

A systematic review of financial toxicity among cancer survivors: we can't pay the co-pay

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Abstract (max 250)

Objective: To determine the extent of financial toxicity (FT) among cancer survivors, identify the determinants and how it is measured.

Methods: A systematic review was performed in MEDLINE, CINAHL and PsycINFO, using relevant terminology and included articles published from 1 January 2013 to 30 June 2016. We included observational studies where the primary outcomes included financial toxicity and study samples were greater than 200. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

Results: From 417 citations, a total of 25 studies were included in this review. Seventy measures of FT were reported with 47 covering monetary indicators, objective and subjective indicators of FT. A total of 28-48% of patients reported FT using monetary measures and 16-73% using subjective measures. The most commonly reported factors associated with FT were: being female, younger age, low income at baseline, adjuvant therapies and more recent diagnosis. Relative to non-cancer comparison groups, cancer survivors experienced significantly higher FT. Most studies were cross-sectional and causal inferences between FT and determinants were not possible. Measures of FT were varied and most were not validated while monetary values of out-of-pocket expenses included different cost components across studies.

Conclusions: A substantial proportion of cancer survivors experience financial hardship irrespective of how it is measured. Using standardized outcomes and longitudinal designs to measure FT would improve determination of the extent of FT. Further research combining reduction of work participation with resulting income losses occurring concurrently with FT and impacts on treatment non-adherence is recommended.

Key Points for Decision Makers

- Financial toxicity can affect a substantial number of patients with cancer, even those in universal health care systems or with health insurance.
- More recognition and research is needed on the dual problem of high out-of-pocket costs and reduced income as work participation declines following cancer.
- Patients and providers need to take control for seeking information on costs and exploring inexpensive options to minimize this problem.

1.0 INTRODUCTION

‘The greater threats to our national public health system lie in the increasing role of consumer co-payments and the power of vested interests that stifle policy innovation in health’ (Stephen Duckett in response to privatisation of Australian Medicare, Director, Health Program, Grattan Institute, June 23, 2016)

Patients with cancer can face serious financial challenges . In part, this is due to the high costs associated with advancements in technologies and treatments such as new pharmacotherapies, surgical techniques, imaging, and genetic testing [1]. Cancer survivors are also living longer with their cancer as a chronic illness and with the accompanying demands to monitor the disease and its sequelae [2]. As most health systems, including both public and private providers, face tight budgets, there is increasing reliance on patients to make larger co-payments and financial contributions to their healthcare. Even in countries where there is universal health care or when individuals have health insurance, additional patient out-of-pocket expenses are commonplace [1, 3].

The term 'financial toxicity' (FT) is defined in oncology research and practice to describe the financial distress or hardship that may be a side-effect of cancer treatment. [1, 4, 5]. Aptly coined for the financial pain of receiving cancer treatment, the term describes persons with high out-of-pocket (OOP) medical expenses and the impacts on poorer quality of life and reduced health care. In this sense, it is very similar to other treatment toxicities like neutropenia, nausea, vomiting, insomnia, or depression that lead to poorer patient outcomes and at times treatment delays/discontinuation. There are several options faced by patients when they are unable to afford medical care [1, 4, 5]: 1) they borrow money 2) they forgo other types of spending to pay for the health care; 3) they reduce their use of care (i.e., forgo or delay appointments, do not fill scripts, ration medications) or, in severe cases; 3) they forgo treatment entirely (including not presenting to a physician to diagnose cancer).

There is no gold standard definition of FT and the terms financial hardship, financial burden and FT are used interchangeably. However, the degree of financial burden has two contributors; high medical payments by individuals and reduced income while being treated or recovering from cancer. The combination of both a household's financial outgoings and incomings determine the extent of financial burden. The ways that individuals cope with financial burden fall into two broad categories: raising income (i.e., seeking financial assistance, early return to work, increasing debt/borrowings) or reducing spending (i.e., forgoing or delaying healthcare, choosing a less expensive option).

The experience of financial hardship varies for citizens in different regions around the world. In low income countries, patients with cancer may not even present to health services for care when symptoms arise or only present to a doctor when the cancer has spread and death is imminent [6]. Exacerbating this problem is the poor provision of a public health sector for citizens or other cultural or geographical barriers to receive cancer treatment [7]. In high income countries, patients with cancer often believe they are sufficiently protected from high medical costs through their health insurance policies only to discover inadequate coverage and subsequent 'bill shock' as invoices arrive [5]. Health systems classified as having 'universal health coverage' may not be comprehensive in practice, for example, Australia does not have universal dental services [3].

Although any disease may cause financial hardship among households, the term 'financial toxicity' originated in the context of cancer [5]. This is due to the very high cost of oncology medicines, the

multiple and protracted treatment regimens, prolonged survival in cancer patients, and ageing populations with subsequent increased prevalence of common cancers [5]. The purpose of this review was to address the following research questions: What is the extent of FT among cancer survivors?, how is it measured?, and what are the factors associated with FT? We intentionally kept this review focused to studies published since January 2013 to provide the most up to date evidence on this topic. This enabled the review to be manageable, reflect current data collections and excluded exploratory studies. We also aimed to identify the latest measurement approaches on this topic, those that may have been derived from the exploratory studies.

2.0 METHODS

2.1 Search strategy

The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews [8]. We reviewed the recent medical literature on FT of cancer care using MEDLINE, PsycINFO and CINAHL. Reference lists of the included articles were screened to identify any other eligible studies. We included all types of cancer and all ages of cancer survivors. Studies that examined FT due to treatment (including cost, productivity loss, expense, treatment cost, out-of-pocket, economic burden, financial toxicity, financial hardship, financial burden, financial effect, financial stress, co-payment) in cancer patients were the primary focus. To increase homogeneity and comparability of included studies, papers assessing productivity losses or return to work issues but did not consider FT were excluded. We excluded studies that did not have solely cancer samples and the following study designs: qualitative studies, literature reviews, cost-effectiveness studies, commentaries and published abstracts. Qualitative studies were excluded because they tend to address why and how participants might be experiencing FT while cost-effectiveness studies primarily deal with evaluating cancer interventions and therefore FT is not their primary focus.

The following inclusion and exclusion criteria were applied:

Inclusion criteria:

- FT of cancer patients due to treatment is primary interest
- Published between January 2013- June 2016
- Any type of cancer
- Quantitative study

Exclusion criteria:

- FT was not the main focus of the article
- Published prior to 2013
- Funded by industry
- Wrong study design (as defined above)
- Small sample size: $n < 200$

2.2 Search terms

We grouped our review topic into four groups: cancer (1), patients (2), cost (3) and health outcomes (4). Synonyms and related terms were detailed (as below) For each of the terms in the four groups,

we used Boolean operator 'OR' and between the groups we used 'AND'.. We used medical subject headings (MeSH) when available.

- 1) *Cancer care, oncology, treatment, management, p(a)ediatric, breast, prostate, colorectal, cervical, thyroid, brain, lung, lymphoma, stomach, liver; MeSH cancer*
- 2) *Patient, survivor, sufferer, family; MeSH patient care*
- 3) *Cost, productivity loss, expense, treatment cost, out-of-pocket, economic burden, financial toxicity, financial hardship, financial burden, financial effect, financial stress, co-payment; MeSH cost analysis*
- 4) *Outcome, life, well-being, effect, health, survival, stress, mental health, impact; MeSH quality of life, MeSH mortality, MeSH morbidity, MeSH burden of illness*

Searches were restricted by date but not limited by language. To increase the accuracy of results and to minimise screening of irrelevant studies, only searches with <50 results were exported and duplicates removed. The search strategy was developed by one researcher and validated by a second researcher. Final searches were performed on 22/7/2016.

2.3 Screening & data extraction

Initially, titles were screened for inclusion according to our pre-specified inclusion criteria. Subsequently abstracts of potentially eligible citations were screened. Reasons for exclusion were documented. This process was independently performed by two authors (KM & LG) and discrepancies were discussed until an agreement was reached.

The assessment of the full text articles retrieved were assessed for inclusion by two reviewers who shared this task equally and together agreed on the final set of included studies. Key information of eligible articles was extracted into a table by two authors (KM & LG) to summarise the features and main findings of the studies.

2.4 Data synthesis & quality

Study quality was assessed using the National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [9]. This tool asks 14 questions about issues relating to the risk of bias in the studies but it is not designed to be scored. Rather the questions prompt the reviewer to assess study limitations. We did not synthesise outcomes in a meta-analysis due to heterogeneous outcomes, cancer types and time frames; rather a narrative synthesis was undertaken.

3.0 RESULTS

3.1 Literature search

Our initial database search revealed 384 citations of which 74 were duplicates. Reference screening of these papers revealed a further 33 potentially eligible studies. After screening 343 titles, 232 were excluded as shown in Figure 1. Abstract screening of 111 citations resulted in 31 full-text articles assessed for eligibility. After further excluding 6 records the final number of studies included in the review was 25 (Table 1). The main reasons for exclusion were due to irrelevant topic, FT not being the primary outcome, focus on non-patient costs, small sample size (<200) and wrong study type.

3.2 Description of studies

The included studies were conducted in a range of countries but predominantly from USA: USA (14)[10-23], Singapore (1)[24], Korea (1)[25], Ireland (2)[26, 27], Italy (1)[28], India (1)[7], Canada (2)[29, 30], Australia (1)[31] and ASEAN nations (2)[6, 32] (Table 1). The 25 studies covered 271,732 cancer survivors, with study samples ranging from 268 to 197,840. Half the studies (14) included participants with any type of cancer [23, 28, 10, 24, 12, 6, 15, 16, 32, 7, 20-22, 25], 1 for adult onset cancers [17], 4 had a mix of 2-3 cancers (including breast and prostate cancers)[11, 19, 26, 27], 2 breast cancer [14, 30], 2 prostate cancer [29, 31], and 2 blood cancers [13, 18]. Eighteen studies (72%) were cross-sectional and the remainder were prospective or retrospective cohort studies. The timing of the participants since their cancer diagnosis varied significantly across the studies but can be divided into those who collected data relatively early after diagnosis (within 2 years), longer term (beyond 2 years) and studies with participants 'any time' since diagnosis.

3.3 Quality of studies

Table 2 presents the outcomes of the quality assessment. The main strengths of the studies were that all had clearly stated objectives, had reasonable sample sizes (mean of 3079 excluding the extremely high sample in Ramsey 2013), many had response rates over 50%, had clear population inclusion criteria, clearly stated outcome and independent variables and mostly used multivariable analyses to address confounding. The main limitations were that few studies were population-based, most were cross-sectional and diverse outcome measures hampered across-study comparisons. With cross-sectional designs, causal inferences between FT and determinants were not possible. It is probable that financial hardship existed prior to the cancer or due to other comorbidities and the cancer experience might have not caused but exacerbated FT. Directionality and temporality issues are also present in these cross-sectional designs. Studies using administrative data sets did not consider sample size calculations and therefore could be considered exploratory analyses. Although some samples were selected from large population-based datasets where response rates were not applicable, others could not be determined [31, 6, 15, 16, 7, 19]. Those conducting surveys or interviews mostly had participation rates over 50% (12 studies) and a few did not [28, 24, 22, 23]. The generalisability of the study samples is therefore questionable. The choice of 'financial burden' outcome was often clearly defined, but remained subjective, unvalidated or tested for reliability. Conversely, the monetary assessments of OOP costs included different cost components, covered different time periods and were still open to recall bias. In addition, the reference of OOP costs to income levels was not made in which to judge burden of health relative to other household expenditures. This is important because, paradoxically, high OOPs paid by patients are only possible with sufficient income and therefore higher OOPs are linked to variables of higher socioeconomic status. Findings from four studies did not present results adjusted for potential confounders [13, 31, 17, 25] and therefore should be interpreted with caution.

3.4 Summary of findings

The measures of FT varied widely among the studies. They were categorised as:

- 1) *monetary measures*: currency values of OOPs and percentage of OOPs to income ratios;

2) *objective measures*: question sets on tangible solutions to ease financial burden such as to increase debt levels, borrow money from family or friends, sell assets, withdraw money from retirement or savings funds, file for bankruptcy; and

3) *subjective measures*: question sets on perceptions of cancer-related financial burden and cover the psychological impact.

Within the monetary measures of OOPs, these included either direct medical expenses or direct and indirect expenses (i.e., travel, accommodation, parking).

The studies reported 47 measures of FT with most reporting more than one measure using the above categories; 22 (47%) monetary measures, 9 (21%) objective measures and 16 (34%) subjective measures. In addition to quantifying FT, the impacts or consequences of FT were also outcomes for some studies (16 total measures). These included treatment non-adherence, changes made to insurances, choice of end-of-life care and health-related quality of life. Also, changes to work participation occurring concurrently with FT were further reported by 7 (10%) studies in the context of FT. Figure 2 specifically outlines the dimensions of financial burden including all the above measures (70 total measures). Direct comparisons across studies was problematic due to different outcome measures, different time periods covered and the statistical approaches used ranging from descriptive statistics or simple ratios to multivariate modelling.

When a definition of FT in monetary terms was provided, these varied from ‘catastrophic spending’ defined as OOPs greater than 30% of household income [6, 32], greater than 20% of household income [11] and the top quartile of OOPs [30]. Nevertheless, the studies indicated the frequency of FT among cancer survivors ranged from 28% to 48% [11, 13, 6, 7, 22, 25]. When FT involved answering objective or subjective questions, the frequency of FT ranged from 16% to 73% [10, 24, 16-19, 26, 23].

Most studies used statistical approaches to control for potential confounding in assessing FT as an outcome variable. Irrespective of the quantitative or subjective FT outcome used, in adjusted statistical models, the determinants of FT included: being female [6, 22], low income at baseline [6, 32, 22], loss of income [30, 22], younger age [29, 17, 18, 20, 22], adjuvant therapies [11, 29, 17, 30], anti-neoplastic therapies [11, 15] more recent diagnosis [29, 31, 22], advanced cancer [32], no health insurance [6, 32] and living further away from treatment centres [28, 30]. Several studies excluded stage of cancer in their analyses [17, 7, 22]. Also some ethnic groups in the USA (African American [19], Hispanics) consistently reported higher financial burden among cancer survivors, even after adjustment for income, education & employment [14, 17, 19, 22, 23]. Similarly individuals with low income in developing countries with no universal health system or low levels of health insurance coverage, reported worse FT, in addition to poor survival rates [6, 32]. These authors point to the competing outcome of mortality when assessing FT in developing countries which is not addressed in studies from developed countries. Baseline levels of FT [32] or financial stress [26] was also associated with FT following cancer treatment in two studies.

To examine FT specifically relating to cancer and no other competing comorbidities, three studies assessed the extent of financial burden in cancer sufferers versus non-cancer control groups [11, 7, 20]. All indicated significantly higher burden for individuals with cancer relative to non-cancer control groups. Cumulative two-year spending on healthcare among a mixed cancer cohort in the US

(1868 patients with cancer and 10,047 without cancer) was observed and 28% of patients with cancer reported a high OOP burden compared with 16% without cancer ($p < 0.001$) [11]. Using propensity matching, a study in India by Mahal et al (2013) found OOPs were significantly higher (Indian Rupee 5311 vs 1079) annually per person in households of cancer survivors and translating to 36-44% of annual household expenditure on cancer-related care [7]. Ramsey *et al.* (2013) reported that patients with cancer were 2.65 times more likely to go bankrupt than age-matched people without cancer [20].

Quality of life impacts were markedly worse for patients experiencing FT in three studies [16, 18, 27] with mental well-being especially affected [16, 18, 27]. FT was reported to be the strongest predictor of quality of life in the US study by Fenn *et al.* (2014) [12]. Compared with individuals not reporting FT, impacts of FT included treatment non-adherence (frequency 27%[10], 32%[6], 35-70%[15]) higher delays in care (17% vs 7.4%)[17], more patients forgoing care [17] and lost insurance (29%)[13]. One study looking at choice of end-of-life care [23], found hospitalised intensive care was more common in those experiencing FT because this shifted costs to third party payers even though dying at home was preferred by patients. Reduced work participation and accompanying income loss was reported as being associated with FT in several studies [13, 30, 22] with a Canadian study reporting wage loss was the most important determinant of decline [30].

4.0 DISCUSSION

This review affirms FT to be a major issue affecting a large proportion of cancer survivors. Up to 48% of participants in the reviewed studies reported FT in monetary terms and this was even higher when measured in subjective terms. There were a range of possible questions or cost calculations that were used to constitute FT and this review has catalogued these as either monetary, objective (or tangible consequences) and subjective measures. The most commonly reported factors linked to FT were: being female, younger age, having a low income at baseline, receiving adjuvant therapies and having a recent diagnosis. High financial burden for cancer sufferers is in excess of that for persons not experiencing cancer (but possibly experiencing other chronic disease). The impact on patients can be debilitating to households, to quality of life and to optimal cancer care.

Our findings are similar to an earlier review of 10 studies, all cross-sectional but focussing on subjective measures of FT [33]. Although FT is a complex problem, greater awareness and acknowledgement of FT is likely to lead to solutions towards optimal patient outcomes by cancer care professionals, governments, patients and families and welfare providers, when necessary. FT is a *household* phenomenon and although this literature predominantly focusses on the financial outgoing expenses, it is also a function of the financial incomings, usually from employment, that are often reduced while undergoing cancer care. This is not apparent in the studies in this review but as the authors of one study stated, wage losses from the cancer treatment and recovery may be more important than OOPs incurred by households [30]. A critical underlying complication of the affordability of medical care is the potential for job loss, work absence and workplace discrimination, experienced during the course of prolonged cancer treatment. This is most apparent in developing countries where those on low incomes experienced higher mortality rates (from lack of health care) and higher catastrophic spending levels [6, 32].

Suggestions to ameliorate the financial burden for patients in tangible ways has included mandating the full disclosure by doctors of estimated fees and charges related to treatment from all sources, improved communication between health professionals and patients to raise any financial concerns and the ability patients to return to work should they need/wish to and creating opportunities for patients to make treatment decisions fully informed of the likely burden. Appropriate discussions about financial concerns should begin from the start of treatment and critical time points (e.g. completion of treatment), preparing patients and their families for the potential financial effects that could have an ongoing impact. Furthermore, screening tools may assist health professionals to identify those patients at high risk and refer them to support services.

A limitation of the review was the complexity of the topic and the absence of firm definitions or a conceptual model informing this body of evidence. Beyond the scope of this review, we omitted the rich data covered by qualitative studies on this topic. However, the categories used in reporting the collective outcomes of the included studies may help researchers design studies in future. It is encouraged that researchers use a standardized tool for assessing FT and there is one now available which was published in 2014 [34]. Briefly, the COST-FACIT was developed by Souza *et al.* (2014), and is an 11-item survey covering objective and subjective questions covering financial stress and work-related issues during the past 7 days and using a Likert scale from 'Not at all' to 'Very much' [34]. In addition, as work income reductions are an important aspect of FT, the IMTA Productivity Cost Questionnaire (iPCQ) may also be useful in future research [35]. The iPCQ measures productivity losses of paid work due to absenteeism and presenteeism and unpaid work with 18 items and phrased over the past 4 weeks [35]. Both these instruments are generic and are not confined to cancer populations and both developers have called for further validation studies [35, 34]. It is advisable to use both these tools to cover the employment and OOP aspects and to minimise use of unvalidated tools.

In addition to being a direct patient concern, FT exposes serious system-level deficiencies around the way health systems are organised. Health system reforms in many settings are critical for minimizing FT and promoting equity in health care. Despite the developments for improving cancer control, the very high costs associated with cancer treatments is raising the issue of the capacity to afford these resources and whether budgets can sustain such spending. The Sustainable Development Solutions Network promotes universal health care and emphasizes that in order for nations to provide equality of access to necessary health care to their entire population, financing options which reduce out-of-pocket spending are fundamental [3]. Re-allocation of health resources can occur through, for example, investing in cost-effective preventive care, reducing use of services that offer little or no benefit, linking payments to the value of services received and increasing the use of information technology to populations in hard-to-reach locations [3]. Omitted from these options are increasing user fees and/or private health insurance coverage which serve only to exacerbate the difficulty for individuals meeting the financial demands of treatments. Health system structures and funding have a large influence on the experience of FT. At the extreme, this is emphasized in countries with poor or no public health system, where households pay entirely to receive treatment and clearly face catastrophic burdens, and high mortality [6]. However, the more granular differences among patients experiencing FT within complex health systems and shared funding models remain unknown. For patients with private health insurance, the review found mixed results as to whether FT was more or less protected. In Australia, men with prostate cancer experienced FT and higher out-of-pocket expenses when they were privately insured versus public hospital patients [31], which

appears to be a product of the unregulated market in which specialists practice price discrimination [36]. However, the opposite was true in the US and other South East Asian countries, where patients without health insurance were more likely to report FT compared to those with health insurance [13, 6, 37, 4, 22] but were not always protected from FT.

In countries such as Australia, New Zealand, Canada and the UK, government funding of new healthcare services and interventions involve organisations that perform health technology assessments that assess the value of new medicines and other services (<http://www.inahta.org/>). Their role is to weigh up the expected costs of their wide adoption in terms of patient outcomes and safety. Often the benefits of new cancer therapies for metastatic disease are small, and may not provide sufficient value at the prices private industry seeks for their provision. While these assessments appear lengthy, they are critical in the balanced and careful adoption of safe, effective and cost-effective treatments [38]. Developing countries in South-East Asia and Latin America are also adopting these systematic value assessments because they offer a thorough and ethical basis for decision-making involving public funds. From the patient's perspective, although new high-cost cancer medicines are often refused or delayed for public funding, leading to patient advocacy, crowd-funding and medical tourism to access them, they may not understand the lack of evidence base supporting these medicines. There is an important role for public engagement in health technology assessment so they are able to have their views incorporated into funding decisions [39].

Further research is warranted on FT and its impacts on treatment non-adherence in the longer term. There are several other reasons aside from affordability explaining non-adherence ranging from patient medication beliefs, patient age, extent of side-effects, multiple doses, and provider education and communication skills [40]. The studies in this review indicate short-term observations of non-adherence but there are likely to be potential health system costs that have not been thoroughly assessed. Non-adherence may be temporarily cost-saving for patients but it has wider downstream implications for health services [41]. For new high-cost oral anti-neoplastic agents within oncology, we are only beginning to understand that high levels of non-adherence occur despite the more convenient oral mode of delivery [40].

5.0 CONCLUSIONS

Minimising FT is critically important for patients and also important for health system structure and reforms. Patients and providers need to take control at seeking information on costs and exploring inexpensive options. More recognition of both the income and expenses side of financial hardship needs to occur among clinicians and researchers. Using standardized tools, prospective and longitudinal designs will improve our understanding of FT.

Table 1: Summary of study findings

First author & Year	N	Country	Type of study	Cancer type	Measured outcomes	Time frame	Main findings
Baili 2016 [28]	296	Italy	Cross-sectional phone interviews	Any cancer site	Mean monthly medical OOP cost by region	5-10 years from diagnosis, 2003-2007	On average, a patient in the north spent €69 monthly, against €244 in the south. The main differences are for transport/ accommodation to cancer treatment centre.
Bestvina 2014 [10]	300	USA	Cross-sectional in-person interviews	Any cancer site	Patient OOP cost, financial distress and odds of drug non-adherence	Baseline and 3 months	16% (n=49) reported high or overwhelming financial distress. 19% (n=56) reported talking to their oncologist about cost. 27% (n=77) reported medication nonadherence. Drug nonadherence was associated with cost discussion OR 2.58; 95% CI, 1.14 to 5.85, financial distress OR=1.64,95%CI, 1.38 to 1.96 and higher financial burden than expected OR=2.89; 95% CI, 1.41 to 5.89.
Chan 2013 [24]	516	Singapore	Cross-sectional study, single-centre, prospective	Any cancer site	Financial burden for patients >50yrs Perceptions of cancer treatment costs	Unclear, received active anticancer drug therapy within 30 days prior to interview date	22.9% of respondents stated they had difficulty paying for their cancer treatment and that this financial burden affected their family. Only 4.8% of respondents stated that they would reject a recommended treatment for financial reasons.
Davidoff 2013 [11]	1,868	USA	Cohort study Retrospective, observational	Breast, lung, prostate, colon, other	OOP costs of Medicare beneficiaries (cancer vs non-cancer)	Cumulative 2-year spending	1868 with and 10,047 without cancer. Mean OOP spending for cancer patients was \$4727. Cancer patients faced an adjusted \$976 (P < .01) incremental OOP spending. 28% of pts with cancer experienced a high OOP burden compared with 16% without cancer (P < .001).
De Oliveira 2014 [29]	585	Canada	Cross-sectional survey population-based	Prostate cancer	Time costs and OOPs and predictors	Long-term (2-13 years) since diagnosis	Mean time costs were \$838/year and mean OOP costs were \$200/year. Although generally low, total costs represented approximately 10 % of income for lower income patients. Radical prostatectomy, younger age, poor urinary function, current androgen deprivation therapy, and recent diagnosis were significantly associated with increased costs.
Fenn 2014 [12]	2,108	USA	Cross-sectional in-person interviews	Any cancer site	Impact of financial burden of cancer on quality of life	Unclear, no time limit (everyone who ever had cancer was eligible)	Patients who reported "a lot" of financial problems rated poorer physical health (18.6% v 4.3%, P < .001), mental health (8.3% v 1.8%, P < .001), and satisfaction with social activities and relationships (11.8% v 3.6%, P < .001) compared to those with no financial hardship. Financial hardship is the strongest independent predictor of quality of life.
Goodwin 2013 [13]	762	USA	Cross-sectional	Multiple myeloma	Financial burden, employment, OOP % of income, insurance, disability	Unclear, any time since diagnosis	33% additional not working, 29% lost insurance, 13% retired during treatment, OOP 36% of income in first year and 28% in most recent 12 months.
Gordon 2015 [31]	289	Australia	Cross-sectional	Prostate cancer	Self-reported OOP costs of prostate	Any time since diagnosis, recently	Men recently diagnosed (n = 65) reported spending a median AU\$8000 (interquartile range AU\$14 000) for their cancer treatment while 75% of men

First author & Year	N	Country	Type of study	Cancer type	Measured outcomes	Time frame	Main findings
			survey Online		cancer diagnosis & treatment, changes in employment	diagnosed within 16 months of the survey	spent up to AU\$17 000 (2012). Large variability in costs. Respondents in paid employment at diagnosis stated they retired 4-5 years earlier than planned.
Jagsi 2014 [14]	1,502	USA	Longitudinal study, prospective	Breast cancer	Long-term self-reported OOP medical expenses, financial decline, privation	9 months since diagnosis & 4 years later	Median out-of-pocket expenses were \$2,000; 17% reported spending > \$5,000; 12% reported having medical debt 4 years post diagnosis. Debt varied significantly by race: 9% of whites, 15% of blacks, 10-17% of Latinas. Ethnic minority patients different even after adjustment for income, education, and employment.
Jan 2015 [6]	4584	8 ASEAN nations	Prospective longitudinal	Any	odds ratios of financial catastrophe (FC), deaths, treatment discontinuation	Baseline and 3-months	Surgical patients only. FC= UMI countries 3%, 38% LI, 48% LMI. Discontinued tx = 32% UMI, 22% LMI, 6% LI, deaths = 3% UMI, 9% LMI, 17% LI. Factors for high FC = women, lower SES affected all outcomes, health insurance protective of discontinuation
Kaisaeng 2014 [15]	3791	USA	Cross-sectional	Any.	2008. Mean OOP per day, per year, discontinuation	12 month data	Study focussed on 5 drugs imatinib, erlotinib, anastrozole, letrozole & thalidomide. Patients on most expensive drugs (imatinib, erlotinib, thalidomide) had daily OOP of \$30, others \$3. Medication discontinuation for 5 drugs ranged from 35% imatinib to 70% thalidomide. Higher OOP linked to more discontinuation.
Kale 2016 [16]	1380	USA	Cross-sectional	Any and any time since tx	Financial burden (≥1 yes to 4 questions of financial problems, HRQoL	65%>5 years from diagnosis 14% 3-5 years from diagnosis	SF12 - MCS and PCS, Kessler and PHQ229% financial burden, financial burden sign linear association with PCS and MCS. MCS stronger than PCS. Multi log reg – odds 1.95 higher depressed mood, 3.41 higher with ≥3xFB. Nationally representative sample from MEPS
Kent 2013 [17]	1556	USA	Cross-sectional	Adult onset cancers – treatment	Cancer-related financial problems 1Q, forgoing or delaying care 3Qs	>1 year from diagnosis	31.8% reported cancer-related financial problems, higher if younger age<65, blacks/Hispanics, recurrence multiple ca, chemo or rad, higher delays 18% vs 7.4%, forgone care much higher if FB
Khera 2014 [18]	268	USA	Cross-sectional	Blood cancers	Subjective and objective financial burden, OOPs	Unclear, median follow-up time 2.3 years (6 mths to 6.9 years)	73% experienced subjective burden, 35% experienced behaviours affecting health (non-adherence to medicines or appts), 37% \$2-5K, 13% >\$5K past 3 months of survivors < 1 year after hemoatopoietic cell transplantation, 26% income decreased by >50%, 25% withdrew funds from retirement account. Younger age and poor mental/phys status linked to worse financial burden.
Kimman 2015 [32]	9513	10 ASEAN nations	Prospective longitudinal	Any. 26% brca, 11% mouth, 10% colorectal, 11% cervix	Odds ratios of financial catastrophe (FC) and deaths	Baseline, 3, 12 mths.	29% had died at 12 mnths. 48% experienced FC (>30% of income on medical OOPs). Determinants of FC and deaths were low income, advanced ca, no health insurance. 54% experienced hardship prior to cancer diagnosis. FC OR 5.86 (95%CI:4.76-7.23).
Lauzier 2013	829+391	Canada	Prospective	Breast cancer	OOP costs,	First year after	For a couple: mean (sd) CAN\$1733 (1451), med \$1329 IQR 716-2275. (CAN

First author & Year	N	Country	Type of study	Cancer type	Measured outcomes	Time frame	Main findings
[30]			longitudinal		determinants of high OOPs (upper quartile)	diagnosis	2003). Low income families 4.3% OOP/income vs 1.3% high income. Factors of high OOP were higher education, working at diagnosis, living >50km away, 2 or 3 types of adjuvant treatment. Wage loss most important determinant of decline.
Mahal 2013 [7]	1645	India	Cross-sectional	Any cancer	Healthcare use, OOP expenditure, workforce participation	One year (2004)	Propensity matched data on socioeconomics - hospital admissions, length of stay, outpatient use significantly higher in cancer households, OOP significantly higher INR 5311 vs 1079 annual per person, slightly lower work participation 3.2%. OOP exp 36 to 44% of annual household expenditure on cancer-related care.
Pisu 2015 [19]	3432	USA	Prospective	40% Lung and 60% colorectal cancer	Economic hardship based on 3 subjective questions	4 and 12 months after diagnosis	Prevalence of hardship in 68% African Americans, 58% Hispanics, 50% Whites. Hardship non-significant after adjustment for baseline factors for African Americans and Hispanics, African Americans significant hardship vs whites (Adjusted OR 1.69: CI 1.24-2.30).
Ramsey 2013 [20]	197,840	USA	Cross-sectional, non-cancer controls	Any cancer	Incidence and relative risk of bankruptcy	1995-2009 in Washington state	Cancer patients were 2.65 times more likely to go bankrupt than people without cancer. Younger patients 2-5 times more likely if <65 years. First year costs important.
Sharp 2013 [26]	654	Ireland	Population-based, cross-sectional	Breast, prostate and lung cancer	Cancer-related financial stress and financial strain on psychological well-being	Diagnosis up to 24 months previously in 2008 enrolment year	Of 654 respondents, 49% reported increased financial stress and 32% increased financial strain due to cancer. Depression risk with financial stress (odds ratio (OR) = 2.79, 95%CI 1.87-4.17) and financial strain (OR = 3.56, 95%CI 2.23-5.67). For severe or worse depression (increased stress: OR= 4.36, 95%CI 2.35-8.10; increased strain: OR= 8.21, 95%CI 3.79-17.77).
Sharp 2016 [27]	740	Ireland	Cross-sectional	Breast and prostate cancer	Cancer-related financial stress and financial strain, predictors	Diagnosis up to 24 months previously in 2008 enrolment year	Financial stress lower in not working RR 0.71 (95% CI 0.58-0.86) or retired RR 0.48 (95%CI: 0.34-0.68). Higher financial stress if dependents, fin stress at baseline, had a mortgage, higher direct OOPs, increased bills post diagnosis.
Stump 2013 [21]	400	USA	Cross sectional, mixed methods	Any cancer	Qs on concerns of treatment costs plus qualitative.	50% 5 years out 29% 5-10 years out 13% >10 years out 8% missing	High prevalence of concerns (e.g. concerns about paying for cancer treatment OR 2.83 (1.92-4.2)), the nature of concerns about costs differed by patient characteristics – young/older, low optimism, low numeracy, income, education.
Tucker-Seeley 2015 [42]	281	USA	Longitudinal, repeated measures	Any cancer	Financial hardship (1Q) and intensive care at end-of-life	Median 4.4 months before death	29% reported financial hardship based on using up savings, this was significantly associated with more intensive care at end-of-life in hospital after adjustment for confounders, intensive care may lower OOPs for families (is covered by insurance or families) but dying at home is preferred.
Yabroff 2016 [22]	1202	USA	Cross-sectional	Any cancer, any time since	Material financial hardship (4Qs)	22% 1-5 years out 42% ≥5 years out	Younger age <65 years more material 28.4% vs 13.8% and psychological 31.9% vs 14.7% hardship. Adjusted analyses – younger, female, non-white, changed

First author & Year	N	Country	Type of study	Cancer type	Measured outcomes	Time frame	Main findings
					and psychological hardship (worry over bills)	10% missing	employment had more material hardship. Uninsured, low income, recent treatment had more psychological hardship.
You 2013 [25]	17000 to 35000	Korea	Time trend, cross-sectional from 2003-2010	Any cancer, hospitalization	Absolute OOP, OOP ratio = OOP/total exp from national insurer	2003 to 2010	OOP ratio 30% down from 45% in 2003, policies to drop OOP but fees increased and new technologies, thyroid cancer highest OOP – 3 x higher than breast

Acronyms: CAN = Canadian; INR= Indian rupee; FC = financial catastrophe; LI = low income; LMI = lower middle income; MCS = mental component score; OOP = out-of-pocket; OR = odds ratio; PCS = physical component score; Q = question; RR = relative risk; UMI = upper middle income

Table 2: Quality assessment of studies

Criteria	Baili 2016	Bestvina 2014	Chan 2013	Davidoff 2013	De Oliveira 2014	Fenn 2014	Goodwin 2013	Gordon 2015	Jagsi 2014	Jan 2015	Kaisaeng 2014	Kale 2016	Kent 2013	Khera 2014	Kimman 2015	Lauzier 2013	Mahal 2013	Pisu 2015	Ramsey 2013	Sharp 2013	Sharp 2016	Stump 2013	Tucker-Seeley 2015	Yabroff 2016	You 2013	
1. Clear research question?	Y	Y	Y	Y	Y	y	y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. study population clearly specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. participation rate least 50%?	48%	86%	41%	NA	53%	61%	76%	CD	68%	CD	CD	CD	61%	56%	55%	83%	CD	CD	54%	54%	68%	CD	31%	49%	NA	
4. recruited from the same or similar populations? Were inclusion and exclusion criteria applied uniformly?	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification?	N	N	N	NA	N	N	Y	Y	N	NA	NA	NA	NA	N	N	N	NA	N	N	N	N	N	N	N	N	NA
6. the exposure(s) prior to the outcome(s) being measured?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N
7. Was the timeframe sufficient?	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	N	N	N	N	Y	N	N
8. examine different levels of the exposure as related to the outcome?	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	
9. Were the exposure measures valid, reliable?	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
10. Was the exposure(s) assessed more than once over time?	N	N	N	N	N	N	N	N	N	N	NA	N	N	N	N	N	NA	N	N	N	N	N	N	N	N	N
11. Were the outcome measures clearly defined, valid, reliable?	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	N	N	N	N	N	N	Y
12. outcome assessors blinded to the exposure status of participants?	CD	CD	N	CD	CD	N	CD	N	N	N	NA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
13. Was loss to follow-up after baseline 20% or less?	NA	Y	NA	NA	NA	NA	NA	NA	Y	NR	NA	NA	NA	NA	Y	Y	NA	NR	NA	NA	NA	NA	N	NA	NA	
14. potential confounding variables measured and adjusted statistically?	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Abbreviations: CD = cannot determine; NA = not applicable; NR = not reported, N = no, Y = yes

Figure 1: PRISMA flow chart of study searches

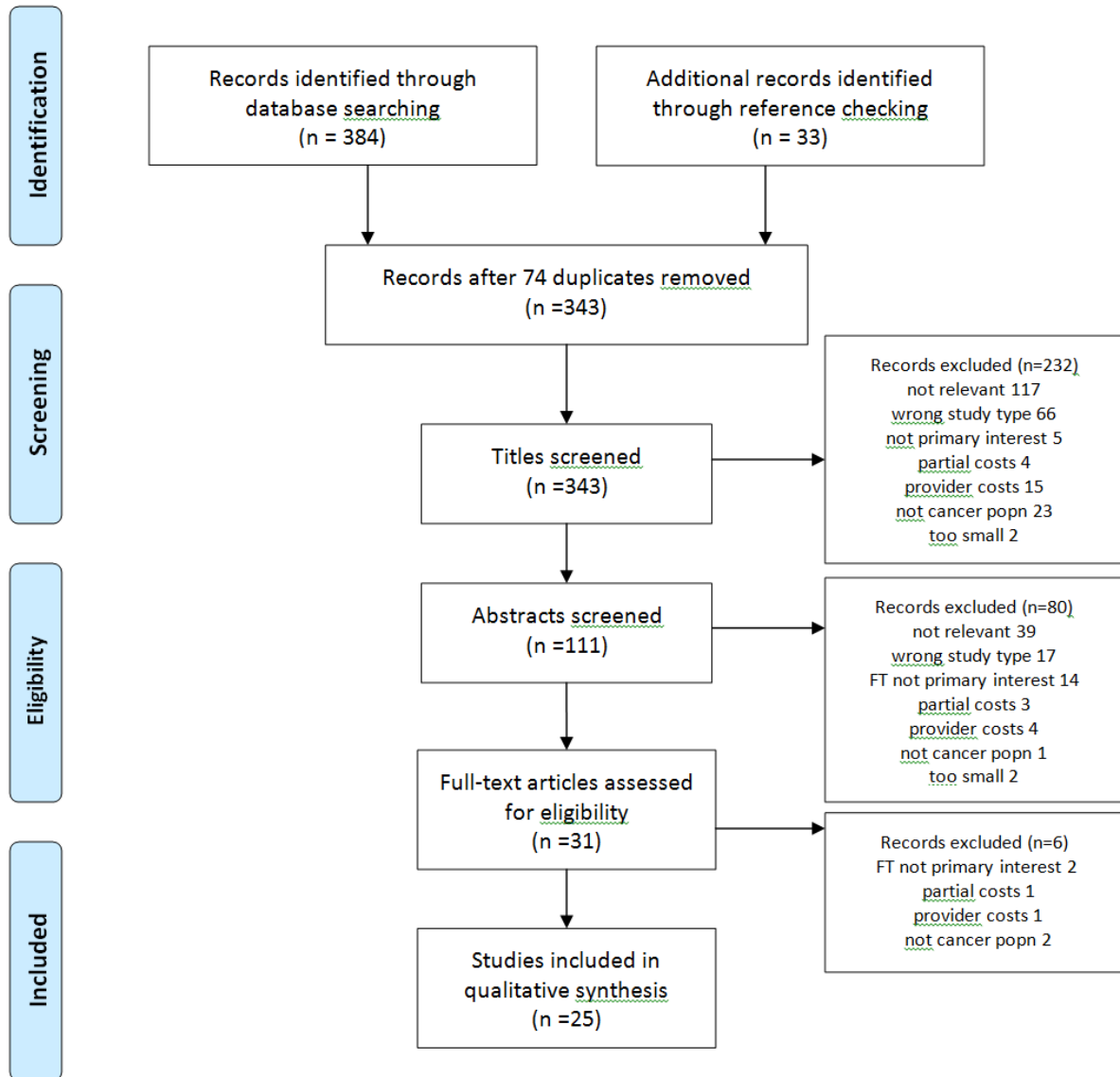
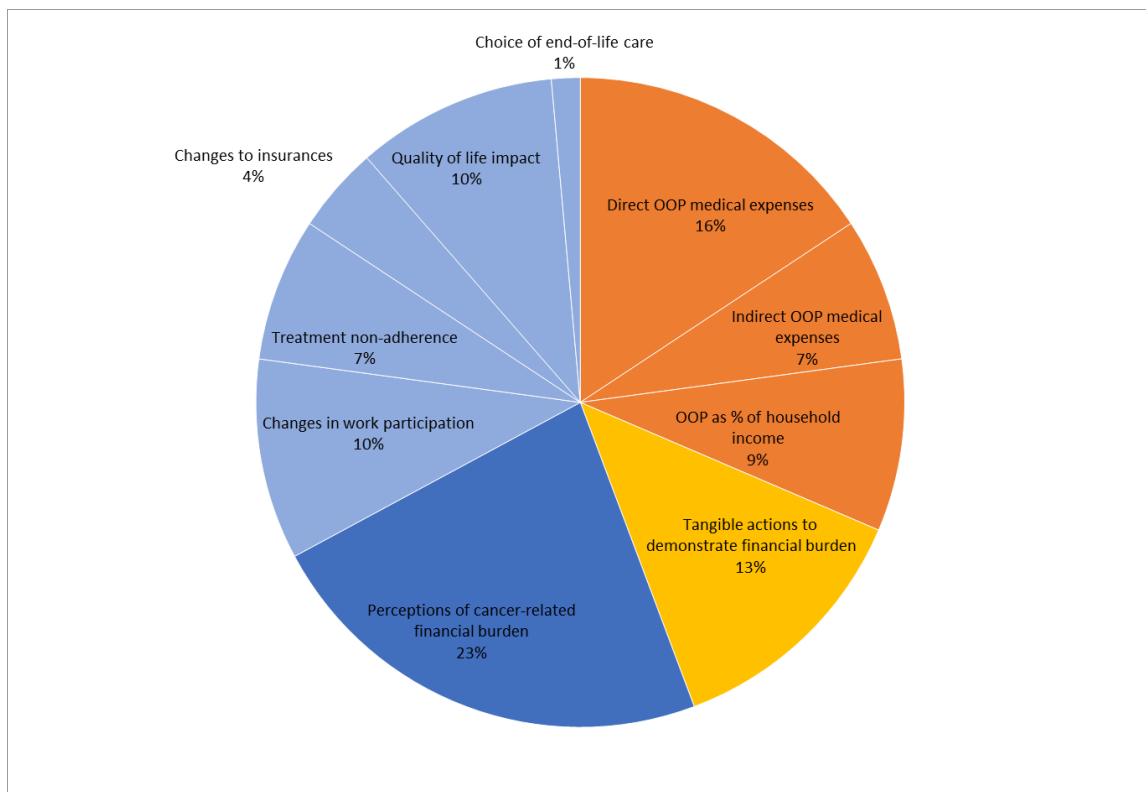


Figure 2: Frequency (%) of financial burden component reported in the included studies



Legend

	Monetary measures
	Objective measures*
	Subjective measures
	Other impacts

*For example included borrowing money, increasing credit card debt, bankruptcy, forgone spending in other areas.
OOP = out-of-pocket

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