limit in the WoS for citation reports.

Then a succession of macros provided for each paper fractional counts of countries from the addresses[2], the research level (1=clinical, 4=basic) based on words in the title (Lewison & Paraje, 2004), the type of research (e.g., chemotherapy, genetics, surgery) and the cancer site (one of 22 selected sites, e.g., breast, lung, prostate)[3]. The identification of the research type(s) and cancer site(s) for each paper was performed by two further macros, each based on sub-filters created in consultation with Professor Richard Sullivan of KCL that consisted of title word strings and (for many of them) journal name strings. Table 2 lists the research types, with four-letter (tetragraph) codes and Table 3 the cancer manifestations, which corresponded closely to the ones listed in the recently-published world disease burden estimates (Murray et al., 2012).

Table 2. List of research types in cancer research defined by sub-filters.

Research type	Code	Research type	Code	Research type	Code
Chemotherapy	CHEM	Palliative care	PALL	Radiotherapy	RADI
Diagnosis	DIAG	Pathology	PATH	Screening	SCRE
Epidemiology	EPID	Prognosis	PROG	Surgery	SURG
Genetics	GENE	Quality of life	QUAL		

[2] For example a paper with two French addresses and one from Germany would be classified as FR = 0.67, DE = 0.33.

[3] Not all papers could be linked to a cancer site or to a research type, but some had more than one.

Table 3. List of 22 cancer manifestations (body sites) for which sub-filters were developed to identify relevant ONCOL papers.

Site	Code	Site	Code	Site	Code
bladder	BLA	liver	LIV	pancreas	PAN
bone	BON	lung, trachea, bronchus	LUN	prostate	PRO
brain	BRA	lymphoma	LYM	stomach	STO
cervix	CER	breast	MAM	testicles	TES
colon / rectum	COL	melanoma	MEL	thyroid	THY
gallbladder	GAL	mouth (head & neck)	MOU	uterus	UTE
kidney	KID	oesophagus	OES		
leukaemia	LEU	ovaries	OVA		

A recent publication by the World Health Organization provides detailed estimates of the burden of disease (both deaths and Disability-Adjusted Life Years, DALYs) for each country and for many individual diseases for the year 2010. The data are provided both as different-sized rectangles within a square representing a country's (or region's, or the whole world's) total disease burden, and they can also be downloaded to file. We did this for the 31 countries of the European region, and for the disease areas relevant to this study; the data selected were for all ages and both sexes. They are in the form of percent of total DALYs for the country, and were then multiplied by the DALY total to give the DALYs for each disease and country. These could then be added to give the total for the EUR31 region, and the pattern of disease burden for each country compared with the European average. For some diseases, the differences were not great, but for others there were big variations in relative burden between countries. For cancer, data were provided on some 24 different manifestations, not all of which corresponded to our analysis of sites (see Table 3 above). However DALYs were provided for 13 sites whose details are given in this paper.

Results

Outputs of cancer research papers by European countries.

For each of the original 31 countries, we determined the integer and fractional count totals, and the numbers in each of the 12 years; we also detemined the annual average percentage

growth rate (AAPG) based on fractional counts. [This was obtained from a plot of the logarithm of the number of papers each year.] Table 4 lists the results: since research output tends to be correlated with Gross National Product (rather than simply with population), we have plotted the countries' fractional paper counts against GDP for a representative year in Figure 1.

This table shows that there are big differences in output, with more than three orders of magnitude between the largest (Germany) and the smallest (Malta). However, some of the smaller countries are expanding their output rapidly – notably Romania, whose fractional count output rose from only 7 papers in 2002 to over 250 in 2013. The comparison with GDP suggests that some countries are publishing much more than their wealth would suggest, notably Iceland (x 2.8), Croatia (x 2.5), Slovenia (x 2.2) and Greece (x 2.0). On the other hand, some other countries are doing much less research than expected, such as Luxembourg (29%), Latvia (40%), Cyprus (53%) and France (62%).

Table 4. Outputs of 31 European countries in cancer research (ONCOL), 2002-13 (12 years) in both the SCI and SSCI. Integer (Int) and fractional (Frac) counts, % foreign contribution and the annual growth rate (aapg). Countries are ranked by fractional outputs. Codes: see Table 1.

Country	Int	Frac	% for	AAPG		Country	Int	Frac	% for	AAPG
DE	60456	45436	24.8	2.6		IE	3367	2247	33.3	9.3
IT	48499	37876	21.9	4.8		PT	3136	2079	33.7	13.3
UK	52465	37541	28.4	2.4		HU	2855	1897	33.6	3.2
FR	40329	30127	25.3	4.1		HR	1720	1429	16.9	9.7
NL	23572	16068	31.8	4.5		RO	1748	1248	28.6	35.7
ES	21453	15654	27.0	7.6		SI	1298	898	30.8	10.6
SE	14881	9205	38.1	2.0		SK	1196	755	36.9	6.6
PL	9699	7543	22.2	10.0		BG	673	453	32.6	10.4
GR	9513	7243	23.9	3.8		LT	396	265	33.0	16.4
CH	12827	6837	46.7	4.1		IS	509	208	59.1	3.7
BE	10891	6253	42.6	2.9		LU	259	116	55.3	14.6
AT	8971	5563	38.0	1.1		EE	208	97	53.2	4.0

DK	7692	4713	38.7	8.0		LV	191	86	55.2	7.3
NO	6650	4054	39.0	6.2		CY	198	79	60.1	18.0
FI	6015	3721	38.1	0.0		MT	51	22	56.5	12.1
CZ	4422	3005	32.0	9.2						

It is also expected that researchers in the scientifically larger countries (e.g., UK, Germany) would find it easier to work with a partner within the country that provided complementary expertise than researchers from small countries (e.g., Estonia, Ireland) and would therefore tend to collaborate less internationally. However we might expect that international transnational links would be much weaker for the Member States in eastern Europe, and so Figure 2 has been plotted to show if this is the case. The figure shows that these "accession" Member States do indeed collaborate less than expected, whereas the five Scandinavian countries, with Belgium, Luxembourg and Switzerland, collaborate internationally more than the trend-line would suggest.

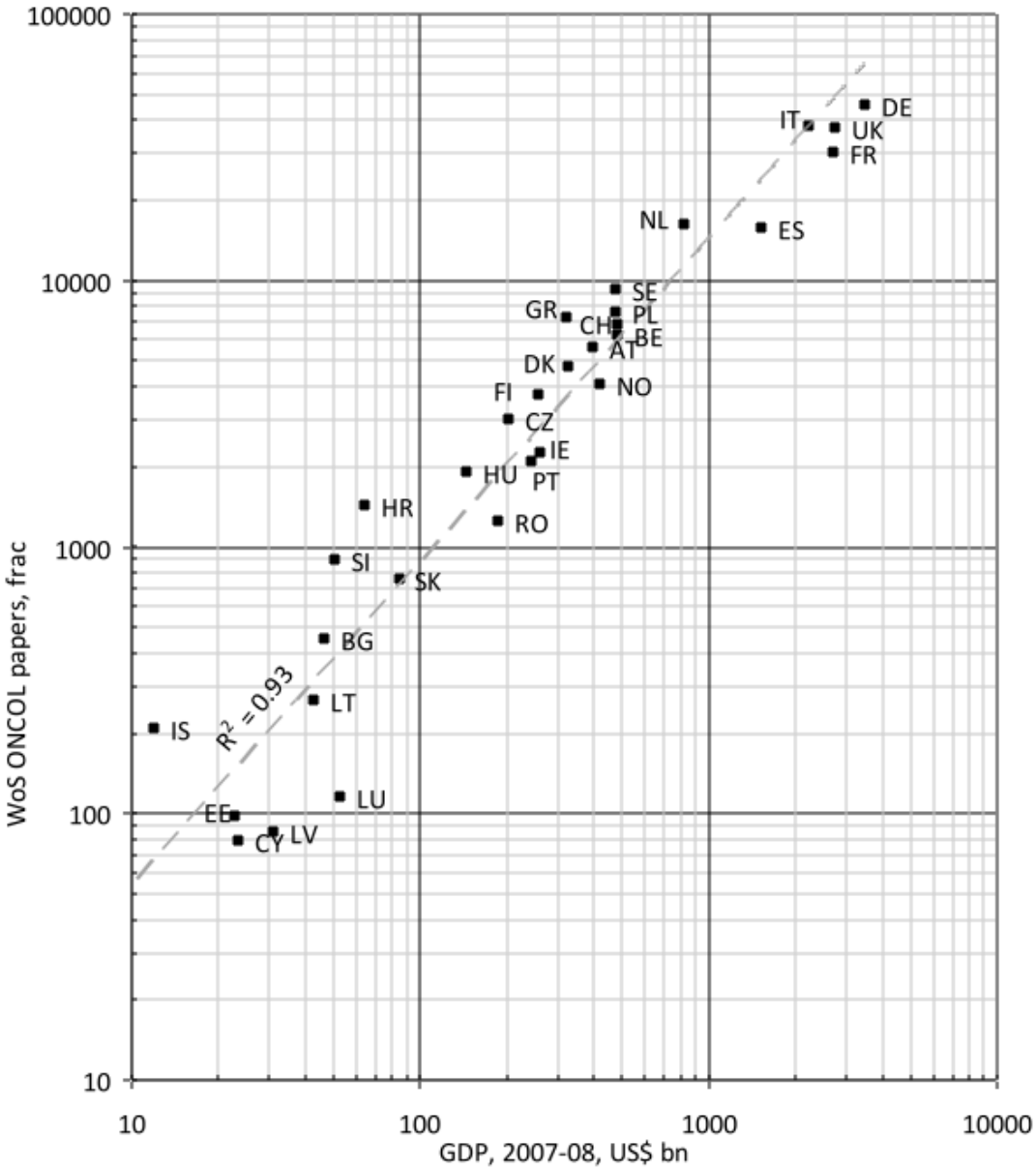

Figure 1. Plot of cancer research output, 2002-13, against GDP for European countries.

Note: MT omitted.

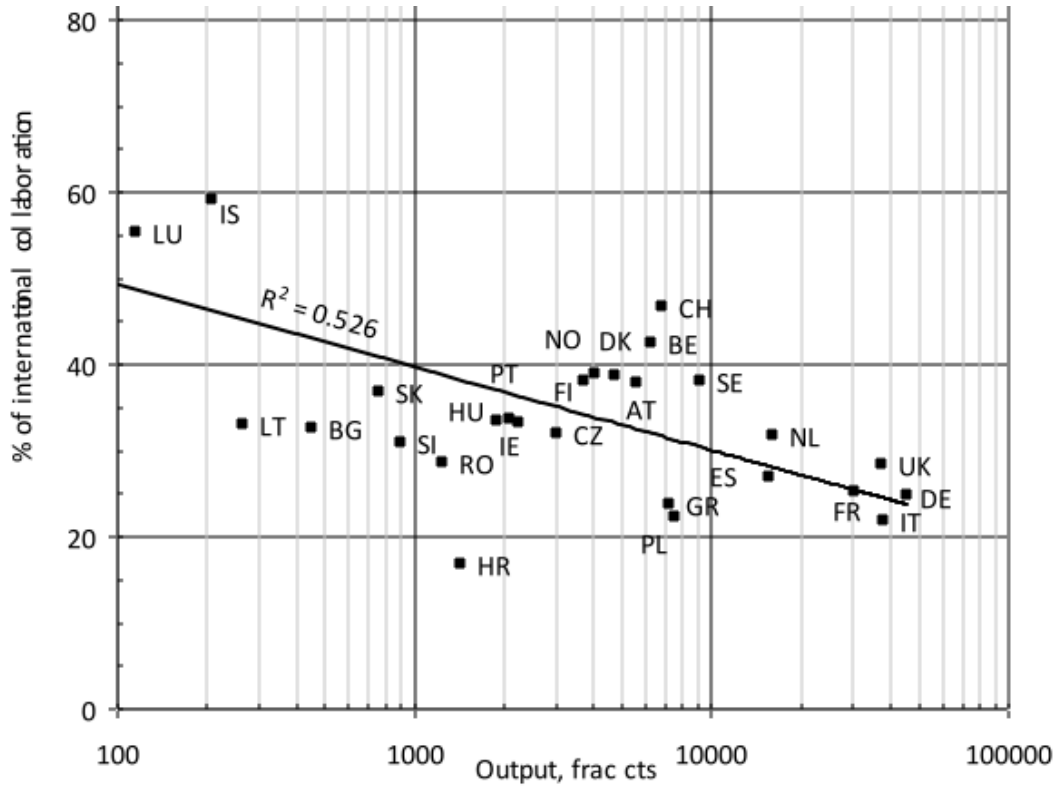

Figure 2. Percentages of international collaboration in cancer research, 2002-13, by European countries plotted against their output (fractional counts of papers).

Citation scores and percentage of reviews

Citation scores in most subject areas have been increasing slowly with time, in part because the WoS now covers more journals than previously, and also because authors are expected to be more punctilious in their acknowledgement of earlier work. Figure 3 shows the progression in cancer research ACI scores from 2002 to 2009; the values for intermediate years (2003-08) for Europe are shown as three-year moving averages in order to smooth out annual fluctuations. The mean score for Europe was slightly below the world average in 2002-03, but since 2006 it has been slightly higher, partly because of the greatly increased world presence of China, whose papers tend to be less well cited than average. Its papers have been becoming slightly more clinical (RL p), although the journals in which they have been published have altered little in terms of research level (RL j), Figure 4.

The mean citations per paper for the EUR31 countries are shown in Table 5. This also shows how many of a country's papers received enough cites to put them in the top 5% of EUR31 papers in the eight-year period, for which the qualification was 53 cites. [There were actually 5.15% of European papers that achieved this number of citations.] This may be a better measure of how effective a country's research output is because it is normally the most influential papers that are really important to the development of a field.

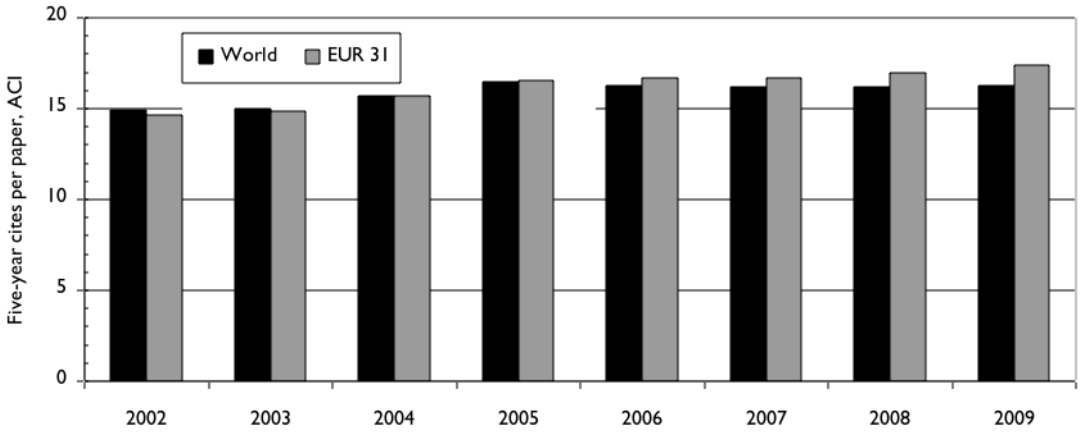

Figure 3. Mean values of five-year citation counts for world and EUR31 papers, 2002-09.

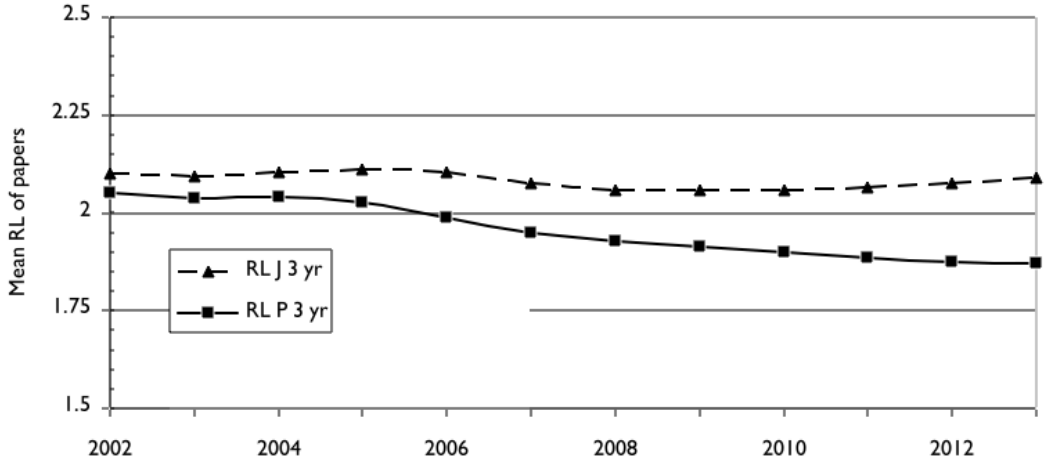

Figure 4. Mean research level of cancer papers from EUR31 countries, 2002-13. RL = 1 is clinical; RL = 4 is basic research

Table 5. Citation performance of EUR31 countries in 2002-09, ranked by the percentage with 53 or more cites in the five years following publication (ACI) (Top) rather than the mean value.

ISO	Mean	Top	%		ISO	Mean	Top	%		ISO	Mean	Top	%
CH	10.8	280.1	6.67		FR	10.9	763.0	4.12		CZ	6.8	27.4	1.66
NL	13.8	603.1	6.17		ES	10.8	366.3	4.11		BG	4.1	3.3	1.27
UK	13.5	1469.1	6.14		IT	11.4	905.5	3.96		PL	6.2	50.9	1.25
IS	8.8	6.9	5.83		IE	9.8	47.0	3.74		RO	3.9	4.3	1.05
BE	10.6	216.6	5.44		NO	9.5	86.3	3.61		LT	3.7	1.2	1.05
DK	11.0	139.2	5.30		LV	4.6	1.5	3.25		SI	5.3	4.1	0.83
FI	10.9	117.4	4.74		PT	8.2	30.9	3.17		EE	4.1	0.3	0.60
SE	10.3	267.7	4.51		GR	7.6	89.9	1.93		MT	2.5	0.1	0.50
AT	10.0	158.0	4.37		CY	4.5	0.7	1.89		HR	4.4	3.7	0.47
LU	7.6	2.4	4.26		HU	6.5	21.7	1.81					
DE	11.1	1211.5	4.22		SK	5.6	7.7	1.75					

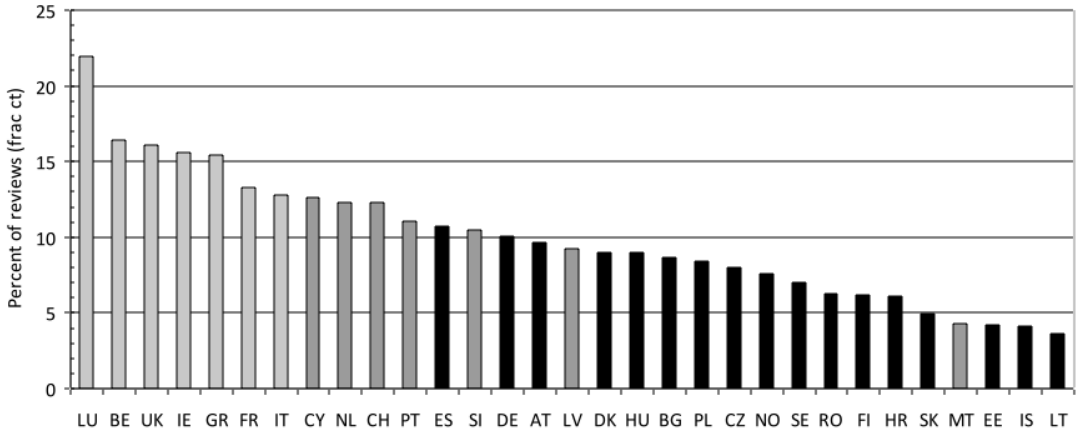

Figure 5. Percentage of reviews among cancer research papers of EUR31 countries, 2002-13. Bars shaded light grey: significantly above EUR31 average; bars in black: significantly below EUR31 average; striped bars: not significantly different from average.

Types of research

The numbers and percentages of papers of the 11 research types listed in Table 2 are shown in Table 6 for the 10 leading European countries in terms of fractional count output.

Table 6. Outputs of papers from 10 leading European countries in 11 different types of cancer research, 2002-13, and their relative commitment compared with the European average. Countries ordered by their fractional count totals.

Values > 2 shown in bold and large type, values > 1.41 in bold, values < 0.71 in italics, values < 0.5 in small italics.

	GENE	CHEM	PROG	SURG	PATH	EPID	RADI	DIAG	SCRE	PALL	QUAL
EUR	48259	28240	27189	26585	19119	12836	12085	11334	3437	3152	1369
%	19.1	11.2	10.8	10.5	7.6	5.1	4.8	4.5	1.4	1.2	0.5
DE	1.03	0.88	0.94	1.09	1.09	*0.69*	1.07	1.12	*0.61*	*0.70*	0.82
IT	0.86	1.35	0.94	1.17	0.96	0.89	0.73	0.93	0.74	0.84	*0.49*
UK	0.96	0.84	1.02	1.03	0.91	1.10	0.97	0.92	1.32	*1.62*	*1.50*
FR	0.85	1.11	0.92	1.06	0.88	0.94	1.17	0.92	0.89	*0.65*	*0.58*
NL	0.97	0.99	1.13	1.07	0.99	1.28	1.76	1.03	*2.07*	1.32	*2.24*
ES	1.12	1.08	1.05	0.75	1.07	0.92	*0.60*	1.11	0.93	0.89	0.78
SE	1.31	0.74	1.31	0.67	0.78	*2.26*	1.08	0.90	1.17	*1.79*	*1.92*
PL	1.28	0.91	0.73	0.74	0.98	0.94	0.83	1.00	*0.45*	0.74	*0.64*
GR	0.99	*1.42*	1.01	1.08	0.98	0.79	*0.70*	0.97	*0.65*	0.94	0.87
CH	0.86	0.94	0.91	0.92	1.08	*0.64*	1.22	1.27	*0.61*	0.74	*0.62*

Screening, palliative care and quality of life research receive little attention, although the UK is prominent in the latter two, as are Sweden and the Netherlands.

Research on different cancer sites

The table below shows values only for the 13 leading cancer sites, but they account for 86% of the papers on any one of the 22 sites listed in Table 3. Breast cancer is the site of greatest research interest, but it accounts for fewer DALYs than colorectal cancer and many fewer than lung cancer in all European countries.

Table 7. Outputs of papers from 10 leading European countries on 13 different cancer sites, 2002-13, and their relative commitment compared with the European average. Countries ordered by their fractional count totals.

Values > 1.41 shown in bold, values < 0.71 in italics, values < 0.5 in small italics.

	MAM	COL	LEU	LYM	PRO	LUN	LIV	STO	BRA	MEL	MOU	KID	OVA
%	9.15	6.17	5.26	4.22	4.04	3.68	3.46	3.40	3.39	3.28	2.33	1.95	1.93
DE	0.75	0.85	1.07	1.05	1.06	0.81	1.16	1.19	1.24	1.12	1.04	1.22	0.78
IT	0.92	0.93	1.08	1.09	0.89	1.15	1.34	1.03	1.10	1.04	0.82	0.90	1.06
UK	1.19	1.15	0.92	0.87	1.09	0.80	*0.68*	0.77	0.83	0.85	1.23	0.83	1.08
FR	0.92	0.89	1.00	1.14	0.99	1.14	1.24	0.92	0.99	0.89	*0.61*	1.35	0.85
NL	1.09	1.33	0.81	0.75	1.10	1.20	0.80	1.03	0.80	1.00	1.52	0.86	0.84
ES	0.99	1.10	0.99	1.25	0.78	1.24	1.18	0.97	1.00	0.95	1.19	1.05	*0.69*
SE	1.17	1.14	1.07	0.87	*1.61*	*0.67*	*0.52*	0.83	1.12	0.85	*0.71*	0.74	0.96
PL	1.01	0.93	*1.43*	*0.71*	*0.47*	1.19	*0.62*	1.16	0.83	1.07	*0.64*	0.96	*1.93*
GR	1.23	1.07	0.88	1.25	0.82	*1.56*	1.03	1.40	*0.71*	*0.67*	1.15	0.85	*1.64*
CH	0.84	0.72	0.73	1.20	0.90	1.01	0.94	*0.65*	1.22	1.38	1.28	0.81	0.63

The correlation between country relative research commitment, as shown above, and its disease burden in DALYs is poor for almost all countries, and is only positive for Italy and France. Prostate cancer, which accounts for almost as many deaths among men as breast cancer does among women, receives far less research attention, although Sweden has a rather high relative commitment to research on the site.

Policy Issues

The tables and figures shown here provide a sample of the data available in the full database, which can be used as contextural and structural analysis for childhood cancers. But already it is clear that the European cancer research portfolio, although very extensive, does not reflect the burden of disease in the different countries, nor a balance between childhood and adult cancers, and that some research domains are relatively neglected by most countries – in particular, those pertaining to end-of-life issues such as palliative care and quality of life. There may well be interactions with mental disorders, and there is an increasing amount of research that covers both these two sub-fields (Purushotham et al., 2013) but the clinical need underlying this research has not been sufficiently explored. There is also a relative paucity of research on radiotherapy and surgery, compared with chemotherapy, and of research on lung cancer, which causes the greatest burden of disease from cancer in Europe.

Implications for national policy. UK – most heavily funded EU country, yet of the top four (with DE, IT and FR) its outputs have grown at a more modest rate. Not simple linear relationship between funding and research activity. Also of note that 'old Europe' has it's research more heavily cited and thus it has greater global influence than research from CEE. This is bound to have a dominance effect in childhood cancers. Although in macroeconomic terms a countries GDP is clearly heavily correlated with it's overall outputs in cancer research, whether that funding is from public or private sources. Clear that 'old European' countries dominate the cancer research landscape with 30-35 times the research activity compared to countries from 'new Europe'. However, many of these latter countries such as Poland and Romania have high annual growth rates in their outputs indicating their potential for increasing their childhood cancer research. Furthermore countries with a smaller mass of cancer research are more inclined to engage with international partners.

Despite avowed drive to translational and clinical research the research outputs for Europe as a whole are becoming more fundamental – link to FP's, IMI, national policies; whether this

is ‘good’ or ‘bad’ for childhood cancer is a debatable issue. This finding is further reinforced when one reflects on the type of research activity from the ten leading EU countries. Fundamental cancer biology and drug development (GENE+CHEM+PROG) dominated with 40.1% of total research activity over the last decade, with the main modalities of care and control – cancer surgery (SURG) and radiotherapy (RADI) constituting only 10.5% and 4.8%, respectively. However, these figures tower over the research outputs in early diagnosis (DIAG+SCRE) and supportive and palliative care (PALL+QUAL), with only 5.9% and 1.7% respectively. Although the NL, SE and UK at a national level buck this trend. This points to a serious disconnection between public policy, the needs of cancer patients and European cancer research portfolio, however.

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