Published in final edited form as:

Eur J Oncol Nurs. 2018 August ; 35: 22–32. doi:10.1016/j.ejon.2018.04.004.

A Systematic Scoping Review of the Recent Literature (~2011–2017) About the Costs of Illness to Parents of Children Diagnosed with Cancer

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Abstract

PURPOSE: The study purpose was to map and identify gaps in the recent (~2011~2017) literature on the costs of illness to parents of children diagnosed with cancer. The costs of illness include direct costs, indirect costs and psychosocial costs.

METHODS: A systematic scoping review was conducted. Data sources included PubMed, CINAHL, PsychInfo and EconLit. Studies were eligible for inclusion if they were conducted in high-income countries, published in the English language, and reported parent perspectives on direct costs, indirect costs and/or psychosocial costs due to financial costs.

RESULTS: 25 studies were eligible. Most were conducted in Canada, the USA, or Sweden. The studies used a variety of designs, target populations, time frames and sample sizes. Intervention studies were lacking. Across studies fathers were underrepresented. While no study comprehensively measured costs of illness, more studies used rigorous methods and considered psychosocial costs. Financial costs were measured using a micro-costing or general estimates approach. Psychosocial costs were measured using a variety of PRO measures, some of which were investigator developed. The studies provide evidence that financial toxicity occurs in pediatric oncology.

CONCLUSIONS: Future studies should comprehensively measure costs using a consistent set of established measures and make efforts to recruit fathers to cost of illness research. Interventions to mitigate financial toxicity are needed.

Keywords

Cancer; child; cost of illness; financial toxicity; systematic scoping review

1. Introduction

Childhood cancer is costly to both the healthcare system (Kaul et al., 2015; Price et al., 2009) and to parents (NASEM, 2015). Costs to parents include the direct (out-of-pocket expenditures) and indirect (productivity loss) costs of meeting their child's medical and

informal caregiving needs. Together, these direct and indirect costs generate illness-related financial burden, which in turn produces psychosocial (somatic and psychological symptoms, quality of life declines) costs for parents and families (Hodgson and Meiners, 1982). In adult oncology, this problem has been termed “financial toxicity” (de Souza et al., 2014; de Souza et al., 2017; Zafar and Abernethy, 2013a; 2013b). Cancer-related financial costs are potentially “toxic” in that, in addition to any psychosocial costs incurred, patients and caregivers may attempt to control cancer-related financial costs by using financial coping behaviors (tangible efforts to ease financial burden). Risky financial coping behaviors include suboptimal adherence to recommendations from health professionals regarding cancer therapy, monitoring for treatment toxicities and disease recurrence, and lifestyle behaviors (regular primary care, healthy dietary intake, regular physical activity) to control risk for co-morbid conditions. Such risky financial coping behaviors can augment existing disparities in cancer-related health outcomes (de Souza et al., 2014). To our knowledge, the term financial toxicity has not been used in the pediatric oncology literature.

To determine the state of knowledge about costs of childhood cancer to parents and families, Tsimicalis and colleagues (2011) systematically reviewed 13 eligible studies published over a 31-year time period (1979–2010) and evaluated their quality. Their review identified considerable methodological heterogeneity in the included studies, which caused difficulties with the evaluation component of the review and limited the researchers’ ability to make across-study comparisons. The review also found that while all included studies identified considerable direct or indirect costs, few assessed both of these cost components or conducted the assessments in methodologically rigorous ways. Further, while two studies included in their review reported negative effects of financial costs on psychosocial aspects of life (vacations, hobbies, social activities), no study assessed psychological costs in detail nor did any study include an established measure of quality of life. The authors concluded that the enormity of the costs of childhood cancer to parents and families remains unclear (Tsimicalis et al., 2011).

Over the six years since publication of the Tsimicalis et al. review, direct medical costs (cost to the healthcare system for providing products and services to a patient or patient population) have persistently risen. Simultaneously, as a means to control direct medical costs, care has continually shifted to outpatient settings, thus increasing caregiving burden and the associated costs to caregivers. During the same time period, job security has been evasive, wages stagnant and the cost of living has mounted. In the United States of America (USA) for example, 41% of working-age adults report not having \$400 to cover an emergency expense (Board of Governors of the Federal Reserve System, 2017), never mind the exorbitant financial costs associated with the diagnosis, treatment and recovery from childhood cancer. Although the 2010 Patient Protection and Affordable Care Act has increased health insurance coverage in the USA, many working-aged adults and their children are under-insured for catastrophic illnesses like cancer. Adults with lower-incomes struggle to pay health insurance premiums, deductibles, co-pays and prescription drug costs (Obama, 2016). Across high-income countries, undocumented refugees, migrants (De Vito et al., 2015) and immigrants (Hacker et al., 2015) experience multiple barriers to accessing even basic health care for themselves and their children.

During the same time period, assessment of persons' perceptions of their health care experiences, that is, person-reported outcomes (PROs) in research and clinical practice have been recognized as critical to improving health care quality (National Quality Forum, 2013). Although costs of illness to patients, caregivers and families (as compared to direct medical costs) have been difficult to measure in the past (Russell and Bernhardt, 2016; Tsimicalis et al., 2011), digital technologies, recognition of the importance of PROs, and development and validation of PRO measures and item sets now provide means to overcome barriers to collecting these data (Basch and Bennett, 2014). Furthermore, strengthening the rigor of research in the area of "financial toxicity" requires comprehensive measurement of the financial components of the costs of illness (direct costs, indirect costs, financial burden), of the financial coping behaviors that interventions might target and of the consequent psychosocial costs overtime, across the illness trajectory and across populations using rigorous methods and validated measures (Gordon and Chan, 2017; Tsimicalis et al., 2011).

In summary, contemporary parents likely bear greater costs due to childhood cancer than in the past due to the socio-economic environment. Measurement of the costs of childhood cancer to parents and families may have improved since the Tsimicalis and colleagues review given the recognition of the importance of PROs and availability of digital technologies for data collection. Moreover, determining the enormity of the costs of illness using established methods is essential to providing high quality evidence-based comprehensive care for children diagnosed with cancer and their families, and to informing policies to support parents who play vital roles in maximizing medical and quality of life outcomes for children diagnosed with cancer (National Academies of Sciences, Engineering and Medicine, 2015).

The objective of this study is to identify advances and gaps in the recent literature about costs of illness to parents of children diagnosed with cancer and their families. To accomplish this objective, we conducted a systematic seeping review of the recent (~2011–2017) research to address the following research questions:

1. What is the map of this research area?
2. How did recent studies measure the cost of illness components?
3. Do these studies suggest that financial toxicity happens in pediatric oncology?
4. What profile describes parents at risk for financial toxicity?

2. Conceptual framework

Consistent with the Tsimicalis et al. review, we examined costs of illness as conceptualized by Hodgson and Meiners (1982) to include the psychosocial costs generated by direct and indirect costs of illness. *Direct costs* include out-of-pocket expenditures related to the diagnosis and treatment of childhood cancer, to supportive care, to post-treatment monitoring and rehabilitation of cancer-related impairments, to end-of-life care, and to maintaining the family household and household routines while parents attend to the patient's medical needs and provide caregiving. *Indirect costs* include productivity loss due to parental work and/or education disruptions due to caregiving (Hodgson and Meiners,

1982). Indirect costs are reflected in reduction in annual household income and allocation of also assets with monetary value, including time, to address the child's illness (Anderson et al., 2007). *Psychosocial costs*, or declines in quality of life, include new onset or worsened stress and psychological symptoms, poorer psychosocial functioning, deteriorated family function, and degraded living conditions due to illness-related financial burden (Hodgson and Meiners, 1982). Psychosocial costs might also include new onset or worsened somatic symptoms, and poorer lifestyle behaviors (The Family Caregiving Alliance, 2016) attributable to illness-related financial costs and financial coping behaviors.

2. Methods

Our review process was guided by the research questions and the steps for conducting systematic scoping reviews as recommended by the Joanna Briggs Institute (Peters et al., 2015). Systematic scoping reviews are well suited to map a research area, clarify concepts and their boundaries, and identify key factors and knowledge gaps to generate recommendations for future research. This type of systematic review is typically undertaken when there are reasons to suspect, as we did, that full synthesis might not be feasible given methodological heterogeneity or dearth of studies that meet the inclusion criteria. Systematic scoping reviews differ from other types of systematic reviews in that evidence from the included papers is summarized, not synthesized. Additionally, formal assessment of the quality of the included studies is not a review component (Arksey and O'Malley, 2005; Levac et al., 2010; Peters et al., 2015; Tricco et al., 2016)

2.2. Inclusion and exclusion criteria

To be included in the review, studies were required to meet the following criteria: (a) the study investigated the costs of any type of childhood cancer from the perspective of parents living in a country with a high-income economy where state-of-the-science medical and supportive care for children diagnosed with cancer is widely available; (b) data were collected regarding direct costs, indirect costs and/or subsequent financial burden to parents; and (c) the financial coping behaviors and psychosocial costs, if any were described, were explicitly tied to childhood cancer-related financial costs or financial burden. The caregiving may have occurred during any phase of the cancer trajectory and in any care setting.

One of our initial assumptions was that, unlike the USA, other countries with high-income economies as defined by the World Bank (World Bank, 2017) have social policies that completely protect their official residents from financial costs of illness. However, screening identified papers by title and abstracted suggested otherwise. Thus, otherwise eligible papers describing studies conducted in any country with a high-income economy were included in the review. Although we did not expect studies using qualitative approaches to have "measured" costs of illness, studies that applied quantitative and/or qualitative approaches were eligible for inclusion. From the qualitative studies, we sought guidance about specific psychosocial costs and other relevant concepts that should be measured in future costs of illness studies using validated measures.

Excluded from the review were: (a) studies of the medical costs of treating childhood cancer or treatment cost-effectiveness on a population level without including parents' perspectives

on the costs to them and their families; (b) systematic reviews published in 2011 or thereafter that included studies published prior to 2011; and (c) 2010 studies included in the Tsimicalis et al. systematic review.

2.3. Searching

A health sciences librarian with expertise in systematic review strategies assisted with the PubMed, PsycINFO, CINAHL and EconLit database searches using keywords to identify published peer-reviewed studies eligible for inclusion in this review. The search strategy is shown in Table 1. Searches were restricted to: index child aged 0–18 years; English language; and dates of publication (July 01, 2010–). To help ensure that eligible studies were not missed, the searches covered publication dates 6-months prior to publication of the Tsimicalis et al. review. Because only indexed studies can be identified through restricted searches and indexing takes up to six months (personal communication, R. Posey), unrestricted searches (July 01, 2016–) were also conducted. The databases were last searched on August 24, 2017.

Titles and abstracts of all citations obtained through database searches were screened by two independent reviewers (authors MKK and SJS) to determine whether the full text should be read. The reference lists for all studies read in full and another prior related systematic review (Pelletier and Bona, 2015) were hand searched to identify eligible studies not identified through database searches. Additionally, reference list for the Tsimicalis et al. review was read in full to identify studies published in 2010 and ineligible for the current review because they were included in that prior review.

2.5. Extracting Results

Two reviewers (authors MKK and SJS) independently used a pre-established standardized form to abstract data from identified studies that met the eligibility criteria. Development of the data extraction form was guided by Hodgson and Meiners' (1982) conceptualization of costs of illness and data needed to describe the studies and address the research questions. The two reviewers piloted the form by independently rating five studies, and then meeting to review their results and discuss any lack of clarity regarding the form. Minor revisions were made to the form, and the revised form was used to abstract data from all the studies that met the eligibility criteria, including the five used to pilot the form. The reviewers met on a regular basis to review the consistency of their abstractions and resolve any inconsistencies through discussion.

3. Findings

Figure 1 shows the flow of information through the systematic scoping review process and reasons for excluding identified studies from inclusion in the review. The computerized database searches identified a total of 1421 studies. An additional 22 studies were identified through hand searches of the references cited (20 studies) and informal discovery (2 studies) of studies by authors of previously identified studies. Ultimately, 25 studies fit the eligibility criteria for inclusion in the review (see Table 2 for summaries of the included studies).

3.1. Map of the research area

Table 2 and Figure 2 show that the recent studies were heterogeneous in multiple ways. They were conducted in a wide range of countries with high-income economies, predominantly countries with universal health coverage and paid family medical leave for one or both parents. Four teams (two in Canada, one in the USA, one in Sweden) produced most of the recent studies. The number of studies published per year peaked in 2013 (seven) and then dropped.

The included studies are heterogeneous in terms of population of interest, timing relative to the child's diagnosis, and sample size. One study (Hoven et al., 2013b) limited enrollment to parents of children with a specific type of cancer. No study enrolled only fathers, three enrolled only mothers (Fletcher, 2010; Okada, et al., 2015; Santos, et al., 2016), and three focused on parents of either sex who had immigrated (Klassen, et al., 2012b) or were single (Granek, et al., 2012; Rosenberg-Yunger, 2013). Across studies that enrolled parents of either sex, fathers were underrepresented among participants. Time relative to the child's diagnosis also varied widely but can be roughly divided into studies that collected data within the first year of diagnosis, within 5 years, any time during active treatment, anytime during survivorship, or after the child's death. The studies enrolled sample sizes that ranged from 9 (Fletcher, et al., 2010) to 551 (Hoven, et al., 2013b).

As shown in Figure 3, the studies were also methodologically heterogeneous. Five studies used a variety of qualitative approaches (Fletcher, 2010; Granek et al., 2014; Klassen, Gulati et al., 2012; Rosenberg-Yunger et al., 2013; Wakefield et al., 2014), 16 used quantitative approaches (Aung et al., 2012; Bona et al., 2014; Bona et al., 2015; Bona et al., 2016; Cernvall et al., 2017; Dussel et al., 2011; Fluchel et al., 2014; Hoven et al., 2013a; Hoven et al., 2013b; Klassen, Dix et al., 2012; Mader et al., 2016; Okada et al., 2015; Rosenberg et al., 2013; Santos et al., 2016; Warner et al., 2015; Wikman et al., 2016), and three used mixed-methods with quantitative methods forefront (Tsimicalis et al., 2013a; Tsimicalis et al., 2012; Tsimicalis et al., 2013b). Overall, about one-third of the studies used a longitudinal design (Bona et al., 2016; Cernvall et al., 2017; Hoven et al., 2013a; Larsen et al., 2013; Tsimicalis et al., 2013a; Tsimicalis et al., 2012; Tsimicalis et al., 2013b; Wikman et al., 2016); just one of these studies used an experimental design (Cernvall et al., 2017) and this study was not a fully powered randomized control trial.

3.2. Measurement of cost of illness components

Table 2 and Figure 4 show that most studies measured more than one cost of illness component. Five studies (Fluchel et al., 2014; Tsimicalis et al., 2013a; Tsimicalis et al., 2012; Tsimicalis et al., 2013b; Warner et al., 2015) measured both direct and indirect costs of illness using rigorous methods. No study comprehensively measured costs of illness, that is, assessed all of its components. The wide variety of quantitative measures used by recent studies can be categorized into two broad types: monetary measures and PRO measures.

3.2.1. Monetary measures—The studies used monetary measures to collect direct, indirect and psychosocial cost data using either micro-costing or general estimates.

3.2.1.1. With micro-costing (Tsimicalis et al., 2013a; Tsimicalis et al., 2012; Tsimicalis et al., 2013b), parents used an established modular diary (Ambulatory Health Care Record (Guerriere et al., 2006) to record 12 weeks of data about the direct and indirect costs of illness incurred by them and their social network members. Parents recorded these costs during 1 week per month for each of the 3 study months. Parents were interviewed at the end of each data collection week and at the end of the study to help assure that recorded costs for a week reflected costs incurred during that month. Except for travel mileage to which the researchers allocated a set cost, parents were asked to assign prices to their out of pocket expenditures. Time used for caregiving and childcare was assigned a value based on national market value and census wages for the caregiver's sex and age. Time lost from schooling, homemaking and leisure activities was assigned the market value hourly wage for child care givers. Recorded costs were categorized, valued in study year dollars and summed to calculate total costs incurred. Percentages of the total costs for the various direct and indirect costs were also calculated. Average annual family income loss for the study year in the country where the research was conducted and the literature regarding unfair (equal to or greater than 5%) to potentially catastrophic (equal to or greater than 15%) financial burden due to the direct and indirect costs provided bases for interpreting parental financial burden.

3.2.1.2. With the general estimates approach (Bona et al., 2014; Bona et al., 2015; Bona et al., 2016), parents were asked to respond to items or item sets about their household income, indirect costs and indirect costs by indicating which ordinal category best described them/ their family or whether the statement applied to them. Reported family income was adjusted by adding reported income lost to reported household income, expressed as a percentage of the USA federal poverty level (FPL) for a family of four for the data collection year, and then stratified into three levels (<200%, 200–400%, >400% FPL). Percent income lost due to indirect costs was calculated by dividing their annual household income by income lost due to caregiving and also stratified into three levels (<10%, 11–40%, >40% income lost) to allow comparisons with the literature regarding unfair burden. Decline in annual income to below the FPL or new onset material hardships (energy insecurity, food insecurity, housing insecurity) due to indirect costs indicated deteriorated quality of life.

3.2.2. PRO measures—The quantitative studies used two types of PRO measures to measure cost of illness components: established measures and investigator-developed measures. Table 3 shows that eight studies measured cost of illness components using a variety of established PRO measures. However, Rosenberg and colleagues (2013) questioned the suitability of using the Kessler-6 (Kessler, et al., 2002) in research for purposes other than screening. Additionally, three studies used established PRO measures to assess factors that might help parents mitigate financial and psychosocial costs of illness. These factors included social support (Klassen et al., 2012a; Rosenberg et al., 2013), family ritual (Santos et al., 2016) and mastery, self-esteem and optimism (Klassen et al., 2012a).

Other quantitative studies used investigator-developed items or item sets to measure cost of illness components. For example, one study (Bona et al., 2016) used a list derived from the pediatric oncology literature to gauge financial coping behaviors but the study did not provide information about scoring or the tool's psychometric qualities. Furthermore, risky financial coping behaviors such as delaying or foregoing aspects of the child's cancer-

directed or supportive care were not among the behaviors listed for endorsement. The list did include one item related to another family member going without health care.

3.3. Does financial toxicity happen in pediatric oncology?

The findings of recent studies imply that financial toxicity occurs in pediatric oncology and can persist beyond the active treatment phase into survivorship or bereavement. Travel-related expenses (gas, parking, meals, lodging) were a main contributor to direct costs (Tsimicalis et al., 2012; Tsimicalis et al., 2013a), especially for families who travelled more than sixty miles or one hour to the treatment center (Fluchel et al., 2014; Warner et al., 2014). In terms of indirect costs, parent work disruptions ranged between 77% and 94 (Bona et al., 2014; Bona et al., 2015; Dussel et al., 2011). In 30–50% of families, one parent ceased paid work to address the child's caregiving needs (Bona et al., 2014; Bona et al., 2015; Fluchel et al., 2014).

Caregivers reported psychological and somatic symptoms due to their illness-related financial costs and the financial burden created by these costs, including anxiety and depression (Cernvall, et al., 2017; Santos et al., 2016), cognition impairments such as forgetfulness and mixing-up dates (Fletcher, 2010), fatigue (Fletcher, 2010; Granek et al., 2014), guilt about needing assistance (Tsimicalis, et al., 2013a), migraine and tension headaches (Fletcher, 2010), posttraumatic stress symptoms (Cernvall, et al., 2017; Wikman, 2016), psychological distress (Rosenberg et al., 2013), sleep disturbances (Fletcher, 2010; Granek et al., 2014) and social isolation (Fletcher, 2010; Rosenberg-Yunger et al., 2013).

Parents also reported deteriorated quality of life due to financial costs of illness, including scores on a standardized measure of psychological health-related quality of life that were substantially below population norms (Klassen, et al., 2012a), sizeable declines (5% to more than 40%) in annual household income (Bona et al., 2014; Bona et al., 2015; Bona et al., 2016), and new onset food insecurity, housing insecurity and/or utility insecurity (Bona et al., 2014, Bona et al., 2015, Bona et al., 2016, Dussel, et al. 2011)

To manage their financial burden, parents reported using financial coping behaviors that can be expected to lead to poorer health and quality of life outcomes. These coping behaviors can be summarized as neglecting their own mental and physical health (Fletcher et al., 2010; Granek et al., 2014), acquiring debt (Bona et al., 2014; Fletcher et al., 2010), depleting assets with monetary value (selling property, early withdrawal of retirement savings) and stopping investments (retirement and college fund deposits, life insurance payments) in their family's financial security in the future (Bona et al., 2015). After their children successfully completed treatment or died, caregivers had difficulty with workforce re-entry due to their child's ongoing caregiving needs and the emotional toll of childhood cancer on parents and on siblings; this difficulty perpetuated financial problems (Mader, et al., 2016; Okada, 2015; Wakefield, 2014). One study found poorer medical outcomes for children (significantly higher prevalence of graft versus host disease) whose families had lower incomes, which could be due to parental financial coping behaviors such as sub-optimal medication adherence (Bona et al., 2015) as has been described in the adult oncology literature (Bestvina et al., 2014; Kent et al., 2013) and more recently among young adult survivors of childhood cancer (Nipp et al., 2017).

3.4. Profile of risk for financial toxicity

Overall, the results of the included studies suggest that the risk profile for toxicity due to childhood cancer-related financial costs includes social determinants of health: low income (Bona et al., 2014; Bona et al., 2015; Larsen et al., 2013; Tsimicalis et al., 2013a), low education level (Larsen et al., 2013; Mader et al., 2016), residence in a rural area (Fletcher, 2010; Fluchel et al., 2014; Tsimicalis et al., 2012) or at a distance from the treatment center (Fletcher, 2010; Fluchel et al., 2014); difficulty communicating in the country's official language (Klassen et al., 2012b; Larsen et al., 2013; Mader et al., 2016), single-parent (Klassen et al., 2012a; Larsen et al., 2013), existing financial difficulties (Larsen et al., 2013), and existing chronic health conditions (Granek et al., 2014; Larsen et al., 2013).

Other risk factors included younger parent age (Santos et al., 2016), strained relationship with the child's other parent or ex-partner (Fletcher, 2010; Granek et al., 2014), history of interpersonal trauma (Granek et al., 2014), other young children in the home (Larsen et al., 2013), the patient's need for more intensive therapy (Hoven et al., 2013; Larsen et al., 2013; Mader et al., 2016), no established local social network (Larsen et al., 2013; Rosenberg-Yunger et al., 2013; Tsimicalis et al., 2013a), and disruptions in paid work to meet the patient's caregiving needs (Bona et al., 2016; Larsen et al., 2013). Mothers (Aung et al., 2012; Hoven et al., 2013) and parents with low incomes (Dussel et al., 2011) were more likely to experience disruptions in paid work due to childhood cancer. Although their work circumstances appear to be more flexible than for parents with lower incomes, small business owners and highly skilled professionals also experienced heightened risk for work disruptions and difficulty with workforce re-entry (Wakefield et al., 2014). One study found that parents with four or more risk factors required intensive support to mitigate the impact of financial burden on the child's treatment outcomes and the family's quality of life (Larsen et al., 2013).

4. Discussion

This systematic scoping review of 25 peer-reviewed costs of illness papers published over the approximately six years since publication of the Tsimicalis et al. review demonstrates: (a) initial growth in this body of research, which is now waning; (b) use of more rigorous methods to estimate direct and indirect costs; and (c) greater use of established PRO measures to assess psychosocial costs of illness. However, as Tsimicalis et al. and later Pelletier and Bona (2015) also found, most of the recent studies used cross-sectional designs and enrolled small samples. Additionally, the PRO measures varied widely across studies, which made comparisons across studies difficult and, although not a focus of this systematic scoping review, raises concerns about the quality of the data obtained with investigator-developed measures. Moreover, no recent study comprehensively assessed costs of illness. Thus, the enormity of the costs of childhood cancer to parents and the family remain unclear. Also unclear is the extent to which the financial and psychosocial costs of illness to parents and families contributes to disparities in childhood cancer outcomes for the children themselves.

Nonetheless, the results show that the costs of childhood cancer to parents and families are substantial and, for some notably, highly unfair. Major contributors to direct and indirect

costs included treatment-related travel, meals and lodging, and parental work disruptions to provide caregiving. Despite accumulating evidence that costs of illness to parents and families is a significant problem in terms of prevalence and severity, especially among those experiencing social determinants of health, studies that develop and test multi-level interventions are lacking. Such interventions might help parents communicate with providers, employers and social network members about financial costs of illness; promote their health insurance literacy; provide them with education about available financial resources; offer tools to help them take care of themselves psychosocially and physically; and empower them to advocate for social policies that are fair to families of children with serious health problems like cancer. Interventions should also target clinicians to enhance their communications with parents about potential and actual financial problems due to childhood cancer, and referrals to existing resources as indicated. Interventions could also assist parents with communications with employers and workforce re-entry to control the impact of work disruptions on psychosocial costs. Also lacking are studies to implement the strongly recommended pediatric oncology standard of care to systematically screen for financial strain across the illness trajectory as a first step in intervening with those at risk for poorer cancer-related health outcomes (Pelletier and Bona, 2015). As Zafar (2016) has stated regarding adult oncology, “it’s time to intervene” and minimize financial toxicity as a source of suffering in pediatric oncology.

Approximately three-quarters of the recent studies were conducted in high-income countries that offer social protections to families including universal access to health insurance coverage, paid family medical leave and prescription drug coverage, that is, outside of the USA. This finding surprised us since, given the social policies of the USA, it seems logical to predict that the financial costs of childhood cancer to parents creates a more prevalent and significant problem and thus the body of research conducted in the USA would be more substantial. On the other hand, the relative lack of cost of illness research in the USA may represent the charged nature of ongoing political debates about government supports for broader perhaps even universal access to health insurance (Obama, 2016) and related challenges to obtaining federal or equivalent levels of funding to conduct costs of illness research.

Although most of the studies were open to parents of both genders, mothers predominated among participants. This finding suggests that, despite equivalent participation in the workforce (World Bank, 2014), women remain more likely than men to take on the primary caregiver role for children with serious illnesses like cancer and thus be present in clinical settings where they can be recruited to research. For many families, this decision may be a practical matter, given that gender wage disparities favor men including in high-income countries, that men are more likely than women to be employed full-time particularly after having children and that, despite men’s increasing participation in parenting activities over the past three decades, social norms typically place caregiving for ill and elderly family members on women (World Bank, 2014). Yet, for seriously ill children with two available and involved parents, how contemporary parents make decisions about who will be the primary caregiver and bear the brunt of the indirect costs with regards to their future career and associated financial entitlements is unknown. Research is needed to address this gap so that parents can make informed decisions about work disruptions, and then develop plans to

address the open-ended and unpredictable financial burden and psychosocial costs that will inevitably arise. At present, the costs of childhood cancer to parents are given inadequate attention by parents and clinicians alike in determining the resources that must be in place to sustain the family through successful completion of treatment for childhood cancer and beyond. This is partly because direct and indirect costs are open-ended, unpredictable and largely dependent on the child's illness course and responses to treatment, which is also unknowable. Nonetheless, few other situations come to mind in which individuals are asked to take on something as expensive and burdensome as childhood cancer caregiving without considering the various potential costs.

Under-representation of fathers in the included studies is consistent with the parenting literature in general (Davison et al., 2016). The relative exclusion of fathers in cost of illness research fails to acknowledge that the diagnosis and treatment of cancer in their child affects both parents (Bailey-Pearce et al., 2017), and the critical roles that fathers play in assuring the security and overall adjustment of children who are seriously ill and the family overall (Swallow et al., 2012). Even those fathers, and mothers too, who manage to avoid disruptions in paid work during their child's treatment for cancer likely experience loss of productivity due to intense emotions, difficulties concentrating, memory problems, and seeing to the child's caregiving needs after official work hours. Our inattention to fathers in parenting research in general and cost of illness research in particular contributes to lack of clarity regarding the enormity of the costs of childhood cancer and other serious childhood illnesses, and has created gaps in the evidence base that can inform interventions to help parents of both genders mitigate these costs and their adverse effects on cancer-related health outcomes.

This review reveals improvements in the methodological rigor with which the direct and indirect costs were measured. Concerns about the micro-costing approach include high participant burden, which is a protection of human subjects issue, and the associated potential for missing data. On the other hand, the data generated with a global estimates approach may seem too vague. Determinations about which approach to use for measuring direct and indirect costs should be guided by the study purpose. For studies intended to directly inform policy, the micro-costing approach seems better suited. Alternatively, if the immediate goal of the research is to generally describe direct and indirect costs and changes in these costs over time, global estimates seem sufficient given the multiple competing demands on these parents.

This review also shows improvement in the comprehensive measurement of costs of illness, particularly psychosocial costs. However, measurements of psychosocial costs were conducted using a wide-variety of tools, which again prohibited comparisons across studies. This problem could be addressed in part by using single and multi-item common data elements (CDEs), that is, by operationalizing and measuring psychosocial costs (e.g., psychological and somatic symptoms, quality of life) and factors that might mitigate these costs (e.g., mastery, optimism, social support) using identical PRO measures across studies. Sources of CDE include the publically available PROMIS® tools. These tools are brief, understandable, psychometrically sound, currently available in more than 40 languages and suited for use in research, policy development and clinical practice across literacy levels and

ethnic groups (National Institutes of Health, 2017). Costs of illness for which CDEs are now lacking should be comprehensively measured using standardized PRO measures that are also consistent across a program, and ideally multiple programs, of research. Possibilities include the COMprehensive Score for financial Toxicity (COST), which was developed (de Souza et al., 2014) and validated (de Souza et al., 2017) for measuring treatment-related financial distress in adult oncology populations and could be adapted and validated for pediatric oncology. Another prospect is to expand the list of financial coping behaviors that Bona et al. 2017 derived from the pediatric oncology literature to include risky financial coping behaviors that have been described in the adult oncology literature but which parents may have been reluctant to report without prompting. The adapted tool could be subjected to psychometric evaluation for use across future cost of illness studies in pediatric oncology.

Conclusion

This scoping review highlights the need for ongoing research on financial toxicity and comprehensive measurement of the costs of illness. Our findings were consistent with the Tsimicalis et al. review and make it even clearer that parents of children diagnosed with cancer incur significant costs of illness. Further, this study adds to the prior review in identifying that multiple social determinants of health place parents at risk for financial toxicity, a term that has been developed since the prior review and thus not considered in that study. Several research gaps were identified; however, it is imperative that we address costs of illness using validated PROs, rigorously designed longitudinal studies, minimally burdensome measurement tools and multi-level interventions to mitigate financial toxicity including the development and implementation of social policies that protect families.

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Figure 1. Flow diagram for the systematic scoping review process

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(7): e1000097. doi:[10.1371/journal.pmed1000097](https://doi.org/10.1371/journal.pmed1000097)

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Figure 2.
Included studies by year and country

Figure 3.
Number of included studies for the main types of study design

Figure 4.

Frequency of the cost of illness components measured in the included studies

Table 1.

Search strategy

((“childhood cancer” OR child OR adolescent OR pediatric OR paediatric OR youth OR children)) AND (cancer OR cancers OR maligna* OR sarcom* OR tumor OR tumors OR tumour OR tumours OR neoplasm) AND (“material hardship” OR “out of pocket” OR “material hardships” OR cost OR costs OR financial OR finance OR poverty OR economic OR economics) AND (family OR caregiver OR parent OR carer OR families OR caregivers OR parents OR carers OR “care giver” OR “care givers” OR mother OR mothers OR father OR fathers))

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Table 2.

Summaries of the included studies

First author Year, Country	Sample	Time frame	Design	Cost of Illness Concepts Measured	Main Findings Related to Costs of Illness
Aung 2012, Singapore	N=79 parents	Child diagnosed prior	Correlative	Indirect Financial burden Psychosocial	Caregivers who quit work to provide caregiving reported significantly higher financial burden ($p=0.03$) as compared to those who remained employed.
Bona 2014, USA	N=71 families/86 parents	Child 2 years old, 2 week history of recurrent progressive or non-responsive cancer	Cross-sectional survey	Indirect Financial burden Financial coping Psychosocial	In 42% of families, at least one parent quit their job and 28% reported great economic hardship due to financial costs of illness. Prevalent financial coping behaviors included fundraising (51%), avoiding big purchases (40%), acquiring credit card debt (40%).
Bona 2015, USA	N=45 parents (37 mothers)	Child had HCST in past 30 days to 12 months	Cross-sectional survey	Indirect Financial burden Financial coping Psychosocial	80% of families reported 1 work disruption due to HSCT. As a result, 20% of families had income loss >40%, and this was more prevalent among lower-income vs. wealthier families (39% v. 7%, $p=0.02$). 38% of families reported material hardship; lower-income families were more likely to report this ($p=0.02$).
Bona 2016, USA	N=99 parents (66 mothers)	Child diagnosed 30 days and receiving chemo	Longitudinal survey	Indirect Financial burden Psychosocial	At 6 months post treatment initiation, 12% of families had fallen into poverty. Families also reported new material hardships including food insecurity (20%), energy insecurity (17%) and housing insecurity (8%).
Cervall 2017, Sweden	N=58 parents (39 mothers)	Child in active treatment	2-group randomized control trial with repeated measures	Indirect Psychosocial	10-week internet-based guided self-help intervention + weekly support via email from a therapist improved the primary outcome (posttraumatic stress symptoms) at post-assessment ($d=0.89$) and 12-months ($d=0.78$).
Dussel 2011, Australia and USA	N=230 families (n=89 Australia; n=141 USA)	Child died 1990–1999 or 1996–2004	Retrospective cross- sectional survey	Indirect Financial burden Financial coping Psychosocial	84% of US (88% AU) families reported substantial work disruptions, 60% of families lost >10% of their annual household income, and 34% US (19% AU) families lost >40%. 16% of US (22% AU) families fell into poverty.
Fletcher 2010, Canada	N=9 mothers	Child had been treated for pediatric cancer	Phenomenology	N/A	Caregivers reported symptoms due to increased financial burden including fatigue, forgetfulness, social isolation, and changes in diet and weight.
Fluchel 2014, USA	N=356 families	Child 3 months post diagnosis and <60 months post treatment	Correlative	Direct Indirect Financial burden	Families in rural areas and those traveling >2 hours to care experienced more workdays missed ($p=0.04$). 36% of participants reported that at least one parent quit or changed jobs. Rural participants reported higher ($p<0.001$) out of pocket expenses due to illness related travel, and greater ($p=0.04$) financial burden.
Granek 2012, Canada	N=29 single parents (24 mothers)	Child 6 months post diagnosis	Constructivist grounded theory	N/A	Single parents did caregiving tasks without emotional or financial support from their ex-partners. Pre-existing financial strain and material hardship worsened when single parents stopped working to provide caregiving. Synergy of cumulative life stressors with caregiving burdens compromised mental and physical health. Financial stress was the most prominent stressor.
Hoven 2013a, Sweden	N=277 parents (139 mothers, 138 fathers)	Child diagnosed with primary cancer 14 days, scheduled for treatment	Longitudinal survey	Indirect	Parents were most likely to experience work disruptions while their child was in treatment as compared to other illness phases. One-year

First author Year, Country	Sample	Time frame	Design	Cost of Illness Concepts Measured	Main Findings Related to Costs of Illness
					post treatment, parents of both genders were working fewer hours than at diagnosis.
Hoven 2013b, Sweden	N=551 parents (406 mothers)	Child <19 at diagnosis and >5 years post primary CNS tumor diagnosis	Cross-sectional cohort survey	Financial burden Psychosocial	Five years post treatment, 18–20% of parents of primary CNS tumor survivors reported significant financial burden and personal strain.
Klassen 2012a, Canada	N=315 parents (40 single, 275 partnered)	Child 2 months post diagnosis, in treatment with curative intent.	Cross-sectional survey	Indirect Financial burden Psychosocial	Caregiving burden and indirect costs were not lessened in two-parent families when one parent continued worked.
Klassen, 2012b, Canada	N=50 parents immigrated from China or South Asia (37 mothers)	Child 6 months post diagnosis and not considered palliative	Constructivist grounded theory	N/A	Immigrant parents lack established available social network knowledge of available welfare systems and to help alleviate direct and indirect costs.
Larsen 2013, Denmark	N=25 parents (n=20 female)	Child hospitalized following HSCT	Longitudinal qualitative	indirect Financial coping Psychosocial	Despite assistance from the Danish social welfare system, >50% of parents reported financial difficulties.
Mader 2016, Switzerland	N=394 parent-couples and 3,341 control parents	Child diagnosed at <21 years of age and survived 5 years	Cross-sectional data from 2 population-based longitudinal surveys	Indirect	Return to work after treatment completion was particularly challenging for mothers, parents with low education or multiple children, and parents whose children required more intensive treatment
Okada 2015, Japan	N=62 mothers	Child diagnosed with cancer before age 15 years and completed treatment	Retrospective cross-sectional survey	Indirect Psychosocial	50% of mothers who continued to work during their child's treatment did that for financial reasons.
Rosenberg 2013, USA	N=81 parents (n=43 female)	Child 2 years old, 2 week history of recurrent progressive or non-responsive cancer	Cross-sectional survey	Financial burden Psychosocial	Psychological distress scores were highest in parents who reported great financial hardship.
Rosenberg-Yunger 2013, Canada	N=29 single parents (n=24 female)	Child 6 months post diagnosis	Constructivist grounded theory	N/A	Presence of a strong social network was critical for single parents.
Santos 2016, Portugal	N=244 mothers	Child diagnosed 3 months prior and in treatment or 60 months post-treatment	Cross-sectional survey	Financial burden Psychosocial	Financial burden was positively correlated with anxiety ($p<0.01$) and depressive ($p<0.01$) symptoms. The family ritual meaning level had a moderating effect on financial burden on anxiety ($p<0.05$) but not depressive symptoms.
Tsimicalis 2012, Canada	N=99 (n=71 female)	Child 21 days post diagnosis	Longitudinal mixed-methods	Direct Indirect	Main contributors to direct costs were travel-related expenses. Mother's caregiving hours exceeded father's hours (976 vs. 435).
Tsimicalis, 2013a, Canada	N=99 (n=71 female)	Child 21 days post diagnosis	Longitudinal mixed-methods	Direct Indirect	Family support networks (FSN) mitigated direct and indirect costs to primary caregivers by providing financial support and caregiving hours. As a result, FSN were lost leisure time and travel costs.
Tsimicalis, 2013b, Canada	N=99 (n=71 female)	Child 21 days post diagnosis	Longitudinal mixed-methods	Direct	The greatest out-of-pocket expenditures were travel-related expenses (56%) and food (18%).
Wakefield 2014, Australia	N=78 parents (44 mothers)	Child diagnosed in past 5 years, post treatment	Qualitative descriptive	N/A	Immediate workforce reentry was not possible for many families due to logistical (i.e. increased number of therapy appointments) and

First author Year, Country	Sample	Time frame	Design	Cost of Illness Concepts Measured	Main Findings Related to Costs of Illness
					psychological barriers (e.g., lowered motivation, lessened interest in career advancement, greater mental fatigue).
Warner 2015, USA	N=254 parents	Child diagnosed age 21, <5 years post diagnosis	Cross-sectional survey	Direct Indirect Financial burden	Factors that heightened perceived financial burden included more unexpected hospitalizations and caregiver quitting or changing job.
Wikman 2016, Sweden	N=152 parents (77 mothers)	Child diagnosed with primary cancer 14 days, scheduled for treatment	Longitudinal descriptive survey	Indirect Psychosocial	Employment status during treatment had little adverse effect on parent employment status 5 years after a child's death or completion of successful treatment. Wages, however, remained stagnant

Table 3.

Established measures used in the included studies

Component	Cost Category	Measure	Used by (author, year)
Financial	Direct	Ambulatory Care Health Record (ACHR) ^a	Tsimicalis, 2012; 2013a; 2013b
	Indirect	Ambulatory Care Health Record (ACHR) ^a	Tsimicalis, 2012; 2013a; 2013b
		Care of my Child with Cancer ^b	Klassen, 2012b
	Financial security	In Charge Financial Distress/Financial Wellbeing Scale ^c	Bona, 2015
	Financial burden	4 financial items, Impact on Family Scale ^{d,e}	Aung, 2012; Hoven, 2013b; Klassen, 2012a; Santos 2016
Psychosocial	Psychological symptoms	Beck Anxiety Inventory ^f	Cernvall, 2017
		Beck Depression Inventory ^g	Cernvall, 2017
		Hospital Anxiety and Depression Scale (HADS) ^h	Santos, 2016
		Kessler-6 ⁱ	Rosenberg, 2013
		Post-traumatic Stress Disorder (PTSD) Checklist-Cancer ^{j,k}	Cernvall, 2017; Wikman 2016
	Quality of life	Short Form (SF)-36 ^l	Klassen, 2012a
		US Household Food Survey Module-6 Item Short Form ^{m,n}	Bona, 2015; 2016

References:

^aGuerriere, et al., 2006;^bWells, et al., 2002;^cPrawitz, 2006;^dStein & Riessman, 1980,^eStein & Jessop, 1985;^fBeck, 1988;^gBeck, 1996;^hZigmond, 1983;ⁱKessler, 2002;^jWeathers, et al., 1993;^kRuggiero, 2003;^lWare et al., 2000;^mBlumberg, et al., 1999;ⁿUnited States Department of Agriculture, Economic Research Service, 2008