International Journal of *Environmental Research and Public Health*

MDPI

Review

Neoplastic Disease: Which Costs in relation to Disability-Adjusted Life Years? A Systematic Review and Meta-Analysis

Jacopo Garlasco [1], Mario Cesare Nurchis [2,*], Valerio Bordino [1], Martina Sapienza [3], Gerardo Altamura [3], Gianfranco Damiani [2,3] and Maria Michela Gianino [1]

[1] Department of Public Health Sciences and Paediatrics, University of Turin, Turin, Italy; jacopo.garlasco@unito.it (J.G.); valerio.bordino@unito.it (V.B.); mariola.gianino@unito.it (M.M.G.)
[2] Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; gianfranco.damiani@unicatt.it
[3] Department of Health Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy; martina.sapienza93@gmail.com (M.S.); gerardoaltamura@outlook.it (G.A.)
* Correspondence nurchismario@gmail.com; Tel.: +39 0630154396

Abstract: Neoplasms currently represent a leading cause of morbidity and mortality, and precisely estimating their burden is crucial for evidence-based decision-making. To understand average costs of neoplasm-related disability-adjusted life years (DALYs) and to highlight possible differences in economic estimates obtained with diverse approaches. We searched four scientific databases to identify all the primary literature simultaneously investigating neoplasm-related costs and DALYs. In view of the different methodologies, studies were divided into two groups: those estimating costs starting from DALYs, and those independently performing cost and DALY analyses. The latter were pooled to compute costs per disease-related DALY: meta-analytic syntheses were performed for total costs and indirect costs, also in relation to the corresponding gross domestic product (GDP) per capita. The quality of included studies was assessed through the Quality of Health Economic Studies instrument. Seven studies were selected. Total and indirect pooled costs per DALY resulted to be, respectively, $9,150 [95%CI: 5,560-15,050] and $3,890 [95%CI: 2,570-5,880]. Substantial heterogeneity was found among different contexts. Costs a priori calculated from DALYs may lead to results widely different from those obtained after data retrieval and model building. Further research is needed to better estimate the economic burden of cancer in terms of costs and DALYs.

Keywords: cost-per-DALY ratio; Health Policy; cancer; chronic diseases; systematic review

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Int. J. Environ. Res. Public Health* **2021**, *18*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Firstname Lastname

Received: date
Accepted: date
Published: date

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Cancer is widely recognized as a global problem for incidence, mortality, years of life lost and years lived with disability. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding non-melanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding non-melanoma skin cancer) occurred in 2020 (Sung et al., 2021). Furthermore, in 2017 cancer caused a global burden of 226.5 million years of life lost and 7 million years lived with disability (Fitzmaurice et al., 2019). Cancer causes health, financial and socioeconomic problems (including expenditure for medical and non-medical services, loss of productivity, and disability), thereby entailing issues at an individual, family and social level.

Measuring the burden of disease related to cancer is a crucial topic for a public health system, as such an evaluation is fundamental to assess the health status of a country and to make comparisons between countries possible (Brown, Lipscomb, & Snyder, 2001). The importance of establishing the disease burden related to cancer as precisely as possible is also dictated by the need to properly allocate the resources available to the national health system for the treatment and prevention of this diverse group of diseases.

Previous studies have used disability-adjusted life years as a measure of the epidemiologic burden of different cancers (Mattiuzzi & Lippi, 2020). The disability-adjusted life-year (DALY) is a health metric combining morbidity and mortality of a disease, as it represents the sum of years lived with disability (YLD) and years of life lost (YLL) (C. J. Murray, 1994; Oostvogels et al., 2015). Expressing disease burdens in DALYs allows comparing different diseases and therefore represents a useful tool for evidence-based healthcare policy-making (Chao, 2020; C. J. L. Murray & Acharya, 1997).

Premature deaths and disability from cancer result in substantial economic costs to the patients, their family and the community as a whole. Therefore, cancer-related DALYs cancer place an enormous burden on national economies. The American Cancer Society estimated that the total economic impact of DALYs from cancer worldwide attained $895 billion in 2008: this figure, which does not include direct costs of treating cancers, represents 1.5% of the world's gross domestic product (GDP) (American Cancer Society, 2010). National costs for cancer care in the United States (U.S.) were estimated to be $190.2 billion in 2015 and $208.9 billion in 2020, with a 10% increase that was found to be primarily justified by the aging and growth of the U.S. population (National Cancer Institute, 2019). Other analyses estimated a direct health expenditure around €58 billion in five European countries only (France, Germany, Italy, Spain and United Kingdom) (Schlueter, Chan, Lasry, & Price, 2020).

Correctly estimating the economic value of cancer-related DALYs should be an important goal for healthcare systems, especially considering that currently 30-50% of cancers can be prevented by avoiding risk factors and by implementing the existing evidence-based prevention strategies. The cancer burden can be also reduced through early cancer detection, appropriate treatment and care of patients who develop cancer (World Health Organization (WHO), 2021). Evaluating the economic burden of cancers would thus lead to better understand the potential economic benefits of such prevention or therapy strategies.

However, the exact economic impact of cancer is not completely understood, even because multiple methodologies have been adopted to estimate the value of DALYs ascribable to cancer, sometimes relying on the assumption that each DALY could be a priori valued at one year's GDP per capita of the nation under investigation (Jimenez de la Jara et al., 2015).

With that in mind, this study aimed at assessing the average cost per DALY of cancer by revising the currently available literature. As different methodologies have been used over time to evaluate the health and economic burden attributable to specific types of cancer worldwide, we also compared the different approaches adopted in the studies, in order to detect possible fluctuations in the magnitude of the obtained estimates.

2. Materials and Methods

2.1. Preliminary considerations

This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021). Approval by an Ethical Board was not required because all collected and analyzed data were retrieved from previously published studies, and our study included no individual patient data. This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42021278753).

2.2. Eligibility Criteria and Study Selection

A systematic literature search was conducted among articles published from inception to March 1st, 2021 in order to identify studies evaluating the economic impact of neoplasms (in terms of direct and/or indirect costs sustained by individuals and/or by institutions due to the disease), in relation to attributable DALYs. We included all primary research contributions providing economic analyses that included figures related to the abovementioned metrics (whether computed, estimated or retrieved from available databases), related to neoplasms. In particular, any observational or experimental study meeting these inclusion criteria was to be considered eligible, as well as any primary economic evaluation, while systematic reviews and other review-type studies were excluded from the analysis.

2.3. Literature Search

A comprehensive search strategy developed by a skilled researcher with background in economics involved searching the following electronic bibliographic databases: Medline, Web of Science, Ovid Embase and Scopus (strings reported in the Supplemental Material). Furthermore, potential additional studies were identified by "hand searching" references from the selected articles (i.e. snowball searching).

2.4. Outcomes

The primary outcome assessed was the cost-per-DALY ratio. However, as this outcome is not always provided for by this kind of studies, costs and DALYs related to the disease were considered as possible surrogate outcomes, useful to compute the cost-per-DALY ratio for the quantitative synthesis. Additional outcomes included components of the disease-related expenditure (i.e., direct and indirect costs).

2.5. Data Extraction

Each title and abstract was independently screened by two of the authors. Full-texts of all the articles identified as relevant were then assessed for eligibility. Two authors, independently and in duplicate, identified studies that met inclusion criteria and extracted data through a predetermined data collection form (Supplementary Material). Consensus on extracted data was reached by discussion, and disagreements were sorted out through arbitration by a third author.

Information extracted from the studies included publication year, country, years along which cost analyses and DALY computations were performed, aim, scope (national, international or global), study design, number of included patients/simulations, currency (and corresponding year), presence/absence of age-weighting and/or discounting (and corresponding parameters, where present), data sources for costs and DALYs, perspective (societal, governmental or healthcare system-based).

Given that no ready-to-use data about the cost-per-DALY ratio was available in any of the eligible studies, crude estimates about costs (both direct and indirect) and DALYs of the relevant neoplastic disease were also extracted, along with their 95% confidence intervals (CIs) where available. For studies with data specifically referred to a country (or a group of countries), the GDP per capita of those countries (in the corresponding year) was also retrieved from the World Bank Data Catalog (The World Bank, 2010).

In view of the different methodologies used for the economic evaluation, articles were divided into two groups: a first group, encompassing studies where cost and DALY estimates had been extracted independently, and not based on previous estimates of the cost-per-DALY ratio itself, and a second group, including studies that opted for a reverse approach and calculated costs based on DALYs. Only the first group was used for the quantitative synthesis of the cost-per-DALY ratio, so as to estimate this parameter by using directly retrieved data. On the contrary, articles of the second group were used as a comparison term for the projection of possibly determined differences in estimates.

2.6. Quality assessment

The quality of included studies was evaluated using the Quality of Health Economic Studies (QHES) instrument, a tool specifically developed (Chiou et al., 2003) and validated (Ofman et al., 2003) for economic evaluations (Walker et al., 2012), which yields a score ranging from 0 (lowest quality) to 100 (highest quality). Since two of the questions were not suitable for the risk-of-bias assessment of the included studies, the maximum obtainable score was correspondingly 86 points, thus the continuous scale was categorized in four groups: extremely poor quality (0–21), poor quality (22–43), fair quality (44–65), and high quality (66–86).

2.7. Statistical analysis

For each study, average estimates were retrieved for both costs and DALYs, along with their 95% confidence intervals (CIs) where available. In the absence of reported uncertainty measures, the 95% CIs were estimated by applying a Monte-Carlo simulation method, with a number of simulations equal to the population (or number of virtual simulations) from which data were extracted (Weir et al., 2018).

All cost-related data were converted to US Dollars (USD) according to the Purchasing Power Parities (PPP) provided by the Organization for European Co-operation and Development (OECD) (Organisation for European Co-operation and Development, 2020), and subsequently discounted to 2018 USD (as the most recent evidence was based on 2018 data) through an on-line inflation calculation tool (Coin News, 2021) based on US Consumer Price Index Data (U.S. Bureau of Labor Statistics, 2021).

As the meta-analytic estimate was based on a ratio (between costs and DALYs), logarithmic transformation of this parameter was performed prior to CI estimation and meta-analytic synthesis: this process was intended to deal with the a priori expected skewed distribution, as commonly acknowledged for ratio distributions like odds ratios and relative risks (Higgins, White, & Anzures-Cabrera, 2008; Katz, Baptista, Azen, & Pike, 1978).

The R package "meta" (version 5.0-0) was used for the meta-analytic computation and plotting (Balduzzi, Rücker, & Schwarzer, 2019). As required when high heterogeneity is a priori expected (Borenstein, Hedges, Higgins, & Rothstein, 2010) (here data were drawn from different countries, and thus from different contexts), the analysis was performed using a random effects model according to DerSimonian and Laird (DerSimonian & Laird, 2015). The synthetic result was reported as an estimate of the cost-per-DALY ratio (equal to the exponential of the meta-analytic mean of the logarithms, computed through the "metamean" function), along with its 95% CI (evaluated through the standard normal distribution method). Study weights were generated using the inverse variance method. Heterogeneity among studies was assessed using the I^2 statistic (threshold level for significant heterogeneity: ≥50%) and the chi-squared test for homogeneity (significance level for heterogeneity: $p<0.1$) (Higgins, Thompson, Deeks, & Altman, 2003).

Since one of the studies was conducted within a different economic context (Unar-Munguía, Meza, Colchero, Torres-Mejía, & de Cosío, 2017), a post-hoc sensitivity analysis was conducted through computation of the average cost-per-DALY ratio by excluding that study. Moreover, the quantitative synthesis was also performed by considering the ratio between the obtained cost-per-DALY and the corresponding GDP per capita, in order to allow for more precise comparisons between studies, since the economic value of DALYs would be obviously affected by the size of the income and GDP per capita.

Subsequently, the same analysis was conducted by considering indirect costs only, which are more closely related to income and productivity losses, and therefore to the GDP itself. For these further analyses, meta-analytic synthesis was conducted and reported as described above for the primary investigation. All statistical analyses were performed using the statistical software R (version 4.0.5) (R Core Team, 2021).

3. Results

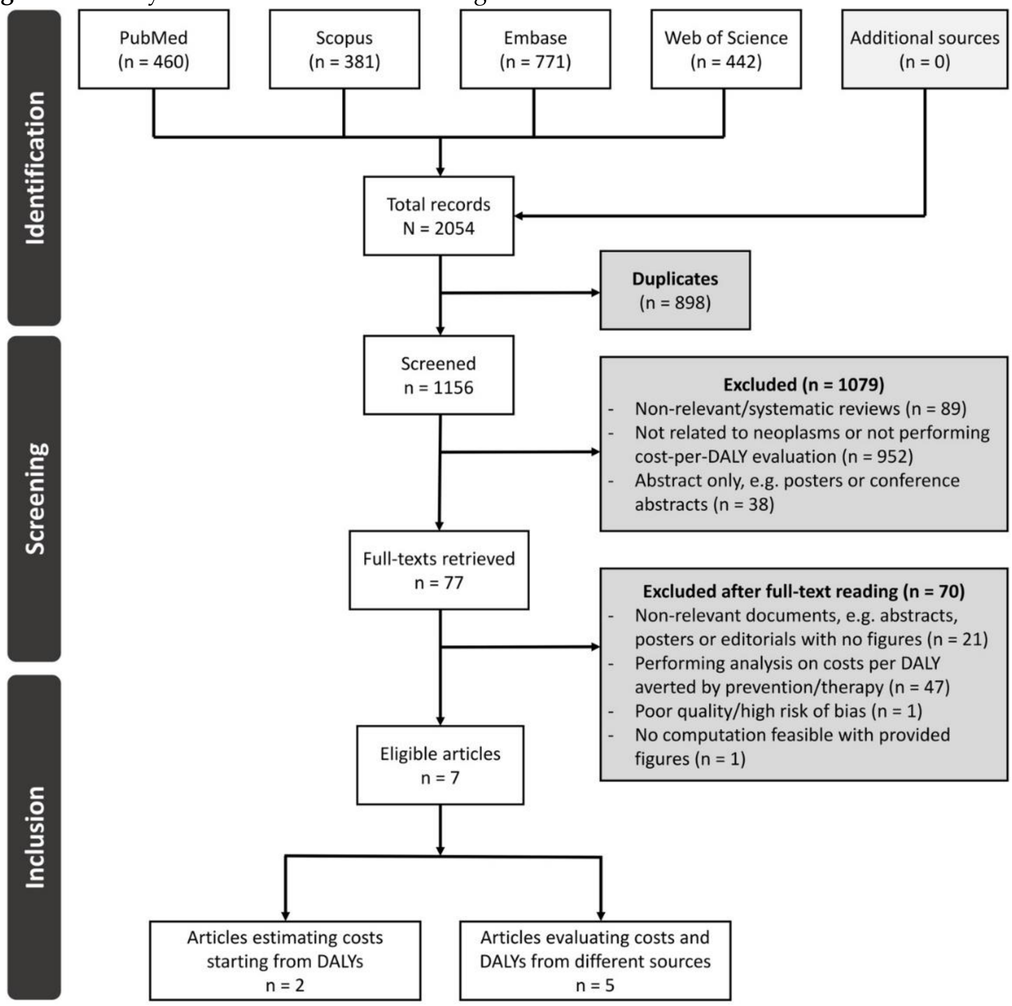
3.1. Study Selection

The study selection process is detailed in Fig. 1. Of the 1156 records obtained after deduplication, 1079 were screened out as they were either review papers or studies not including both cost and DALY analyses, or alternatively simple posters or conference abstracts. Among the 77 articles selected by the screening process, 21 were non-relevant documents and 47 were related to studies about costs per DALY averted by cancer prevention (e.g., vaccination or screening) or therapy, and not the costs per DALY of the disease itself.

Furthermore, one study (Jimenez de la Jara et al., 2015) was potentially eligible according to inclusion criteria, but was excluded as it performed a simple scoping analysis based on DALYs and GDP per capita without providing clear specification of data sources and methodologies deployed. Eventually, one study (Schlueter et al., 2020) was not included because it failed to provide figures feasibly allowing the computation of the cost-per-DALY ratio (i.e., both absolute or standardized per 100,000 persons).

As a result, 7 studies were included in this review, of which five (Neves et al., 2021; Noh et al., 2020; Oh et al., 2012; Unar-Munguía et al., 2017; Vondeling, Rozenbaum, Dvortsin, Postma, & Zeevat, 2016) were also eligible for quantitative synthesis since they provided directly retrieved cost and DALY estimates. On the contrary, 2 studies (John & Ross, 2010; Ranganathan et al., 2021) provided only rough estimates of costs starting from DALYs and pre-determined parameters (per-capita GDP or value of a statistical life, VSL), and therefore were kept as a comparison term for estimate difference projections.

Figure 1. – Study selection flow-chart according to the PRISMA Standard.



3.2. Characteristics of included studies

The 7 studies included in this review were published between 2012 and 2021. Six of these studies (John & Ross, 2010; Noh et al., 2020; Oh et al., 2012; Ranganathan et al., 2021; Unar-Munguía et al., 2017; Vondeling et al., 2016) adopted a societal perspective, and only one (Neves et al., 2021) chose a healthcare system perspective. Characteristics of all studies are summarized in Tables S1-S2.

The 5 studies retrieving costs and DALYs from independent sources were based on national data from 4 countries (Korea, Mexico, the Netherlands and Portugal). These studies were basically aimed at assessing health and economic burden of neoplastic disease in the relevant country: 3 of them (Neves et al., 2021; Noh et al., 2020; Vondeling et al., 2016) were longitudinal retrospective studies based on data from different time spans (i.e. 5-20 years), one (Oh et al., 2012) was designed as a prevalence study and one (Unar-Munguía et al., 2017) was based on a virtual prospective cohort. Data sources included: for direct costs, national pension institutes, health authorities and insurance corporations; for indirect costs, central statistics bureaus and national ministries; for DALYs, databases from (and/or software based on) surveys developed by supranational institutions (i.e. World Health Organization and European Union), national institutes for statistics or cancer registries.

The other 2 studies were economic evaluations (in one case (Ranganathan et al., 2021) nested into a prevalence study) on a wider scale, either international or worldwide. They basically aimed at estimating the economic burden of one or more neoplasms, and they were based on DALY-related data coming from the Global Burden of Disease studies and from other authorities, such as the Institute for Health Metrics and Evaluation and the World Health Organization. In these studies, costs were estimated by multiplying DALYs for pre-determined parameters, i.e. GDP per capita (John & Ross, 2010) and Value of Statistical Life (VSL) (Ranganathan et al., 2021) respectively.

3.3. *Quantitative analyses*

Considering the five studies independently performing cost and DALY analyses on a national scope, burdens of neoplasms included in each analysis differed appreciably among the studies under investigation, with health burdens ranging from 8.93 to 679 thousand DALYs, and relevant costs from 94.23 to 3,515 USD million. This corresponded to a cost-per-DALY ratio spanning from around 5,200 to 25,800 USD for each DALY ascribable to the disease (Table 1a).

Table 1. — Outcomes of included studies. (a) For studies performing separately economic analyses related to costs and DALYs, relevant figures are reported for both measures of the burden (first two columns): the cost-per-DALY ratio was computed (third column), and the table reports also the GDP per capita of the corresponding countries, as retrieved by the World Bank Data (last column). (b) For the remaining studies, assumed cost-per-DALY ratios were retrieved from the studies, along with DALY and derived cost estimates. All data were reported after discounting to 2018 USD.

(a) Studies performing separately economic analyses related to costs and DALYs

1st author, year	Income group	Costs [2018 USD mlns]	DALYs [thousands]	Cost-per-DALY ratio (*a posteriori*) [2018 USD/DALY]	GDP per capita [2018 USD]
Neves *et al*, 2021	High	106.9	8.93	12,000	27,736
Noh *et al*, 2020	High	2,460	355	6,900	30,015
Vondeling *et al*, 2018	High	1,666	64.6	25,800	58,846
Oh *et al*, 2012	High	3,515	679	5,200	24,949
Unar-Munguia *et al*, 2017	Upper-middle	94.23	15.8	6,000	11,160

(b) Studies estimating costs based on disease burden (DALYs) and a priori assumed cost-per-DALY ratios

1st author, year	Income group	Costs [2018 USD mlns]	DALYs [thousands]	Cost-per-DALY ratio (*a priori*) [2018 USD/DALY]
John *et al*, 2010	All groups represented	High income: 853,000 Upper-middle income: 90,600 Low-middle income: 85,700 Low income: 14,700 **Total costs: 1,044,000**	High income: 18,094 Upper-middle income: 8,727 Low-middle income: 34,389 Low income: 21,645 **Total DALYs: 82,855**	High income: 47,100* Upper-middle income: 10,400* Low-middle income: 2,500* Low income: 680*
Ranganathan *et al*, 2020	Low-middle	**Sub-Saharan Africa: 1,964** **Southern Asia: 2,090** India: 1,419	**Sub-Saharan Africa: 604.9** **Southern Asia: 1,294** India: 840.4	**Sub-Saharan Africa: 3,250*** **Southern Asia: 1,615*** India: 1,689* (GDP per capita: 1,701)

	Bangladesh: 153 Bhutan: 1.235 Nepal: 14.3 Pakistan: 473	Bangladesh: 119 Bhutan: 0.439 Nepal: 18.2 Pakistan: 311	Bangladesh: 1,285* (GDP per capita: 1,323) Bhutan: 2,813* (GDP per capita: 2,916) Nepal: 786* (GDP per capita: 955) Pakistan: 1,521* (GDP per capita: 1,437)

mlns: millions; USD: United States dollar; DALY: Disability-adjusted Life Years; GDP: Gross Domestic Product.

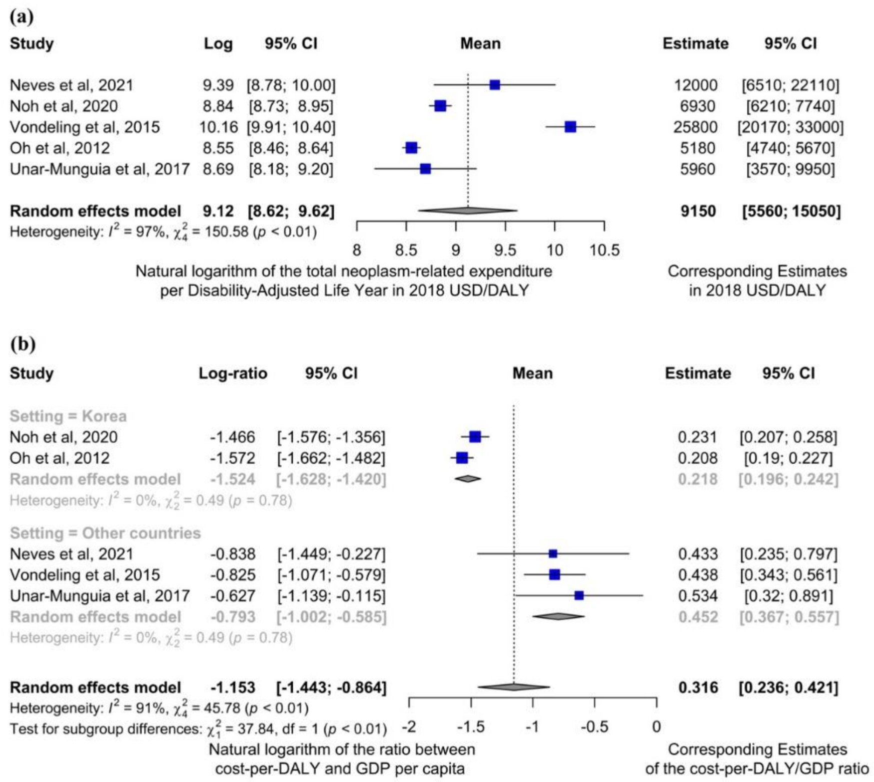
* The estimates were computed based on the reported data

† Where data is referred to a specific country, the corresponding GDPs per capita were also reported (source: World Bank Data Catalog)

The meta-analytic estimate of this cost-per-DALY ratio showed that this parameter could be reasonably quantified in 9,150 (95%CI: [5,560–15,050]) 2018 USD per DALY ascribable to the disease (Fig. 2a). As four of the studies (Neves et al., 2021; Noh et al., 2020; Oh et al., 2012; Vondeling et al., 2016) included in this quantitative synthesis were conducted in high-income countries, while one (Unar-Munguía et al., 2017) was set in a country with a different economic framework (upper-middle income), the same analysis was run excluding the latter study, resulting in a substantially unchanged estimate (10,070 USD/DALY, 95%CI: [5,730–17,660], Fig. S1).

In all these five studies, this estimate was much lower than the numerical value of the GDP per capita (Table 1a). Meta-analysis conducted on the ratio between the obtained cost per disease-related DALY and the corresponding GDP per capita showed that the cost per DALY is on average 31.6% (95% CI: [23.6–42.1]) of the national GDP per capita. This analysis also pointed out the heterogeneity (I^2=91%) among different geographical and socioeconomic contexts, as further shown by the post-hoc subgroup analysis ($p<0.0001$) conducted by separating the two studies sharing the same origin (i.e. Korea) (Noh et al., 2020; Oh et al., 2012), where this ratio was as low as 21.8% (95% CI: [19.6–24.2]), from the others located in different settings, where the same parameter was estimated around 45.2% (95% CI: [34.7–55.7], Fig. 2b).

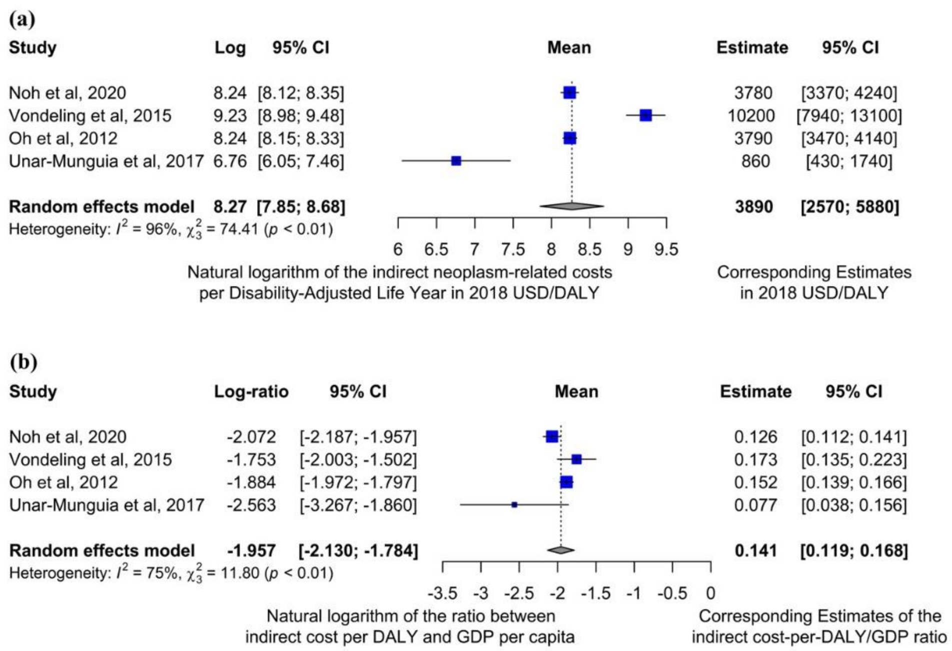
Figure 2. – Forest plots for outcomes related to the cost-per-DALY ratio, according to meta-analytic computations described in the Methods. Meta-analytic estimate of the average cost per DALY ascribable to neoplastic disease (and its 95% CI), performed considering all studies eligible for the quantitative synthesis (*a*). Expenditures per DALY were also considered in relation to the corresponding GDP per capita (*b*): given that two studies were set in the same context (Korea)[32,34], a *post-hoc* subgroup analysis was also performed by separating them from other settings.



A similar meta-analytic computation was performed on the ratio between indirect costs and DALYs, which showed that every DALY ascribable to neoplastic disease is responsible for an average indirect expenditure around 3,890 (95% CI: [2,570–5,880]) 2018 USD (Fig. 3a). Considering high-income countries only, these average indirect costs rise up to 5,150 (95% CI: [3,450–7,680]) 2018 USD (Fig. S2).

Meta-analysis conducted on the ratio between the obtained indirect cost per disease-related DALY and the corresponding GDP per capita showed that the indirect expenditure is on average 14.1% (95% CI: [11.9–16.8]) of the numerical value of the national GDP per capita (Fig. 3b). Again, remarkable heterogeneity (I2=96%) could be spotted among different geographical and socioeconomic contexts.

Figure 3. – Forest plots for outcomes related to the ratio between indirect costs and DALYs, according to meta-analytic computations described in the Methods. Meta-analytic estimate of the average indirect cost per DALY ascribable to neoplastic disease (and its 95% CI), performed considering all studies eligible for the quantitative synthesis (*a*). Indirect expenditures per DALY were also considered in relation to the corresponding GDP per capita (*b*). One study[31] was not included in this computation due to absence of indirect cost data.



3.4. *Quality assessment*

The quality and risk-of-bias assessment of studies included in this review is reported in the Supplementary Material (Table S3). One study (Ranganathan et al., 2021) resulted to be of poor quality, four studies (John & Ross, 2010; Neves et al., 2021; Noh et al., 2020; Oh et al., 2012) were classified as fair and two showed valuable methodological quality (Unar-Munguía et al., 2017; Vondeling et al., 2016). Interestingly, two of the included studies (Noh et al., 2020; Ranganathan et al., 2021) lacked precise reporting of the currency and pricing date. Moreover, one study did not adopt a society perspective, focusing on direct costs only (Neves et al., 2021).

4. Discussion

This study was intended to provide an insight into the currently available literature about cost and DALY analyses of neoplastic disease. Moreover, in view of the various approaches adopted by the studies, this review also aimed at investigating the extent to which diverse estimation and computation methodologies might lead to differences in magnitude among the obtained estimates, thereby resulting in possibly disparate advice provided to policy-makers.

Despite the recent efforts to quantify the economic loss due to cancer, few papers examining both costs and DALYs have been published. Several studies evaluated either DALYs (Melaku et al., 2018; Safiri et al., 2019) or Costs (Huang, Chen, Liao, Ko, & Hsiao, 2020; Luengo-Fernandez, Leal, Gray, & Sullivan, 2013; Yabroff, Lund, Kepka, & Mariotto, 2011), but there is still paucity of simultaneous analyses of these two parameters in relation to neoplasms.

The present systematic review and meta-analysis of economic evaluations showed a pooled cost-per-DALY ratio of around nine thousand 2018 USD per DALY accountable to neoplasms. Results also displayed that the total cost per DALY equals approximately one third of the national GDP per capita. Considering only indirect costs, the pooled ratio was around four thousand 2018 USD. Relating the indirect costs-per-DALY ratio to the national GDP results in an indirect expenditure per DALY equaling one seventh of the annual country's economic output per person.

The quality of the studies reviewed was heterogeneous. There were differences on DALY computation with regard to the use of discounting, since three (Ranganathan et al., 2021; Unar-Munguía et al., 2017; Vondeling et al., 2016) of the seven studies adopted a discount rate although not recommended by current standards (World Health Organization (WHO) - Department of Data and Analytics, 2020). In fact, supranational bodies as the WHO and evidence in the scientific literature advised against the use of discounting and weighting in DALY computation, as no intrinsic reason appeared to provide ground for decreasing the value of a year of health simply because in the future (Tsuchiya, 2002), especially in the context where DALY are explicitly used to quantify loss of health, rather than the social value of this loss (Anand & Hanson, 1997; Barendregt, Bonneux, & Van der Maas, 1996; C. J. L. Murray & Acharya, 1997).

However, the meta-analysis clearly demonstrates the potentially substantial differences among estimates provided by studies conducted through different methodologies. Costs a posteriori evaluated after data collection and model building showed that the overall neoplasm-related indirect expenditure and productivity losses per DALY ascribable to the disease were much lower than the numerical value of the GDP per-capita (Fig. 3), and the same held for the total expenditure (i.e., also including direct costs, Fig. 2). This implies that the actual estimates of global costs of disease may be quite different from the "economic value" obtained multiplying DALYs by the GDP per capita. For a mere example, the fact that cost estimates would be cut by around 70% (Fig. 2b) implies that, if a posteriori computed parameters were used, the global cost estimate forecast by John et al. (John & Ross, 2010) would be reduced from one billion to 300 million 2018 USD.

This might be explained by the fact that GDP measures the monetary value of all final goods and services produced in a country in a given period (generally a year). Consequently, GDP is composed of goods and services produced for sale in the market and also includes some non-market production (e.g., defense or education services provided by the government) (Callen, 2020), which may entail an excess computation of costs in relation to the actual economic burden of the disease when the GDP is taken as a predetermined proxy of the cost per DALY.

The remarkable differences highlighted by this analysis cast doubts on the reliability of estimates obtained by valuing the monetary burden from simple analyses based on DALYs and GDP per capita, a methodology widely used not only for neoplastic disease (Jimenez de la Jara et al., 2015), but also in many other sectors such as, for example, infectious disease (Townsend, Greenland, & Curtis, 2017), injuries (Dalal & Svanström, 2015) and maltreatment-related illnesses (Mo et al., 2020).

A limitation of our calculation lies in the fact that meta-analytic estimates were obtained from studies conducted in high-income countries only: therefore, the results in terms of cost-per-DALY ratio may not be generalizable to low-income or low-middle income countries (LMICs). However, the magnitude of the difference in global estimates according to the methodology is unlikely to be affected by these latter countries, since their relative contribution to global costs is limited (Table 1b).

Another study used the VSL as a proxy of the cost per DALY: the VSL can be defined as the monetary value of a mortality risk reduction that would prevent one statistical death (Ashenfelter & Greenstone, 2004; Kniesner & Viscusi, 2019). When the tradeoff values are based on choices in market contexts, the VSL can be adopted as an indicator of the marginal cost of enhancing safety and the population's willingness to pay for mortality risk reduction (Bellavance, Dionne, & Lebeau, 2009).

The use of the VSL as a proxy of the cost per DALY has already been applied to genetic (Gong et al., 2021), occupational (Lebeau, Duguay, & Boucher, 2014) and infectious diseases (Herrera-Araujo, Mikecz, & Pica-Ciamarra, 2020). However, it is interesting to notice that figures obtained by Ranganathan et al. (Ranganathan et al., 2021) using the VSL methodology appeared to provide a cost-per-DALY estimate absolutely comparable to the value of the GDP per capita, with no appreciable difference in the magnitude of estimated costs: in fact, the ratio between VSL and GDP per capita ranged between a minimum of 0.823 (in Nepal, 786/955) and a maximum of 1.058 (in Pakistan, 1,521/1,437, see Table 1b for detailed figures). Thus, it is likely that, as previously observed for the case of

GDP per capita, even using the VSL may equally lead to overestimating total costs of DALYs.

In light of the above, some implications emerge for both researchers and policy-makers. First of all, the availability of reliable estimates on the cost of neoplasms is absolutely required in order to steer targeted choices at the several levels of the decision-making process and to accurately allocate resources. For this reason, further studies are needed to provide a reasonable cost-per-DALY parameter that can be used to estimate costs of neoplasms starting from relevant DALYs, similarly to the approach already adopted for different sectors (Miller et al., 2020), where previously published cost-per-DALY estimates (Hirth, Chernew, Miller, Fendrick, & Weissert, 2000; Viscusi & Masterman, 2017) were considered and applied instead of fixed parameters like GDP or VSL. This would imply more challenging research but would also lead to understanding more clearly the actual economic burden ascribable to cancer.

Subsequently, more precise computations of this burden would allow policy-makers to quantify the amount of resources deployed in relation to DALYs, and therefore to conversely evaluate the economic benefits resulting from the reduction of these pathologies (Coons & Craig, 2008; World Cancer Leaders' Summit, 2014). As a result, this would also help policy-makers to assess the need of improving healthcare policies in terms of primary prevention, screening programs and early diagnosis of neoplastic diseases (Emmons & Colditz, 2017).

The present findings should be assessed in light of this study's weaknesses and strengths. Along with the systematic search and analysis methodology, widely referenced in the scientific literature, this study is, to our knowledge, the first attempt to provide a quantitative synthesis of data inherent to costs per DALY ascribable to neoplastic disease. However, some limitations are present: firstly, the systematic review took into account studies investigating several types of neoplasms and/or a pool of neoplasms: the limited sample size prevented us from performing any subgroup or stratified meta-analysis for different neoplasm types. The presence of studies investigating different types of neoplasms – from breast cancer to multiple myeloma, thus with treatment pathways and prognoses, which would result in different costs per DALY – is probably one of the reasons for the substantial heterogeneity of the obtained results. Moreover, another source of heterogeneity was represented by the fact that the retrieved original studies were conducted in different countries, and therefore in different social and economic contexts: trying to overcome this limitation was the main reason for which the cost-per-DALY ratio was also analyzed in relation to GDP per capita, so as to lower as much as possible the biasing impact of income differences on the pooled estimate. However, an important fact to be noted is that, although the heterogeneity of results should be carefully considered, the differences between GDP-based evaluations and a posteriori calculated data are always wide, since even the highest estimates provided by the studies for the cost per DALY did not exceed 53.4% of the respective GDP per capita.

Further studies are needed to investigate the extent to which these estimates, computed for a specific country, can be generalized to other settings, both in absolute terms and in relation to wealth and income indicators such as the GDP per capita. This holds particularly for low- and low/middle-income countries, where detailed research still has to be conducted on costs and DALYs of neoplastic disease. Eventually, an additional line of research could involve assessing how the adoption of different cost-per-DALY computations may affect the prioritization of interventions.

5. Conclusions

Neoplasms represent a major health issue, concerning both the clinical burden (in terms of morbidity and mortality) and the consequent economic implications. With regard to the latter, DALYs are often used to measure the burden of disease, since they are a compound unit encompassing both disability and mortality, but substantial heterogeneity occurs when they are translated to monetary value.

Each DALY due to neoplasms has showed to averagely cost around nine thousand 2018 USD in upper and upper-middle income countries, although this computation is strongly influenced by fluctuations depending on cancer type and other parameters (e.g. country, prices). Moreover, the use of a priori established parameters, such as GDP or VSL, leads to presenting rough estimates that, though, have appeared to be highly different (even threefold) from what has been a posteriori computed by directly retrieving figures and/or building models out of available data. Therefore, further research is needed to understand the actual value of DALYs connected to neoplasms, and to elaborate reliable cost estimates that may provide reasonable ground to policy-makers for appropriate decision-making.

Supplementary Materials: Search string; data collection form; Figure S1: Forest plot for the cost-per-DALY ratio: sensitivity analysis. Meta-analytic estimate of the average cost per DALY ascribable to neoplastic disease (and its 95% CI). This quantitative synthesis was computed and plotted as in Figure 2a, but excluding the only study not conducted in a high-income country (Unar-Munguía et al.); Figure S2: Forest plot for the indirect cost-per-DALY ratio: sensitivity analysis. Meta-analytic estimate of the average indirect cost per DALY ascribable to neoplastic disease (and its 95% CI). This quantitative synthesis was computed and plotted as in Figure 3a, but excluding the only study not conducted in a high-income country (Unar-Munguía et al.); TABLE S1 – Descriptive characteristics of included studies: general characteristics of included studies. White rows indicate studies performing separately economic analyses related to costs and DALYs (included in the quantitative synthesis), whereas shaded rows contain studies that deduce costs starting from DALYs (not included in the meta-analysis); TABLE S2 – Descriptive characteristics of included studies: economic parameters and data sources. White rows indicate studies performing separately economic analyses related to costs and DALYs (included in the quantitative synthesis), whereas shaded rows contain studies that deduce costs starting from DALYs (not included in the meta-analysis); TABLE S3 – Quality assessment of included studies according to the Quality of Health Economic Studies (QHES) instrument.

Author Contributions: Conceptualization, M.M.G. and G.D.; Methodology, J.G., M.C.N., M.M.G. and G.D.; Software, J.G.; Validation, M.M.G. and G.D.; Formal Analysis, J.G. and M.C.N.; Investigation, J.G., M.C.N., M.M.G. and G.D.; Data Curation, J.G. and M.C.N.; Writing – Original Draft Preparation, J.G., M.C.N., V.B., M.S. and G.A.; Writing – Review & Editing, J.G., M.C.N., V.B., M.S. and G.A.; Supervision, M.M.G. and G.D.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable

Data Availability Statement: In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics. You might choose to exclude this statement if the study did not report any data.

Acknowledgments: In this section, you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest.

References

American Cancer Society. (2010). *The Global Economic Cost of Cancer*. Retrieved 8 December 2021 from https://web.archive.org/web/20151002194754/http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf

Anand, S., & Hanson, K. (1997). Disability-adjusted life years: A critical review. In *Journal of Health*

Economics (Vol. 16). Retrieved from https://doi.org/10.1016/S0167-6296(97)00005-2

Ashenfelter, O., & Greenstone, M. (2004). Estimating the Value of a Statistical Life: The Importance of Omitted Variables and Publication Bias. *American Economic Review*, 94(2), 454–460. Retrieved from https://doi.org/10.1257/0002828041301984

Balduzzi, S., Rücker, G., & Schwarzer, G. (2019). How to perform a meta-analysis with R: A practical tutorial. *Evidence-Based Mental Health*, 22(4), 153–160. Retrieved from https://doi.org/10.1136/ebmental-2019-300117

Barendregt, J. J., Bonneux, L., & Van der Maas, P. J. (1996). DALYs: the age-weights on balance. *Bulletin of the World Health Organization*, 74(4), 439–43.

Bellavance, F., Dionne, G., & Lebeau, M. (2009). The value of a statistical life: A meta-analysis with a mixed effects regression model. *Journal of Health Economics*, 28(2), 444–464. Retrieved from https://doi.org/10.1016/j.jhealeco.2008.10.013

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, 1(2), 97–111. Retrieved from https://doi.org/10.1002/jrsm.12

Brown, M. L., Lipscomb, J., & Snyder, C. (2001). The Burden of Illness of Cancer: Economic Cost and Quality of Life. *Annual Review of Public Health*, 22(1), 91–113. Retrieved from https://doi.org/10.1146/annurev.publhealth.22.1.91

Callen, T. (2020). Gross Domestic Product: An Economy's All. Retrieved 13 December 2020, from https://www.imf.org/external/pubs/ft/fandd/basics/gdp.htm

Chao, T. E. (2020). Beyond outcomes: applying cost-effectiveness analysis to policy making. *British Journal of Anaesthesia*, 125(6), 850–852. Retrieved from https://doi.org/10.1016/j.bja.2020.08.034

Chiou, C. F., Hay, J. W., Wallace, J. F., Bloom, B. S., Neumann, P. J., Sullivan, S. D., … Ofman, J. J. (2003). Development and validation of a grading system for the quality of cost-effectiveness studies. *Medical Care*, 41(1), 32–44. Retrieved from https://doi.org/10.1097/00005650-200301000-00007

Coin News. (2021). U.S. Inflation Calculator. Retrieved 5 October 2021, from https://www.usinflationcalculator.com

Coons, S. J., & Craig, B. M. (2008). Assessing Human and Economic Benefits of Cancer Prevention. In D. S. Alberts & L. M. Hess (Eds.), *Fundamentals of Cancer Prevention* (2nd ed., Vol. 1, pp. 13–30). Berlin, Heidelberg: Springer-Verlag.

Dalal, K., & Svanström, L. (2015). Economic Burden of Disability Adjusted Life Years (DALYs) of Injuries. *Health*, 07(04), 487–494. Retrieved from https://doi.org/10.4236/health.2015.74058

DerSimonian, R., & Laird, N. (2015). Meta-analysis in clinical trials revisited. *Contemporary Clinical Trials*, 45(0), 139–145. Retrieved from https://doi.org/10.1016/j.cct.2015.09.002

Emmons, K. M., & Colditz, G. A. (2017). Realizing the Potential of Cancer Prevention — The Role of Implementation Science. *New England Journal of Medicine*, 376(10), 986–990. Retrieved from https://doi.org/10.1056/NEJMsb1609101

Fitzmaurice, C., Abate, D., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdel-Rahman, O., … Murray, C. J. L. (2019). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-Adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. *JAMA Oncology*, 5(12), 1749–1768. Retrieved from https://doi.org/10.1001/jamaoncol.2019.2996

Gong, J., Cheung, S., Fasso-Opie, A., Galvin, O., Moniz, L. S., Earle, D., … Daly, A. (2021). The impact of inherited retinal diseases in the united states of america (Us) and canada from a cost-of-illness perspective. *Clinical Ophthalmology*, 15(June), 2855–2866. Retrieved from https://doi.org/10.2147/OPTH.S313719

Herrera-Araujo, D., Mikecz, O., & Pica-Ciamarra, U. (2020). Placing a monetary value on the human health component of zoonotic diseases: A methodological note with an application to cysticercosis in Africa. *Preventive Veterinary Medicine*, 175(November 2019), 104862. Retrieved from https://doi.org/10.1016/j.prevetmed.2019.104862

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, 327(7414), 557–560. Retrieved from https://doi.org/10.1007/s10844-006-2974-4

Higgins, J. P. T., White, I. R., & Anzures-Cabrera, J. (2008). Meta-analysis of skewed data: Combining results reported on log-transformed or raw scales. *Statistics in Medicine*, 27(29), 6072–6092. Retrieved from https://doi.org/10.1002/sim.3427

Hirth, R. A., Chernew, M. E., Miller, E., Fendrick, A. M., & Weissert, W. G. (2000). Willingness to pay for a quality-adjusted life year: In search of a standard. *Medical Decision Making*, 20(3), 332–342. Retrieved from https://doi.org/10.1177/0272989X0002000310

Huang, S. Y., Chen, H. M., Liao, K. H., Ko, B. S., & Hsiao, F. Y. (2020). Economic burden of cancers in Taiwan: A direct and indirect cost estimate for 2007-2017. *BMJ Open*, 10(10), 1–9. Retrieved from https://doi.org/10.1136/bmjopen-2019-036341

Jimenez de la Jara, J., Bastias, G., Ferreccio, C., Moscoso, C., Sagues, S., Cid, C., … Owen, G. I. (2015). A snapshot of cancer in Chile: analytical frameworks for developing a cancer policy. *Biological Research*, 48(1), 10.

John, R. M., & Ross, H. (2010). Economic value of disability adjusted life years lost to cancers: 2008. *Journal of Clinical Oncology*, 28(15_suppl), 1561–1561. Retrieved from https://doi.org/10.1200/jco.2010.28.15_suppl.1561

Katz, D., Baptista, J., Azen, S. P., & Pike, M. C. (1978). Obtaining Confidence Intervals for the Risk Ratio in Cohort Studies. *Biometrics*, 34(3), 469–474.

Kniesner, T. J., & Viscusi, W. K. (2019). The Value of a Statistical Life. *SSRN Electronic Journal*. Retrieved from https://doi.org/10.2139/ssrn.3379967

Lebeau, M., Duguay, P., & Boucher, A. (2014). Costs of occupational injuries and diseases in Québec. *Journal of Safety Research*, 50, 89–98. Retrieved from https://doi.org/10.1016/j.jsr.2014.04.002

Luengo-Fernandez, R., Leal, J., Gray, A., & Sullivan, R. (2013). Economic burden of cancer across the European Union: a population-based cost analysis. *The Lancet Oncology*, 14(12), 1165–1174. Retrieved from https://doi.org/10.1016/S1470-2045(13)70442-X

Mattiuzzi, C., & Lippi, G. (2020). Cancer statistics: A comparison between World Health Organization (WHO) and Global Burden of Disease (GBD). *European Journal of Public Health*, 30(5), 1026–1027. Retrieved from https://doi.org/10.1093/eurpub/ckz216

Melaku, Y. A., Appleton, S. L., Gill, T. K., Ogbo, F. A., Buckley, E., Shi, Z., … Fitzmaurice, C. (2018). Incidence, prevalence, mortality, disability-adjusted life years and risk factors of cancer in Australia and comparison with OECD countries, 1990–2015: findings from the Global Burden of Disease Study 2015. *Cancer Epidemiology*, 52(December 2017), 43–54. Retrieved from https://doi.org/10.1016/j.canep.2017.11.007

Miller, T. R., Waehrer, G. M., Oh, D. L., Boparai, S. P., Walker, S. O., Marques, S. S., & Harris, N. B. (2020). Adult health burden and costs in California during 2013 associated with prior adverse childhood experiences. *PLoS ONE*, 15(1), 1–15. Retrieved from https://doi.org/10.1371/journal.pone.0228019

Mo, X., Gai, R. T., Tachibana, Y., Bolt, T., Takahashi, Y., & Nakayama, T. (2020). The burden of disease and the cost of illness attributable to child maltreatment in Japan: long-term health consequences largely matter. *BMC Public Health*, 20(1), 1296. Retrieved from https://doi.org/10.1186/s12889-020-09397-8

Murray, C. J. (1994). Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bulletin of the World Health Organization*, 72(3), 429–45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8062401

Murray, C. J. L., & Acharya, A. K. (1997). Understanding DALYs. *Journal of Health Economics*, 16(6), 703–730. Retrieved from https://doi.org/10.1016/S0167-6296(97)00004-0

National Cancer Institute. (2019). *Financial Burden of Cancer Care*. *Cancer Trends Progress Report* (Vol. 103). Retrieved from https://progressreport.cancer.gov/after/economic_burden#field_most_recent_estimates

Neves, M., Trigo, F., Rui, B., João, C., Lúcio, P., Mariana, N., … Geraldes, C. (2021). Multiple Myeloma in Portugal: Burden of Disease and Cost of Illness. *PharmacoEconomics*, 39(5), 579–587. Retrieved from https://doi.org/10.1007/s40273-020-00993-5

Noh, J., Jang, H., Cho, J., Kang, D. R., Kim, T. H., Shin, D. C., & Kim, C. (2020). Estimating the disease burden of lung cancer attributable to residential radon exposure in Korea during 2006–2015: A socio-economic approach. *Science of the Total Environment*, 749, 141573. Retrieved from https://doi.org/10.1016/j.scitotenv.2020.141573

Ofman, J. J., Sullivan, S. D., Neumann, P. J., Chiou, C. F., Henning, J. M., Wade, S. W., & Hay, J. W. (2003). Examining the value and quality of health economic analyses: implications of utilizing the QHES.

Journal of Managed Care Pharmacy : JMCP, 9(1), 53–61. Retrieved from https://doi.org/10.18553/jmcp.2003.9.1.53

Oh, I. H., Yoon, S. J., Yoon, T. Y., Choi, J. M., Choe, B. K., Kim, E. J., … Park, Y. H. (2012). Health and economic burden of major cancers due to smoking in Korea. *Asian Pacific Journal of Cancer Prevention*, 13(4), 1525–1531. Retrieved from https://doi.org/10.7314/APJCP.2012.13.4.1525

Oostvogels, A. J. J. M., De Wit, G. A., Jahn, B., Cassini, A., Colzani, E., De Waure, C., … Mangen, M. J. J. (2015). Use of DALYs in economic analyses on interventions for infectious diseases: A systematic review. *Epidemiology and Infection*, 143(9), 1791–1802. Retrieved from https://doi.org/10.1017/S0950268814001940

Organisation for European Co-operation and Development. (2020). Purchasing Power Parities (PPP). Retrieved from https://doi.org/10.1787/1290ee5a

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372(n71), n71. Retrieved from https://doi.org/10.1136/bmj.n71

R Core Team. (2021). R: A language and environment for statistical computing. *R Foundation for Statistical Computing*. Vienna. Retrieved from https://www.r-project.org/

Ranganathan, K., Singh, P., Raghavendran, K., Wilkins, E. G., Hamill, J. B., Aliu, O., … Momoh, A. O. (2021). The Global Macroeconomic Burden of Breast Cancer. *Annals of Surgery*, 274(6), 1067–1072. Retrieved from https://doi.org/10.1097/sla.0000000000003662

Safiri, S., Sepanlou, S. G., Ikuta, K. S., Bisignano, C., Salimzadeh, H., Delavari, A., … Malekzadeh, R. (2019). The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology and Hepatology*, 4(12), 913–933. Retrieved from https://doi.org/10.1016/S2468-1253(19)30345-0

Schlueter, M., Chan, K., Lasry, R., & Price, M. (2020). The cost of cancer – A comparative analysis of the direct medical costs of cancer and other major chronic diseases in Europe. *PLOS ONE*, 15(11), e0241354. Retrieved from https://doi.org/10.1371/journal.pone.0241354

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, 71(3), 209–249. Retrieved from https://doi.org/10.3322/caac.21660

The World Bank. (2010). GDP per capita (constant 2010 US$). Retrieved 20 October 2021, from https://data.worldbank.org/indicator/NY.GDP.PCAP.KD

Townsend, J., Greenland, K., & Curtis, V. (2017). Costs of diarrhoea and acute respiratory infection attributable to not handwashing: the cases of India and China. *Tropical Medicine & International Health*, 22(1), 74–81. Retrieved from https://doi.org/10.1111/tmi.12808

Tsuchiya, A. (2002). Accounting for time and age in summary measures of population health. In C. J. L. Murray, J. A. Salomon, C. D. Mathers, & A. D. Lopez (Eds.), *Summary Measures of Population Health: Concepts, Ethics, Measurement and Applications* (pp. 657–662). Geneva: WHO Press. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/42439/9241545518.pdf

U.S. Bureau of Labor Statistics. (2021). Consumer Price Index (CPI). Retrieved 5 October 2021, from https://www.bls.gov/cpi/

Unar-Munguía, M., Meza, R., Colchero, M. A., Torres-Mejía, G., & de Cosío, T. G. (2017). Economic and disease burden of breast cancer associated with suboptimal breastfeeding practices in Mexico. *Cancer Causes and Control*, 28(12), 1381–1391. Retrieved from https://doi.org/10.1007/s10552-017-0965-0

Viscusi, W. K., & Masterman, C. J. (2017). Income Elasticities and Global Values of a Statistical Life. *Journal of Benefit-Cost Analysis*, 8(2), 226–250. Retrieved from https://doi.org/10.1017/bca.2017.12

Vondeling, G., Rozenbaum, M., Dvortsin, E., Postma, M., & Zeevat, F. (2016). Burden of Early and Advanced Breast Cancer in The Netherlands. *Value in Health*, 19(7), A756. Retrieved from https://doi.org/10.1016/j.jval.2016.09.2337

Walker, D. G., Wilson, R. F., Ritu Sharma, M., John Bridges, B., Niessen, L., Bass, E. B., & Kevin Frick, M. (2012). *Methods Research Report Best Practices for Conducting Economic Evaluations in Health Care: A Systematic Review of Quality Assessment Tools*. Retrieved from www.ahrq.gov

Weir, C. J., Butcher, I., Assi, V., Lewis, S. C., Murray, G. D., Langhorne, P., & Brady, M. C. (2018). Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: A systematic review. *BMC Medical Research Methodology*, 18(1), 1–14. Retrieved from https://doi.org/10.1186/s12874-018-0483-0

World Cancer Leaders' Summit. (2014). *The Economics of Cancer Prevention & Control*. *Data Digest*. Retrieved 6 December 2021 from https://www.uicc.org/sites/main/files/atoms/files/WCLS2014_economics_of_cancer_FINAL.pdf

World Health Organization (WHO). (2021). Cancer - Key Facts. Retrieved 8 December 2021, from https://www.who.int/news-room/fact-sheets/detail/cancer

World Health Organization (WHO) - Department of Data and Analytics. (2020). *WHO methods and data sources for global burden of disease estimates 2000-2019*. Geneva: WHO Press. Retrieved from https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_daly-methods.pdf

Yabroff, K. R., Lund, J., Kepka, D., & Mariotto, A. (2011). Economic Burden of Cancer in the United States: Estimates, Projections, and Future Research. *Cancer Epidemiology Biomarkers & Prevention*, 20(10), 2006–2014. Retrieved from https://doi.org/10.1158/1055-9965.EPI-11-0650