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The Indirect Cost Burden of Cancer Care in Canada: A Systematic Literature Review

Nicolas Iragorri^{1,2,4} · Claire de Oliveira^{1,2,3} · Natalie Fitzgerald¹ · Beverley Essue^{1,2}

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Abstract

Background and objectives Cancer poses a substantial health and economic burden on patients and caregivers in Canada. Previous reviews have estimated the indirect cost burden as work-related productivity losses associated with cancer. However, these estimates require updating and complementing with more comprehensive data that include relevant dimensions beyond labor market costs, such as patient time, lost leisure time and home productivity losses.

Methods A systematic review of the literature was conducted to identify studies published from 2006 to 2020 that measured and reported the indirect costs borne by cancer patients and their caregivers in Canada, from the patient, caregiver, employer, and societal perspectives. Study characteristics and cost estimation methods were extracted from relevant studies. Costs estimates were reported and converted to 2020 CAD for the following categories: lost earnings, caregiving time costs, home production losses, patient time (leisure), morbidity-, disability-, premature mortality-related costs, friction costs, and overall productivity losses. A quality assessment of individual studies was conducted for included studies using the Newcastle–Ottawa Assessment Tool.

Results In total, 3980 studies were identified, of which 18 Canadian studies met the inclusion criteria for review. One-third of the studies used or developed prediction models, 38% enrolled patient cohorts, and 27% used administrative databases. Over one-third of the studies were conducted at a national level (38%). All studies employed the human capital approach to estimate costs, and 16% also used the friction cost approach. Lost earnings were higher among self-employed patients (43% vs 24% among employees) and females (\$8200 vs \$3200 for males). Caregiver costs ranged from \$15,786 to \$20,414 per patient per year. Household productivity losses were estimated to be up to \$238,904 per household per year. Patient time (leisure) costs were estimated to be between \$13,000 and \$18,704 per patient per year. Premature annual mortality costs were estimated to be \$2.98 billion overall in Quebec. Friction costs incurred by employers were estimated between \$6400 and \$23,987 per patient per year. Societal productivity losses associated with cancer were estimated between \$75 million to \$317 million, annually.

Conclusions This review suggests that the indirect cost burden of cancer is considerable from the patient, caregiver, employer, and societal perspectives. This up-to-date review of the literature provides a comprehensive understanding of the indirect cost burden by including non-labor market activity costs and by examining all relevant perspectives. These results provide a strong case for the government and employers to ensure there are supports in place to help patients and caregivers buffer the impact of cancer so they can continue to engage in productive activities and enjoy leisure time.

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✉ Nicolas Iragorri
nicolas.iragorri@mail.utoronto.ca

Extended author information available on the last page of the article

Key Points for Decision Makers

Cancer patients, their caregivers, and employers bear a considerable indirect cost burden related to cancer care in Canada.

The indirect cost burden of cancer is not limited to the productive labor market costs incurred by patients. Patient leisure time and home-production losses are important cost categories that must be considered when measuring the indirect cost burden.

The caregivers of pediatric patients, women, younger patients, and those who were self-employed face higher indirect costs in Canada.

1 Introduction

Cancer is a common chronic disease that has a large impact globally, including in Canada. Around half of the population is expected to develop cancer in their lifetime [1], and it remains the leading cause of premature mortality [2]. Furthermore, cancer poses a substantial health and economic burden on patients, their caregivers, and the healthcare system, given its high incidence (over 200,000 cases per year in 2019), long-term health effects, and rising treatment costs [3].

The economic burden is typically conceptualized as three distinct categories: direct, indirect, and psychosocial [4]. Cost of illness studies are often conducted to estimate the direct and indirect costs associated with a given disease; in turn, these estimates are used to support cost-effectiveness analyses, which are critical for informing resource allocation decisions [5]. Although the direct burden of cancer in Canada has been previously described [6], evidence around the indirect costs associated with cancer care is sparse and limited. The indirect burden includes the monetary losses associated with lost patient/caregiver time and lost opportunities due to disease morbidity and related premature mortality (also defined as opportunity costs) [7]. These costs are incurred by patients, caregivers, employers, and society as a whole; however, because lost opportunities are usually not reflected in monetary transactions, the value of the time lost must be approximated. Thus, to obtain an overall estimate of the indirect cost burden, the time that cancer patients spend in obtaining treatment, loss from not working due to short- or long-term cancer-related disability, and the lost productivity due to premature death are monetized and combined [7].

In a report conducted by the Public Health Agency of Canada, work-related productivity losses due to cancer were estimated to be \$586,000,000 in 2008 [8]. Subsequently, a review conducted in 2010 identified studies published before 2008 that had estimated wage losses due to cancer [9] and found that newly diagnosed cancers in Canada generated an average wage loss of \$3.18 billion per year. However, these studies only included labor market-related production losses. Considering the lack of up-to date and comprehensive estimates, and the fast pace at which cancer care has evolved in the last decade [10], the evidence around the indirect cost burden of cancer in Canada needs to be re-evaluated to include recent studies that also capture non-labor market activities, such as home production, leisure, and caregiving time. Therefore, the aim of this review was to evaluate the most recent Canadian literature on the indirect cost burden associated with cancer from the perspectives of patients, families, caregivers, employers, and society.

2 Methods

2.1 Data Sources and Search Strategies

A systematic review of the literature was conducted to identify studies that estimated and/or reported on the indirect cost burden of cancer in Canada. We searched MEDLINE, EMBASE (Excerpta Medical Database), CINAHL, Econlit, PsychINFO, Cochrane, and Erudit (this last to capture literature published in French). We also searched Open Gray to account for relevant gray literature. All databases were searched between January 1, 2006 and January 8, 2020. Search terms combined medical subject headings (MeSH), Embase subject headings (Emtree), and keywords for cancer (e.g. oncology), economic burden (e.g. costs), and indirect costs (e.g. productivity loss). In addition, we searched the reference lists of all included studies to identify additional relevant studies. The full search strategy and key words can be found in Appendix 1. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11] as presented in Appendix 2.

2.2 Eligibility Criteria

We included any study that reported and/or estimated the indirect cost burden of cancer patients and/or their caregivers. No study design or language restrictions were applied to the search. Studies were excluded if at least one of the following criteria was met: studies evaluated non-cancer populations, only reported or measured costs that were not defined as indirect costs (e.g. out-of-pocket), were not full-text articles (e.g. conference abstracts), or were conducted without employing Canadian data. After running the search,

the identified records were screened by title and abstract, followed by a full-text review by two independent reviewers (NI and BE). Any article that either reviewer included at the title/abstract review stage was included for full-text review. Disagreements at the full-text stage were settled by discussion until a consensus was reached with a third reviewer (CdO).

2.3 Data Extraction

We extracted the following data from the included studies: authors' names, title of the study, year of publication, type of publication (e.g. article, report), jurisdiction (e.g. federal-, province- or territory-level analysis), cancer site, cancer care continuum (from diagnosis to end-of-life care), study population, type of study (e.g. prospective), sample size, mean age of population examined, proportion of females reported in the study, employment status, income level, control/comparison group, and databases/sources used. Regarding the outcome of interest, we extracted data on the definition of the indirect cost, methods, and tools (e.g. surveys) used to measure the indirect costs, cost estimates, currency, currency year, and time frame or recall period. Costs were reported and divided by different categories: (1) lost earnings (at the patient level), (2) caregiving time costs; (3) home production losses, defined as production activities within the household, which are usually not remunerated (e.g. cleaning). Caregiving costs and home production losses were reported separately, as caregiving might not always be delivered at home; (4) lost patient time (i.e. lost leisure time) (5) morbidity-, disability-, and premature mortality-related costs (productivity losses and time lost due to cancer-related disability and mortality); (6) friction costs (costs that employers incur when replacing absentees); and (7) aggregated productivity losses from a societal perspective.

2.4 Quality Assessment

Quality assessment was ascertained using the Newcastle-Ottawa Assessment Tool [12] and conducted by two independent reviewers (NI and BE). Prospective and retrospective studies were evaluated with specific versions adapted to cohort and cross-sectional study designs, respectively [12]. Three domains were evaluated for all prospective and retrospective studies: selection (i.e. representativeness of the sample), comparability (i.e. comparability of subjects, inclusion of confounding factors), and outcome (i.e. assessment of outcome, statistical test used). A 'star system' was used to judge the extent to which each individual study accounted for issues concerning these three categories. Each domain was assessed for risk of bias (unclear, low, or high) according to the total score assigned and the pre-specified and validated thresholds identified by the tool developers. For

retrospective studies, the maximum scores for the Selection, Comparability and Outcome domains were 5, 2, and 3 stars, respectively. Studies were identified as having low risk of bias if their overall score was 8 or higher. Studies with an overall score below 5 were identified as having a high risk of bias. For prospective studies, the maximum scores for the Selection, Comparability and Outcome domains were 4, 2, and 3 stars, respectively. Studies were identified as having low risk of bias if the Selection, Comparability, and Outcome domains scored at least 3, 1, and 1 star(s), respectively. Studies were identified as having high risk of bias if the Selection domain scored less than 2 stars, or if the Comparability or Outcomes domains scored no stars. Quality assessment was not conducted for studies that used predictive models based on incidence cost approaches.

2.5 Evidence Synthesis

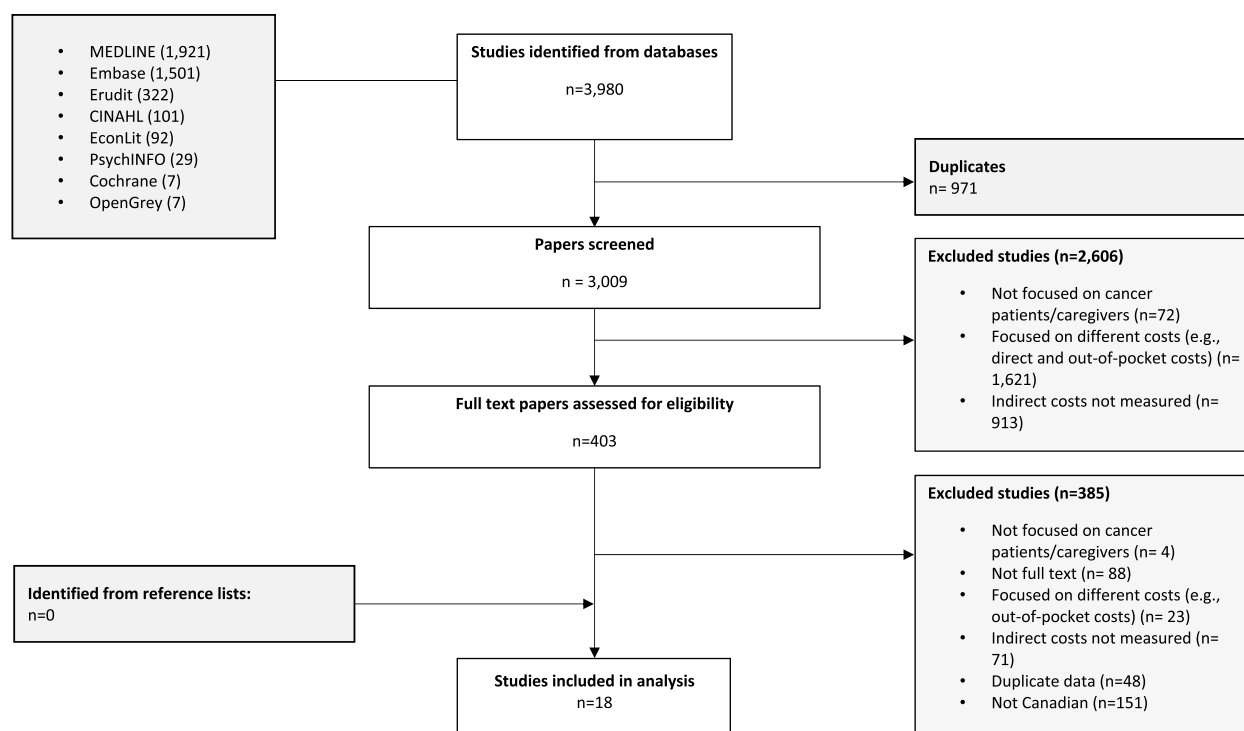
We provided a description of the different types of costs reported in the literature and conducted a narrative synthesis of the estimation methods employed. Indirect costs were reported as an annual expenditure, and converted to 2020 Canadian dollars (CAD) using the Consumer Price Index from the Bank of Canada Inflation Calculator [13]. A meta-analysis was not undertaken due to the heterogeneity of the patient populations and cost definitions. Therefore, we undertook a narrative synthesis of the literature.

3 Results

3.1 Summary of Studies

Searches on the electronic database identified 3980 records, of which 3009 were unique (971 duplicates); 403 were included for full-text review. Among the 403 studies, 18 Canadian studies were ultimately retained [14–31]. The results of the electronic searches, the eligibility criteria and the reasons for exclusion are presented in Fig. 1. Over half of the excluded records (62%) in the title/abstract review stage reported costs that were not relevant (e.g. direct costs), and 18% of the full-text studies failed to explicitly report or measure indirect costs. Non-Canadian studies were only excluded during the full-text review ($n = 151$).

The study characteristics of the included studies are summarized in Table 1. The combined sample size of the 18 studies was 550,501 cancer patients and/or caregivers and ranged from 50 to 196,050 individuals. Studies with large samples usually identified cases through the linkage of various administrative datasets, such as the Canadian Cancer Registry, census data, the Labour Force Survey, the Canadian Community Health Survey, and the tax files. A total of 547,162 cancer patients were identified through



Note: This diagram shows the flow of information through the different sections of the systematic review, including the identified, excluded and included studies after the title/abstract and full-text reviews.

Fig. 1 Preferred reported items for systematic reviews and meta-analyses (PRISMA) diagram

these databases. Cohort studies were usually smaller due to the elevated costs associated with enrolling and following patients over time and collecting data on their incurred indirect costs; a total of 1962 patients and 1377 caregivers were enrolled in the prospective studies. Seven studies were prospective (38%), five were retrospective (28%) and 6 used mathematical models (33%) to predict cancer cases and estimate the indirect cost burden. The papers with predictive models employed Markov chains [19], population attributable fractions [20, 25], and incidence-based approaches using data from cancer registries [14, 21, 26]. The publication years ranged from 2006 to 2018. Seven studies (38%) reported on the indirect cost burden of cancer at the national level, while 6 (33%) focused exclusively on Ontario, 3 (17%) on Quebec, and 1 (5%) on Nova Scotia. One study (5%) evaluated the indirect cost burden on multiple provinces (Manitoba, Quebec, and Nova Scotia). Regarding patient populations, half evaluated multiple cancer types. Among these, two focused exclusively on pediatric populations. The remaining studies estimated costs for individual cancer sites, including breast, bladder, colorectal, lung, prostate, lung, mesothelioma, and melanoma. The mean age of the non-pediatric populations ranged from 48 to 73 years of age, while the mean age for the pediatric populations was 7.8 years. The percentage of females was close to 50% for most

studies. Finally, half of the studies evaluated the indirect burden across the entire cancer care continuum, from diagnosis to palliative and end-of-life care. Three studies (16%) focused exclusively on patients undergoing cancer treatment; two (11%) on palliative and end-of-life care, and two (11%) on survivorship.

3.2 Indirect Costs

The reported indirect costs were extracted and divided into the following categories: lost earnings, caregiver time costs, home production losses, patient leisure time costs, premature death/disability costs, friction costs, and societal productivity losses:

1. Lost earnings

The estimates of the indirect costs were reported by category and presented in Table 2. Further information regarding the cost definitions and methods of estimation for each study is summarized in Appendix 3. The most commonly reported indirect costs were lost earnings for cancer patients and their caregivers. After transforming all estimates to annual costs, the average wage loss ranged from \$4538 (in 2020 CAD) for the members of the families' support networks who resided outside the families'

Table 1 Study characteristics

First author and year	Jurisdiction	Study population	Databases	Cancer site	Cancer care continuum	Sample size	Mean age (SD)	% of sample female	% of sample employed	Mean income
<i>Prospective individual-level studies</i>										
Dumont et al. 2015 [16]	Manitoba, Nova Scotia, and Quebec	Cancer patients in palliative care and their caregivers, from urban and rural settings	Enrolled patients in a regional palliative care program	Multiple	Palliative care	Total = 416 125 patients and 127 caregivers from urban areas 80 patients and 84 caregivers from rural areas	66.7 (11.2)	59.80%	31% of caregivers NR for patients	NR
Lauzier et al. 2010 [22]	Quebec	Breast cancer patients and their caregivers	Patients enrolled	Breast	Treatment, Survivorship	50 (26 patients and 24 caregivers)	NR	100% of patients (NR for caregivers)	NR	NR
Lauzier et al. 2008 [23]	Quebec	Breast cancer patients and their caregivers	Patient medical records	Breast	Treatment, Survivorship	800	50.3 (7.2)	100%	57%	702 (537) weekly
Longo et al. 2006 [24]	Ontario	All outpatient cancer clinic patients aged > 18 years receiving treatment for breast, colorectal, lung, or prostate cancer	Patients enrolled	Breast, Colorectal, Lung, Prostate	Treatment	282	60.6	44%	NR	36% earned < 20,000 per year
Tsimicalis et al. 2013 [28]	Ontario	Households with children with cancer	Patients enrolled	Pediatric cancer (e.g. leukemia, lymphomas)	Treatment	99	7.8 (5.2)	57%	NR	NR
Tsimicalis et al. 2012 [29]	Ontario	Households with children with cancer	Patients enrolled	Pediatric cancer (e.g. leukemia, lymphomas)	Treatment	99	7.8 (5.2)	57%	NR	NR
Yu et al. 2015 [31]	Ontario	Patients with terminal cancer and their caregivers	Patients enrolled	Malignant neoplasm	Palliative, End-of-life	186 patients and their caregivers	NR	55%	48%	NR
<i>Retrospective studies employing patient records and/or administrative datasets</i>										
de Oliveira et al. 2014 [15]	Ontario	Prostate cancer survivors	Ontario Cancer Registry, patient charts	Prostate	Survivorship	585	73 (NR)	0%	77% were retired 18% employed	42% reported total annual incomes < \$40,000

Table 1 (continued)

First author and year	Jurisdiction	Study population	Databases	Cancer site	Cancer care continuum	Sample size	Mean age (SD)	% of sample female	% of sample employed	Mean income
Jeon et al. 2017 [17]	Canada	Cancer patients aged < 62 years, who survived for at least 3 years after diagnosis	1991 Census-Longitudinal Worker File [LWF], Canadian Cancer Database, and LWF), Canadian Cancer Registry, Vital Statistics Registry, personal	Multiple	Survivorship	2597	48.12 (NR)	62.80%	NR	\$43,689 per year
Jeon et al. 2017 [18]	Canada	Spouses of cancer patients aged < 59 years	Canadian 1991 Census of Population, Canadian Cancer Database (CCDB), Canadian Mortality Database (CMDB), Canadian Longitudinal Worker File (LWF), T1 Family File (T1FF)	Multiple	From cancer diagnosis onward	4755	48.3 (NR)	43%	93% for men, and 79% women	100,339 (household)
Tompa et al. 2017 [27]	Canada	Mesothelioma and asbestos-related lung cancer patients in 2011	2011 Canadian Labour Force Survey, Canadian National Accounts, 2005 General Social Survey (GSS), Ontario Workplace Safety and Insurance Board, Surveillance Epidemiology and End Results (SEER) registry, 2010 Canadian Survey of Labour and Income Dynamics (S	Lung, Mesothelioma	From cancer diagnosis onward	2331	NR	10%	NR	Tompa et al. (2017)

Table 1 (continued)

First author and year	Jurisdiction	Study population	Databases	Cancer site	Cancer care continuum	Sample size	Mean age (SD)	% of sample female	% of sample employed	Mean income
Wranik et al. 2017 [30]	Nova Scotia	Occupational cancer cases from 1996 to 2013 in Nova Scotia	Workers Compensation Board of Nova Scotia administrative claims, Association of Workers Compensation Boards of Canada provincial aggregated cancer claims statistics	Multiple	Diagnosis, Treatment, Survivorship	304	NR	NR	100%	NR
<i>Predictive models</i>										
Boucher et al. 2010 [14]	Quebec	Predicted cancer patients in 2008	Institut de la statistique du Quebec data on GDP and other Quebec administrative data, Fichier des tumeurs du Quebec (1984-1998)	Multiple	From cancer diagnosis onward	103,000 cancer cases	NR	52%	NR	NR
Jung et al. 2018 [19]	Canada	Occupational bladder cancer patients	Cancer Care Ontario (five-year survival probability data), Alberta Oncology Guideline, 2011 Labour Force Survey (LFS), 2010 Survey of Labour and Income Dynamics (SLID)	Bladder (occupational)	From cancer diagnosis onward	196,050 estimated cases	NR	NR	NR	NR
Krueger et al. 2016 [20]	Canada	Model-based attributable cancer cases to multiple risk factors	2000-2001 and 2011-2012 Canadian Community Health Survey 2000-2001; Statistics Canada's CANSIM table 103-055035 (cancer incidence)	Multiple	From cancer diagnosis onward	169,580 cancer cases in 2013	NR	NR	NR	NR
Krueger et al. 2010 [21]	Canada	Melanoma cases in 2004	Cancer Surveillance On-line; Canadian Cancer registries	Melanoma	From cancer diagnosis onward	4775 cases in 2004	NR	47%	NR	NR

Table 1 (continued)

First author and year	Jurisdiction	Study population	Databases	Cancer site	Cancer care continuum	Sample size	Mean age (SD)	% of sample female	% of sample employed	Mean income
Mofidi et al. 2018 [25]	Canada	Model-based attributable cancer cases to solar radiation	2010 Canadian Community Health Survey (CCHS), 2009–2011 Canadian Population Life Expectancy, 2011 Canadian System of National Accounts (CSNA), 2005 General Social Survey (GSS), 2011 Canadian Labour Force Survey (LFS), 2011 Occupational Cancer Research Cen	Non-melanoma skin cancer (occupational)	From cancer diagnosis onward	53,696 cases, of which 4,556 were attributed to solar radiation	NR	NR	100%	NR
Smetanin et al. 2011 [26]	Ontario	Lung cancer cases in 2011 and predictions for 2041	Cancer Care Ontario (CCO), CCR database, CANSIM	Lung	From cancer diagnosis onward	8298 new cases on lung cancer in 2011 - 11,568 predicted cases in 2041	68 (NR)	48%	NR	NR

CCR Cancer Care Registry, NR not reported, SD standard deviation

Table 2 Reported indirect costs by category

Cost category	Author	Original cost estimate	Cost per year in 2020 CAD	Unit	Province	Cancer type
Lost earnings (patients)	Jeon et al. 2017 [17]	Lost earnings unconditional on working = \$4832 per year (9.8% reduction compared with controls)	\$5743	Per patient	Canada	Multiple
	Jeon et al. 2017 [18]	Lost earnings for males = \$2700, and \$6900 for females per year	\$3209 (males) \$8201 (females)	Per patient	Canada	Multiple
	Jung et al. 2018 [19]	Total lost productivity = \$71,562 per case per year	\$83,256	Per patient	Canada	Bladder (occupational)
	Lauzier et al. 2010 [22]	Lost earnings among self-employed patients = 37% median wage loss and 18% among salaried employees	-	-	Quebec	Breast
	Lauzier et al. 2008 [23]	Average wage loss of 27% (\$9311) of the projected annual salary, after taking into account financial compensation (43% among self-employed, and 24% among employees)	\$12,440	Per patient	Quebec	Breast
	Longo et al. 2006 [24]	20% patients who were working lost mean income of \$1270 over 30 days \$101 per day of work missed	\$46,900	Per patient	Ontario	Breast, colorectal, lung, prostate
	Tompa et al. 2017 [27]	Wage loss for mesothelioma: \$26,501,879 in 2011 (\$62,102 per case) Wage loss for asbestos-related: \$126,275,066 in 2011 \$66,314 per case)	\$72,250 (mesothelioma) \$ 77,151 (asbestos-related lung cancer)	Per patient	Canada	Lung, mesothelioma
	Tsimicalis et al. 2013 [28]	Monetary work loss over 3-month period: \$910	\$4538	Per patient	Ontario	Pediatric cancer (e.g. leukemia, lymphomas)
	Yu et al. 2015 [31]	Cost of lost time from employment: \$84.06 over the entire palliative trajectory	-	-	Ontario	Multiple

Table 2 (continued)

Cost category	Author	Original cost estimate	Cost per year in 2020 CAD	Unit	Province	Cancer type
Caregiving time costs	Boucher et al. 2010 [14]	Cost supported by caregivers was of \$177.7 million in Quebec in 2008 (cost per family = \$7468)	\$9145	Per household	Quebec	Multiple
	Dumont et al. 2015 [16]	Rural areas: \$4616 caregiving time per 6 months Urban areas: \$4559 caregiving time per 6 months	\$10,972 (rural areas) \$10,836 (urban areas)	Per household	Manitoba, Nova Scotia, and Quebec	Multiple
	Jung et al. 2018 [19]	Informal caregiver costs = \$17,547 per case per year	\$20,414	Per patient	Canada	Bladder (occupational)
	Longo et al. 2006 [24]	35% of family caregivers lost \$700 per month	-	-	Ontario	Breast, colorectal, lung, prostate
	Tompa et al. 2017 [27]	Cost for informal care: Mesothelioma: \$5,790,544 (\$13,569 per case) Asbestos-related: \$32,857,086 (\$17,255 per case)	\$15,786 (mesothelioma) \$20,074 (asbestos-related lung cancer)	Per patient	Canada	Lung, mesothelioma
	Tsimicalis et al. 2012 [29]	Opportunity cost of providing care to child: \$1,259 to 49,236 Mean family opportunity cost: \$22,873 per 3 months	\$1569–\$61,388	Per patient	Ontario	Pediatric cancer (e.g. leukemia, lymphomas)
Home production losses	Jung et al. 2018 [19]	Home production losses - \$20,864 per case per year	\$24,273	Per patient	Canada	Bladder (occupational)
	Mofidi et al. 2018 [25]	Basal cell carcinoma: \$491,744 per year (\$173 per case) Squamous cell carcinoma: \$499,990 per year (\$292 per case)	\$201 (basal cell carcinoma) \$339 (squamous cell carcinoma)	Per patient	Canada	Non-melanoma skin cancer (occupational)
	Tompa et al. 2017 [27]	Mesothelioma: \$87,632,043 (\$205,347 per case) Asbestos-related: \$356,526,546 (\$187,232 per case)	\$238,904 (mesothelioma) \$217,829 (asbestos-related lung cancer)	Per patient	Canada	Lung, mesothelioma
	Yu et al. 2015 [31]	Household work-related costs: \$2085.17 over the entire palliative trajectory	-	-	Ontario	Multiple

Table 2 (continued)

Cost category	Author	Original cost estimate	Cost per year in 2020 CAD	Unit	Province	Cancer type
Patient time-leisure costs	de Oliveira et al. 2014 [15]	Time costs: \$838 (\$442–1233) per year	\$1044	Per patient	Ontario	Prostate
Morbidity, short-term disability, and premature mortality	Krueger et al. 2010 [21]	Non-workforce participation costs = \$250M (leisure time and unpaid work)	\$331.8 billion	Society	Canada	Melanoma
	Tsimicalis et al. 2013 [28]	Monetary leisure time over 3-month period: \$3751	\$18,704	Per patient	Ontario	Pediatric cancer (e.g. leukemia, lymphomas)
	Yu et al. 2015 [31]	Leisure time-related costs: \$13,728.42 over the entire palliative trajectory	-	-	Ontario	Multiple
Morbidity, short-term disability, and premature mortality	Boucher et al. 2010 [14]	Premature mortality: \$2.42 billion for Quebec in 2008	\$ 2.98 billion	Society	Quebec	Multiple
	Krueger et al. 2016 [20]	Short-term disability among females – \$51M	\$57.1 million – short term (females)	Society	Canada	Multiple
		Short-term disability among males – \$66M	\$73.9 million – short term (males)			
		Long-term disability among females – \$282M	\$315.7 million - long term (females)			
		Long-term disability among males – \$369M	\$413 million – long term (males)			
	Krueger et al. 2016 [20]	Premature mortality among females – \$3.1B (\$1.3B attributable to tobacco) Among males – \$4.0B (\$2.0B attributable to tobacco)	\$3.47 billion (females) \$4.48 billion	Society	Canada	Multiple
Krueger et al. 2010 [21]	Indirect costs due to premature mortality: \$457 million for 2004, \$741.96 million for 2031; morbidity: \$8.7 million for 2004, \$17.98 million for 2031	\$ 606 million (premature mortality) \$ 11.5 million (morbidity)	Society	Canada	Melanoma	
Friction costs	Boucher et al. 2010 [14]	\$72.2 million in Quebec in 2008	\$88.4 million	Society	Quebec	Multiple
	Jung et al. 2018 [19]	\$20,618 per case per year	\$23,987	Per patient	Canada	Bladder (occupational)
	Tompa et al. 2017 [27]	Mesothelioma: \$2,360,170 (\$5531 per case) Asbestos-related: \$10,542,816 (\$5537 per case)	\$6434 (mesothelioma) \$6450 (asbestos-related lung cancer)	Per patient	Canada	Lung, mesothelioma

Table 2 (continued)

Cost category	Author	Original cost estimate	Cost per year in 2020 CAD	Unit	Province	Cancer type
Lost productivity (society)	Boucher et al. 2010 [14]	\$258.9 million for decrease in labor participation rate in Quebec in 2008	\$317 million	Society	Quebec	Multiple
	Mofidi et al. 2018 [25]	Basal cell carcinoma: \$650,515 Squamous cell carcinoma: \$6988,950	\$756,822 (basal cell carcinoma) \$8,131,090 (squamous cell carcinoma)	Society	Canada	Non-melanoma skin cancer (occupational)
	Smetanin et al. 2011 [26]	Total wage-based productivity lost for 2011 = \$135.4 M Total wage-based productivity lost for 2041 = \$1.1B	\$157 million (2004) \$1.8 billion (2041 prediction)	Society	Ontario	Lung
	Tompa et al. 2017 [27]	Total productivity losses: Mesothelioma: \$117,130,994 in 2011 (\$276,143 per case) Asbestos-related: \$498,309,077 in 2011 (\$261,690 per case)	\$321,270 (mesothelioma) \$304,455 (asbestos-related lung cancer)	Society	Canada	Lung, mesothelioma
	Wranik et al. 2017 [30]	Total cost from 1996 to 2013 for Canada: \$1,228,763,000 Average annual cost for Canada: \$68,265,000	\$75,571,107	Society	Nova Scotia	Multiple

CAD Canadian Dollars

home in Ontario [28] to \$83,256 among patients with bladder cancer nationwide [19]. The evidence suggests that self-employed patients faced higher earning losses compared to salaried patients. Two studies conducted in Quebec estimated that self-employed patients with breast cancer experienced a wage loss of 48% and 37% of their projected salary, compared with 24% and 18% among salaried patients, respectively [22, 23]. On the other hand, a study that used a prediction model to calculate the productivity losses of the spouses of cancer patients estimated higher annual mean costs among females compared to males (\$8201 and \$3209, respectively) [18].

2. Caregiver time costs

Caregiver time costs were reported to account for non-labour market-related costs. Six studies reported a monetary value associated with the time that people spent caring for cancer patients. The average annual cost ranged from \$15,786 among patients with mesothelioma [27] to \$20,414 for patients with bladder cancer nationwide [19]. One study estimated average caregiver time costs, which ranged from \$1569 to \$61,388 for parents caring for a child with cancer in Ontario [29]. Another study conducted in Manitoba, Nova Scotia, and Quebec estimated that caregivers from rural and urban settings faced similar average annual indirect costs related to informal care (\$10,972 and \$10,836, respectively) [16].

3. Home production losses

Home production losses are a different type of non-market activity costs, which pertain to production activities within the household, such as cooking and childcare, and that do not usually involve a monetary transaction. Home production losses were estimated using an average hourly wage for housekeepers and related occupations. Therefore, home production was often measured as zero for terminal cases due to the inability to work at home. Four studies reported home production losses, with annual average estimates ranging from \$201 for patients with basal cell carcinoma (skin cancer) [25] to \$238,904 among patients with mesothelioma [27]. Average household productivity costs were estimated at around \$2500 per patient per year in Ontario [31].

4. Patient leisure time costs

Patient leisure time costs were estimated in four studies (three conducted in Ontario and one at the national level) by determining the total personal/leisure time lost by patients and their caregivers due to cancer. As an example, de Oliveira et al. (2016) defined these costs as the time taken by patients and an accompanying person to visit health professionals as well as lost leisure time [15]. This time spent seeking care is considered an opportunity cost, as it could have been used to work or spent on different productive or non-productive activities (e.g. leisure). Although these estimates are not nec-

essarily related to the labour market, all were estimated using an average hourly wage to assign a monetary value to the time lost. Krueger et al. estimated total nationwide costs related to lost leisure time and unpaid work as a result of cancer to be around \$331 billion per year [21]. Tsimicalis et al. estimated lost leisure time of \$18,704 per year per parent who cared for children with cancer in Ontario [28]; Yu et al. estimated a similar cost of \$13,000 per year per cancer patient [31].

5. Premature death/disability costs

Premature mortality and disability-related costs are specific types of productivity losses, which are associated with a loss of earnings/time due to the disease. Cancer patients who cannot go back to work (in the labor market or in the household) due to disease-related disabilities incur additional indirect costs. Patients who eventually die of cancer face similar costs due to premature mortality. Therefore, younger patients usually incurred higher premature mortality costs due to overall productivity losses [20]. Four studies estimated these costs. Two studies concluded that males faced higher average short- and long-term disability-related costs relative to females (\$66 million vs \$51 million, and \$369 million vs 282 million, respectively) [20]. A study in Quebec estimated an annual indirect cost associated with cancer-related mortality at around \$2.98 billion [14]. Another study estimated an annual cost of \$606 million due to premature mortality, and \$11.5 million due to morbidity caused by melanoma at a national level [21]. Finally, the indirect cost associated with premature cancer-related mortality attributable to tobacco was estimated at \$2.4 billion for males and \$1.7 billion for females at the national level [20].

6. Friction costs

Friction costs were estimated in three studies. The friction cost approach defined friction costs as the costs and time that employers incur to replace workers who become absent due to cancer and to train the new workers who replace them [32]. In Quebec, the total friction cost faced by employers was estimated to be about \$88.4 million per year [14]. This cost accounted for the chain effect of job vacancies and friction time that occur as people shift between positions as they become available. Other studies found an annual friction cost of \$23,987 per patient among a bladder cancer population [19], and \$6400 per patient with lung cancer [27].

7. Societal productivity losses

Finally, five studies estimated productivity losses at the societal level. Unlike the previous categories, these estimates accounted for different types of indirect costs, such as lost productivity and home productivity losses in a single value. The overall productivity loss to society represents a multidimensional and more comprehensive measure of the indirect cost. The annual productivity

loss due to a decrease in labor market participation associated with cancer was estimated at \$317 million in Quebec [14]. The same cost was estimated to be around \$157 million in Ontario among lung cancer patients [26]. Lastly, Wranik et al. estimated total productivity losses in Canada due to cancer from 1993 to 2013 and found an average cost of \$75 million per year [30].

3.3 Approaches to Measuring Indirect Costs

Productive labor market costs: All studies, which estimated work productive labor market costs, employed the human capital approach [33]. To obtain total and per-patient indirect cost estimates, some studies used a setting-specific average wage to assign a monetary value to the time lost from work and multiplied it by the overall time lost attributed to cancer. Other studies estimated patient-level costs based on the individual reported wages from tax files, surveys, or interviews. Three studies also employed the friction cost approach to estimate the short-term costs that employers incur due to absenteeism (staying home while sick) of cancer patients and their caregivers [14, 19, 27]. These costs pertain to the time required by employers to recruit and train new workers.

Productive non-labor market costs: These costs pertain exclusively to activities that are not related to labor market activities. Studies that reported on these costs also used the human capital approach to assign a monetary value to the leisure time lost, the time spent caring for patients, home production losses, and unpaid work.

3.4 Quality Assessment

The risk of bias assessment of retrospective and prospective studies is presented in Figure 2 and Appendix 4. While more than half of the studies had a low risk of bias, the studies with unclear and high-risk of bias usually failed to provide a thorough description of patient recruitment or the tools utilized to measure and report the outcome of interest. Overall, 60% of the retrospective studies had a low risk of bias, mainly due to a selection of an adequate and representative sample. Most of these studies employed administrative databases that allowed the identification of large samples that are usually generalizable. Furthermore, some of these studies with low risk of bias defined a control group of non-cancer patients to estimate incremental costs rather than net costs. They also employed various regression and statistical analyses that allowed controlling for potential confounder variables to further explain how different factors might be associated with indirect costs. However, 40% of the studies failed to provide a detailed and adequate methodology to select a representative sample size. Since the comparability and outcome dimensions were complete and appropriately defined, these studies were identified as having unclear risk of bias. No cross-sectional study had a high risk of bias. A similar proportion of prospective cohort studies had a low risk of bias (57%). These studies adequately ensured that most patients were adequately followed-up and that the outcome assessment of the indirect cost burden had well-defined time horizons. Studies with unclear (29%) and high risk of bias (14%) usually lacked a description of the

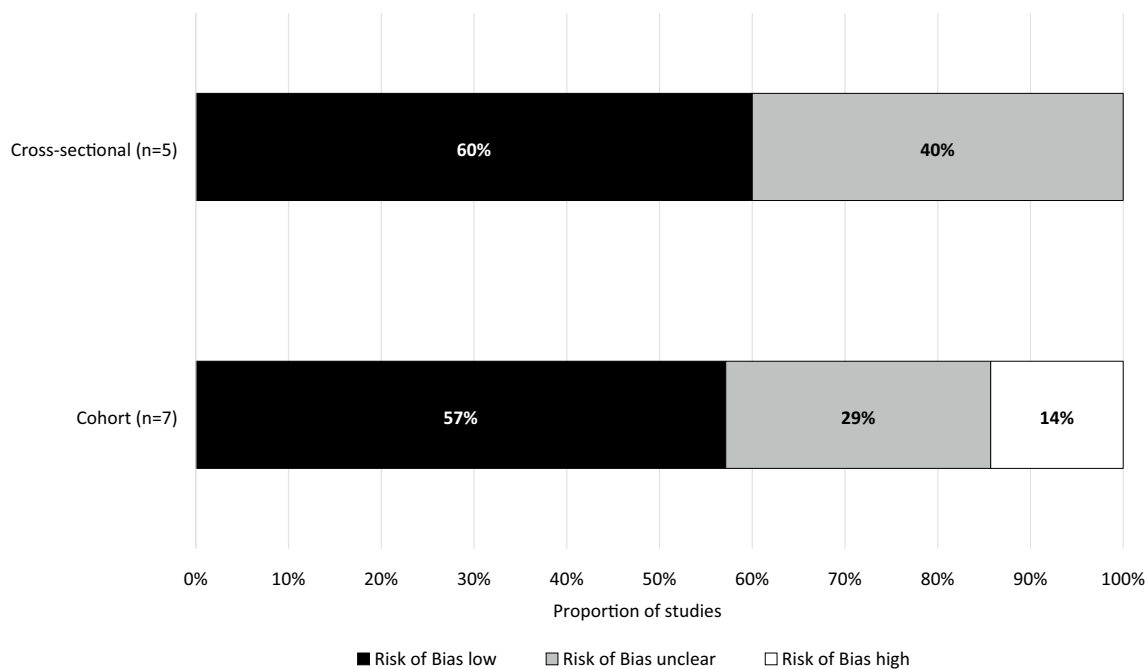


Fig. 2 Quality assessment of individual studies using the Newcastle-Ottawa Assessment Tool

recruitment process to ensure representativeness of the sample or lacked a thorough description of how the outcomes were assessed (i.e. self-reports).

4 Discussion

This study presents an up-to-date and comprehensive review of the most recent literature on the indirect cost burden of cancer in Canada. We systematically reviewed studies that estimated labor and non-labor market-related costs, ranging from lost earnings to household productivity losses. The evidence suggests that cancer patients and their caregivers face a substantial indirect cost burden due to premature mortality and short- and long-term disabilities. Most of the reported costs were work-related productivity losses, rising to \$80,000 per patient per year. Leisure time costs and home production losses were also considerable, with maximum estimates of \$18,000 and \$240,000 per patient per year, respectively. Friction costs borne by employers were estimated at around \$24,000 per patient per year. Annual productivity losses at the societal level ranged from \$75 million in Nova Scotia to \$317 million in Quebec. We also found that caregivers of pediatric patients, women, younger patients, and those who were self-employed tended to face higher indirect costs.

A previous report by the Public Health Agency of Canada (PHAC) used a prevalence-based approach to evaluate the economic burden of chronic conditions between 2005 and 2008, and estimated the indirect cost of cancer to be around \$586,000,000 in 2008 [8]. However, this value was likely underestimated, since the definition of the indirect cost burden was limited to the production losses due to illness, injury or premature death [8]. Other costs associated with non-labor market activities, such as leisure time and informal caregiving, were not considered. Similarly, Hopkins et al. conducted a multi-database literature search on the national wage loss from cancer in Canada [9]. The studies identified in this review also limited their analyses to work-related costs. Our results provide an up-to-date and complete review of the indirect cost burden of cancer in Canada, by including literature published within the last 15 years and non-market-related costs, which account for a considerable portion of the burden. This review highlights the importance of ensuring that future reports and reviews reflect a more comprehensive assessment of the indirect burden of cancer to better account for all of the dimensions identified in this study in Canada.

Two methods were identified in the literature to measure indirect costs – the human capital and the friction cost approaches. The human capital methodology applies average wages by sex and age to estimate the value of the time lost, usually from a labor market perspective [33]. Even though some indirect costs are not explicitly linked with workplace productivity (e.g. leisure time, or home productivity losses),

the human capital estimation method allows assigning a monetary value to time (however defined). On the other hand, the friction cost approach assumes that work-related productivity losses are expected to be mitigated due to the eventual replacement of absentees [32]. As such, this theory suggests that in the long run, the society will adapt and reach the original production level as patients who leave the workforce are eventually replaced after an adaptation period. The costs associated with this short-term cycle are defined as friction costs. Some authors suggest that the friction cost method yields more accurate estimates compared to the human capital approach [8]. This is because friction costs do not overestimate the productivity losses by only considering the time it takes for society to replace the cases of absentees instead of assuming permanent vacancies. However, the friction cost approach usually neglects non-productive time (e.g. household production, leisure time) [33]. Although the human capital approach can be used to estimate non-market activity costs, the underlying assumptions need to be questioned to produce more nuanced and useful estimates. In particular, using a median wage to estimate lost wages due to cancer as opposed to actual wages could produce estimates that can be generalized across a broader population, which includes people who work at low-wage jobs. There are inherent assumptions about the value of time involved in the human capital approach, namely that the costs to individuals, families, and societies are higher if individuals earn higher wages; however, the burden is often highest for those with lower incomes. In other words, there are ethical implications to choices surrounding how to value indirect costs across a population.

We identified a trade-off between collecting primary data from patients and family members prospectively and using cross-sectional and longitudinal databases. Results from studies employing large administrative datasets are more easily generalizable to the overall population (if selected appropriately) and allow for the collection of individual-level cost data for those who are represented therein. However, they have inherent limitations associated with the lack of quality controls and missing data issues. Prospective studies, on the other hand, allow for more precise data collection and, therefore, a more nuanced understanding of how cancer affects families across the care continuum. But these studies tend to be smaller in scale and may not address selection issues; their data collection may also be burdensome to patients and families. As such, it is fundamental to acknowledge the different types of data sources to understand the different ways in which the indirect cost burden can be reported. Although they provide an estimate of the indirect cost burden at different scales, both the micro (i.e. patient) and macro (i.e. societal) perspectives must be synthesized and understood to adequately shape policy focused towards reducing this burden. This two-pronged approach

will provide a more comprehensive picture of the full indirect cost burden that individuals and society incur.

4.1 Limitations

There were some limitations associated with the review. By limiting our search to studies published after 2006, we may have missed relevant papers and reports, grey literature, or non-academic references that the previous reviews failed to capture. There were also limitations with the evidence identified. Although cost estimates can be useful in directing resources for programming, cancer care is highly variable according to clinical factors such as tumor site, stage of cancer care, and stage of diagnosis; population demographics; geographic location; and coverage of oral chemotherapy and other types of medical and non-medical costs. Therefore, while aggregated cost estimates may help raise awareness of the overall cancer burden and allow for comparisons, greater efforts are needed to showcase the particular relevance to policy or programming to help address needs and barriers. Key clinical and population variables to consider across all cost areas include cancer survival probability and curative intent (vs palliative care), stage of diagnosis and stage of life at diagnosis, the level of invasiveness of treatment and the consequences of treatment interventions, and variability in access by different populations to cancer treatment. Therefore, there is a need for stratified cost estimates by cancer site, patient groups, and the cancer care continuum. Furthermore, future work should focus on understanding the provision of support and access to resources across different settings, provinces, and workplaces, which are intended to help mitigate indirect costs.

5 Conclusion

This review makes an important contribution to the literature on the economic burden of cancer in Canada, in particular the indirect burden. Measuring and describing the indirect costs faced by cancer patients and their caregivers allows for a better understanding of the different types of productivity losses and time costs. Once the different categories of the indirect costs are understood, it is important to consider ways to integrate these inputs in economic evaluations to get a better picture of the actual burden of illness from different perspectives. For instance, when indirect costs to patients (e.g. missed days of work while hospitalized) are accounted for in economic evaluations, drug expenses could be considered to be cost effective. However, work-related productivity losses are not the only indirect costs that should be considered when conducting economic evaluations from a more comprehensive societal perspective. According to the guidelines

for the economic evaluation of health technologies in Canada from the Canadian Agency for Drugs and Technologies in Health (CADTH), when conducting an evaluation from a societal perspective, all relevant costs to the patients, caregivers, and employers must be considered (e.g. patient out-of-pocket costs, patient time, lost productivity, home production costs, friction costs) [34]. This review suggests that the work productivity losses and the non-labor-market costs are considerable and should be considered in order to adequately measure the indirect burden from a societal perspective. These results will also help support a research agenda to fill the knowledge gaps with respect to direct and indirect costs of cancer across provinces and territories, and population sub-groups in Canada.

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Affiliations

Nicolas Iragorri^{1,2,4}  · Claire de Oliveira^{1,2,3} · Natalie Fitzgerald¹ · Beverley Essue^{1,2}

¹ The Canadian Partnership Against Cancer, Toronto, ON, Canada

² Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, The University of Toronto, Toronto, ON, Canada

³ Centre for Health Economics and Hull York Medical School, University of York, Heslington, York, UK

⁴ University of Toronto, 27 King's College Cir, Toronto, ON M5S, UK