Relationships between Financial Toxicity and Symptom Burden in Cancer Survivors: A Systematic Review

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Abstract

Context. Financial toxicity (FT) is used to describe the financial distress/hardship associated with cancer and its treatment.

Objectives. The aim of this review was to explore the relationship between FT and symptom burden.

Method. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched MEDLINE, EMBASE, and CINAHL (from January 2000 to January 2018) and accepted quantitative, mixed-methods and qualitative studies. Data were extracted and appraised by two reviewers. Due to significant heterogeneity in the included studies, a narrative synthesis was performed.

Results. Nine studies involving 11,544 cancer survivors were included. Of these nine studies, eight were of high quality. The relationships between FT and psychological symptoms and physical symptoms were examined in eight and three studies, respectively. Six studies reported a positive relationship between FT and depression. Three studies found a positive association between FT and anxiety. Limited evidence was found for an association between FT and stress, fear of recurrence, spiritual suffering, pain, and overall symptom burden.

Conclusions. A relatively clear association exists between FT and psychological symptoms. Clinicians should regularly screen for, assess, and manage emotional distress that may be attributed to FT. While the causal pathway is not known, future intervention studies aimed at minimising or preventing FT should evaluate psychological symptoms as secondary outcomes. Little is known about the relationships between FT and physical symptoms. Future research should overcome methodological limitations by incorporating longitudinal data collection, use of mixed-methods approaches, and homogeneity of samples.

Keywords:
cancer survivors; financial toxicity; financial burden; symptom distress; symptom burden; systematic review
1. Introduction

Cancer care is one of the fastest growing components of global healthcare costs. In the United States alone, approximately $87.8 billion was spent on cancer care in 2014. While advances in science, technology, and consumers’ expectations have improved patient outcomes, they are associated with significant costs to the healthcare system and to patients. Cancer treatments have direct and in-direct impacts on the finances of patients and their family caregivers. The term financial toxicity (FT) is used to describe the financial distress or hardship associated with cancer and its treatment.

A recent systematic review reported that FT occurred in 28% to 48% of cancer survivors using monetary measures like ‘percentage of household income’ (spent on medical services) and in 16% to 73% of cancer survivors using self-report measures such as impact on everyday living expenses. In another systematic review of 45 studies, 12% to 62% of cancer survivors reported being in debt due to their treatment and 47% to 49% of survivors experienced some form of financial distress. Common outcomes associated with FT included: reduced treatment compliance, medication non-adherence, and treatment refusal. While several studies found that higher financial burden was associated with reductions in health-related quality of life, especially with emotional well-being, little is known about the relationship between FT and symptom burden, especially the occurrence and severity of symptoms.

Undoubtedly, the relationships between FT and symptom burden are complex. Therefore, investigations that evaluate how FT and symptom burden may interact with each other are warranted. Currently, it is unclear whether the relationships between FT and symptom burden are causal, bi-directional, or modifying. For example, it is reasonable to postulate that
patients with a higher symptom burden (e.g., fatigue, pain, cognitive dysfunction, depression, peripheral neuropathy) may reduce hours at work or not be able to return to work,\textsuperscript{14} which may exacerbate financial pressures. On the other hand, FT can contribute to depression and anxiety,\textsuperscript{15} which may in turn influence physical symptoms such as sleep disturbance and fatigue. Increased knowledge of the associations between FT and symptom burden will inform the development and testing of interventions to alleviate symptom burden associated with FT.\textsuperscript{13} Therefore, the primary aim of this review was to explore the relationships between FT and symptom burden in cancer survivors.

2. Methods
This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered prospectively in PROSPERO (ID 42016036924).

Identification of studies and inclusion criteria
The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for articles published from January 2000 to January 2018. In addition, we searched the reference lists of any relevant studies and reviews as well as Google Scholar. The limits on the years of publication were set due to the rapidly evolving cancer treatment and care experiences of cancer survivors. We defined “cancer survivors” as people living with cancer from the time of diagnosis until the end of life.\textsuperscript{16,17} The search strategies were guided by the following four groups of search terms: (i) cancer, (ii) patients, (iii) cost, and (iv) symptom burden. Synonyms and related terms are detailed in Table 1. 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. To be included in this current review, studies were required to meet following pre-specified criteria: published in English; published or were in press in a peer reviewed journal; and examined and reported the relationships between FT and symptom burden in cancer survivors. Symptom burden could be (i) assessed using the following dimensions: symptom occurrence, severity, frequency and/or distress; (ii) measured using valid and reliable measures or investigator-constructed instruments; and (iii) reported by patients, proxy, or healthcare professionals. Where symptom burden was reported as part of a quality of life measure, symptom burden had to be explicitly evaluated and reported. Definitions and measures of FT used in this review were informed by our previous systematic review.4 These measures were categorised as: (i) monetary: currency values of out-of-pocket expenses and percentage of out-of-pocket spending to income ratios; (ii) objective: 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 (iii) subjective: question sets on perceptions of cancer-related financial burden. No limitations were placed on cancer stage or time since diagnosis. We accepted quantitative, mixed-methods, and qualitative research studies.

**Study screening and data extraction**

The Endnote X8.2 referencing management software (Clarivate Analytics, Philadelphia) was used for the screening and inclusion of studies. One author (OAA) pre-screened all search results (i.e., titles and abstracts) for possible inclusion and selected articles for full-text assessment. Two authors (RC, OAA) independently assessed the full-text articles for inclusion. All articles that met the pre-specified inclusion criteria were included in this review. Data extraction was conducted by one author (RC) and checked by another author.
(CM). Data extracted included: study methods, authors, publication year, country, study
design, setting, demographic characteristics (i.e., age, income levels, educational levels,
health insurance and employment status), clinical characteristics (i.e., disease, disease stage,
time since diagnosis), outcome measures, and key findings.

**Study quality assessment and data synthesis**

Quality assessment was conducted independently by two authors (RC, OAA) using pre-
defined criteria adapted from Mols et al.’s standardised checklist (See Supplementary Data
1). The checklist included criteria for the quality indicators concerning methodology,
reporting, and interpretation of results. Across the 12 items that were evaluated, if the study
met the quality indicator, it received one point. If the study did not fulfil the specific criterion,
did not sufficiently describe whether the criterion was fulfilled, or did not mention the
criterion at all, a score of zero was assigned. Studies that scored ≥75% of the maximum
attainable score (i.e., ≥9 points) were considered ‘high quality’. Studies that scored between
50% and 75% were considered ‘moderate quality’. Studies scoring <50% were considered
‘low quality’ (i.e., ≤6 points).

We did not exclude studies based on study quality. For the included studies, we expected
significant heterogeneity in terms of methods and populations. While we initially planned to
conduct a narrative synthesis, due to the broad range of cancer survivors who were
evaluated in the included studies, we summarised our study findings using two broad groups,
namely cancer survivors with mixed stages of disease or cancer type, and those with
advanced disease. For studies that provided measures of strength of association, the strength
of association for correlation coefficients is described as: weak if < 0.3, moderate if 0.3 to
0.5, strong if 0.5 to 0.7 and very strong if > 0.7, and for odds ratios as: weak if < 2.5,
moderate if 2.5 to 4.0, strong if 4.0 to 10.0 and very strong if > 10.0.
3. Results

The database searches resulted in 7,162 titles. After the addition of records identified through reference lists and other sources (n=7) and the removal of duplicates (n=1,396), a total of 5,773 were screened and 24 full-text articles were retrieved for full assessment. Of these 24 articles, a total of nine were included. The PRISMA flowchart is shown in Figure 1. The study characteristics and key findings are reported in Table 2.

Study characteristics and quality assessment

Of the nine included studies, eight 3, 8, 12, 22-26 examined the relationships between FT and psychological symptoms. Three studies examined the relationships between FT and physical symptoms 22, 23, 27. Eight studies 3, 8, 12, 22-26 adopted a cross-sectional design and one longitudinal study 27 collected data over two time points. Six were conducted in the United States 3, 8, 12, 23, 25, 27, with the remainder in Australia 24, France 22, and Ireland 26. The sample sizes ranged from 100-500, 3, 22, 23, 25 501-1,000 26, 1,001-5,000, 8, 12, 24 and >5,000. 27 All of the studies used a quantitative observational design. Six studies 8, 12, 24-27 included cancer survivors at various time points post-diagnosis, with the remainder including patients with advanced cancer. 3, 22, 23 Five studies recruited patients from population-level registries, 8, 12, 24, 26, 27 and four recruited from local cancer centres, 3, 22, 23, 25 A range of self-report measures of FT and symptom burden were used across the nine studies. Only one study 26 measured FT using monetary measures in addition to subjective measures. However, this study only assessed and reported the relationships between the subjective measures of FT and symptom burden. 26 These measures are described in detail in Table 2. The majority of studies were of high quality (≥9). 3, 8, 22-27 One study was judged as low quality (≤6), 12 mainly due to lack of use of validated measures, insufficient reporting of cancer treatment types and informed
consent, and a relatively low response rate. Supplementary Data 1 summarises the quality assessment criteria and results for each study.

**Relationships between financial toxicity and symptom burden**

Table 3 summarises the findings on the relationships between FT and symptom burden reported across the nine studies. A number of studies reported weak-to-moderate, positive relationships between FT and depression,8, 22-24, 26, 27 anxiety,22, 23, 26 overall psychological distress,3, 22, 25 stress, fear of recurrence,8, 12 spiritual suffering,22 pain,27 and overall symptom burden.22, 27 In terms of the relationships between FT and symptom burden, seven studies3, 8, 12, 24-27 reported results from their multivariable analyses controlling for a number of demographic and clinical characteristics, whereas the remaining two22, 23 were limited to uni- and bi-variate analyses.

**Cancer Survivors (mixed stage of disease and cancer diagnosis)**

In an Irish study of 654 breast, prostate, and lung cancer survivors (who were >6 months post-diagnosis), the multivariable analyses suggested that the risks of depression and anxiety increased almost threefold among those with increased cancer-related financial stress and strain 26. In this study, depression risk increased by three-fold in survivors who reported increased cancer-related financial stress (OR=2.79, 95% CI 1.8-4.17) and increased cancer-related financial strain (OR=3.56, 95%CI 2.23-5.67). Risk estimates were higher for those survivors with severe or worse depression, and who reported increased financial stress (OR=4.36, 95CI% 2.35-8.10), and increased financial strain (OR=8.21, 95%CI 3.79-17.77).26 Similar associations were found for anxiety and distress.26 Similar effect sizes were reported in the multivariable analysis from another cross sectional study of 1,380 cancer survivors (mixed cancer diagnoses) who were at various time points post-diagnosis.8 Specifically,
higher levels of depression, psychological distress, and fear of recurrence were associated with a higher number of financial problems (i.e., borrowed money or declared bankruptcy, worried about paying large medical bills, unable to cover costs of medical care visits, other financial sacrifices). In a multivariable analysis, compared with those who did not report financial problems, the odds for depression and being worried about cancer recurrence were 3.4 and 3.5 times more likely, respectively for people with three or more financial problems. In terms of worry about cancer recurrence, in a US study of 2,108 cancer survivors, those who reported a higher level of cancer-related financial problems were more likely to worry “all the time”, that the cancer would return (43%), compared to those who did not worry about cancer recurrence (28%) (p<0.001).

In an Australian study of 1,414 haematological cancer survivors, trouble meeting day-to-day expenses, difficulty paying bills, stopped work, travel time to treatment, and using home services in the last month were not associated with anxiety and depression. However, not having private health insurance was an independent predictor of depression. Difficulty paying bills (OR: 1.94 95% CI: 1.03-3.67) was an independent predictor of stress. Using up savings was an independent predictor of depression (OR: 1.79, 95% CI: 1.10 -2.92) and stress (OR: 1.81, 95%CI 1.07-3.05).

To allow for a greater understanding of the direct and indirect relationships between FT, emotional distress, and overall distress, in a small US study (n=120) that examined the relationships between these constructs in insured cancer survivors, financial distress was associated with overall distress both directly (accounting for 76% of the effect) and indirectly (accounting for 24% of the effect) via mediation by emotional distress. Within this structural equation model, a 1-unit increase on the financial distress scale (which indicates improved
financial well-being) led to a 0.3-unit decrease on the emotional distress scale (which indicates less emotional distress) (p=.008).²⁵

Of the six studies that involved cancer survivors at various time points post-diagnosis, only one study assessed physical symptoms.²⁷ In a longitudinal study of 5,343 lung and colorectal survivors, those individuals with greater financial strain (defined as less financial reserves – the length of time patients could continue to live at their current address and standard of living if they lost all of their current sources of income and had to live off their savings) had significantly higher levels of pain (adjusted mean difference (MD), 5.03 [95% CI, 3.29 to 7.22] and MD = 3.45 [95% CI, 1.25 to 5.66], respectively, for lung and colorectal), and greater (overall) symptom burden (MD = 5.25 [95% CI, 3.29 to .22] and MD = 5.31 [95% CI, 3.58 to 7.04]). At 12 months after diagnosis, financial strain was an independent predictor of pain and depression (results not reported).²⁷

Cancer survivors with advanced cancer

Three studies of patients with advanced cancer (mixed cancer diagnoses) reported positive relationships between FT and depression²², ²³ anxiety²², ²³ and psychological distress³ (all p<0.05). In a French study of 143 patients with advanced cancer, a significant difference in spiritual suffering was found between those with financial distress compared to those without (p=0.045).²² In addition, patients with FT had higher levels of depression (p=0.007), anxiety (p=0.009), and total symptom burden (p=0.005). In a research instrument validation study (n=233),³ higher psychological distress was independently associated with worse self-perceived FT (p=0.003).³ Of the three studies that included patients with advanced cancer, only one study (n=149) evaluated psychological and physical symptoms.²³ This study reported positive correlations between FT (defined as financial distress) and anxiety (r = .2, p = .015) and depression (r = .18, p = .034). However, no associations were found between FT
and a range of physical symptoms including: pain, fatigue, nausea, drowsiness, dyspnoea, appetite, sleep, feeling of well-being, and spiritual pain.23

Discussion

Although the literature on FT has grown exponentially over recent years,4 the relationships between FT and symptom burden are not well understood. To our knowledge, this systematic review is the first to evaluate the literature that explored these relationships. In this review, six studies found positive relationships between increases in FT and higher levels of psychological symptoms (i.e., depression and anxiety). This finding has an immediate implication for practice. Clinicians should regularly screen for, assess, and manage emotional distress related to FT when it occurs.13, 28 The distress thermometer and problem checklist29 could be considered as a screening tool for distress potentially attributed to FT. The checklist items relevant to FT included those within the “Practical Problems” domain, which include childcare, housing, insurance/financial, transportation, work/school, and treatment decisions. Future intervention studies that aim to minimise or prevent FT should evaluate psychological symptoms as secondary outcomes. A limited amount of emerging evidence suggests that positive relationships exist between FT and psychological (or existential) symptoms other than depression and anxiety (e.g., fear of recurrence,12, 25 spiritual suffering,22 stress).24 Measuring these variables in future investigations of FT may increase our understanding of the mechanisms that underlie the associations between FT and symptom burden.

In this review, only two out of the nine studies evaluated and reported physical symptoms.23, 27 In the two studies that examined the association between pain and FT, the findings were inconsistent.23, 27 Given the high occurrence rates for fatigue, cognitive dysfunction, pain, and sleep disturbance in cancer survivors, additional research is warranted to examine the
relationships between these symptoms and FT. In addition, it is important to consider symptoms that may potentially affect work productivity (e.g., cognitive dysfunction, fatigue) and in turn lead to financial distress. In future studies, symptom inventories that are more comprehensive in nature and tailored for the appropriate populations (e.g., patients undergoing active treatment, long term cancer survivors) should be considered. Besides evaluating self-perceived symptoms using patient-reported outcome tools, objective measures to quantify symptom burden (e.g., neuropsychological tests, biomarkers) should be included in future investigations. Further, it is important to determine if the relationships between symptom burden and FT depend on which measure of FT is used. The three types of FT measures (i.e., monetary, objective and subjective measures) could capture different dimensions of financial burden experienced by cancer survivors. The findings from this review highlight that no study has assessed the relationship between symptom burden and FT using monetary measures. Although the use of validated subjective FT measures (i.e. FACIT-COST) has increased, well-recognised, monetary and objective measures are yet to be developed and validated. This gap should be addressed in future studies.

The relationships between FT and symptom burden are undoubtedly complex and warrant more in-depth investigations. Below, we highlight a number of gaps that should be addressed in future studies. Most of the studies in this review involved a heterogeneous sample of cancer survivors with various cancer diagnoses, time points since diagnosis, and stage of disease. These studies mainly focused on the long-term impact of FT and symptom burden after treatment ends. Because FT may occur at the time of or even before diagnosis, the studies cited in this review do not provide a comprehensive understanding of when FT occurs and how FT is associated with and/or interacts with symptom burden at an early stage of the cancer trajectory. The lack of longitudinal studies with multiple measures of both FT and
symptoms limit our ability to develop predictive models. Future research should use a longitudinal design and examine which phenotypic and symptom characteristics are associated with a worse FT trajectory and the direction of these relationships. As financial distress can emerge from causes unrelated to cancer, the use of control groups is important to determine the proportion of financial distress attributable to cancer, especially since a significant portion of FT outcomes are subjectively reported by patients. Interestingly, we were unable to locate any mixed-methods or qualitative studies in our search. A mixed-methods approach will likely offer insights into these complex relationships. Qualitative approaches will allow investigators to explore and understand aspects of financial toxicity not adequately described by outcomes defined in quantitative studies. This approach will provide a more comprehensive picture of financial toxicity and can further assess if FT outcomes evaluated in existing studies are sufficiently sensitive to describe the financial distress experienced by cancer survivors. In addition to investigating the relationships between FT and individual symptoms, there might be value in understanding the relationships between FT and symptom burden (as a collective measure).22, 27

Several limitations warrant consideration. First, we did not do an exhaustive search including the “grey literature” and databases that are suitable for publications in South America and China. In addition to key medical literature databases (i.e. MEDLINE, CINAHL, and EMBASE), we hand-searched the reference lists of all relevant articles and reviewers, as well as Google Scholar. It is unlikely that any English articles were missed. Second, the included studies involved samples from high-income, developed countries including the United States, Australia, France, and Ireland. It is likely that people in different health systems have different experiences of FT. With the limited studies conducted with high variations in the study samples across a small number of countries, it makes comparisons across multiple
countries or health systems impossible. Therefore, the findings from this review cannot be
generalised to other parts of the world. Third, publication bias could potentially exist where
negative findings were not published at all or were not published in the English language.
However, given the small number of included studies, we were not able to assess publication
bias. Despite these limitations, this review is the first to explore the relationships between FT
and symptom burden and provided recommendations for future research.

Conclusions

Based on the findings from this review, relatively clear evidence supports an association
between FT and psychological symptoms. Clinicians should regularly screen for, assess, and
manage emotional distress that is attributable FT. While the causal pathway is not yet clear,
future intervention studies aimed at minimising or preventing FT may incorporate
psychological symptoms as secondary outcomes. Little is known about the relationships
between FT and physical symptoms. Future research should overcome the methodological
limitations of the current literature including the lack of longitudinal data collection, use of
mixed-methods approaches, inclusion of validated monetary, subjective, and objective FT
measures, and homogeneity of samples. While the aim of this review was to examine FT
outcomes, workability and work productivity is closely related to FT, an evaluation of the
association between symptom burden, financial hardship, and workability and productivity
outcomes might provide insights to support the development of future interventions.

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drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

Declarations of interest

None
References

<table>
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<tr>
<th>Search Terms</th>
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<tr>
<td><strong>1. Cancer:</strong> cancer care, oncology, treatment, management, p(a)ediatric, breast, prostate, colorectal, cervical, thyroid, brain, lung, lymphoma, stomach, liver, MeSH cancer</td>
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<td><strong>2. Patients:</strong> patient, survivor, sufferer, family, MeSH patient care</td>
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<td><strong>3. Costs:</strong> 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</td>
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<td><strong>4. Symptom Burden:</strong> symptom management, symptom burden, symptom occurrence, symptom distress, symptom severity, symptom experience, symptom frequency, pain, fatigue, depression, anxiety, psychological stress</td>
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<tr>
<td>Author, Year, Country, Sample Size, Study Purpose</td>
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| Sharp, Carsin & Timmons, 2013, Ireland, N=654 | Setting: A population-based sample from the National Cancer Registry Ireland (patients >6 months post-diagnosis) | **Financial toxicity measures:**  
- Direct medical and non-medical costs and indirect costs as a result of cancer  
- Objective Family Financial Stress Index  
- Subjective financial strain - assessed by one question on how the respondents had felt about the household's financial situation since their cancer diagnosis  
- Cancer-related financial stress – assessed by one question on the impact of the cancer diagnosis on the household's ability to make ends meet  
**Symptom burden and other relevant measures:**  
- DASS 21  
**Analysis:**  
- Logistic regression  
**Key findings:**  
- Depression risk increased by three-fold in participants reporting increased cancer-related financial stress (OR=2.79, 95% CI 1.8-4.17) and increased cancer related financial strain (OR=3.56, 95%CI 2.23-5.67).  
- Risk estimates were higher for severe or worse depression, increased financial stress (OR=4.36, 95CI% 2.35-8.10), and increased financial strain (OR=8.21, 95%CI 3.79-17.77).  
- Similar associations were reported for anxiety and distress.  | Quality score: 9  
**Strengths:**  
- Relatively large sample size (n = 654)  
**Weaknesses:**  
- Participants had varying time since diagnosis  
- 97% were cancer types associated with higher socioeconomic status (i.e. breast and prostate) |
| Delgado-Guay et al., 2015, United States, N=149 | Setting: CCC and GPH | **Financial toxicity measures:**  
- Participants were asked to rate the impact of financial distress using a “strongly agree” to strongly disagree” statement  
- Four self-rated items on “subjective financial burden”, “financial concerns”, “financial difficulties”, “financial worries” and using a numeric rating scale (0 = absent, 10 = worst)  
**Symptom burden and other relevant measures:**  
- ESAS, HADS, FACT-G, and MSPSS  
**Analysis:**  
- Pearson and Spearman correlation  
**Key findings:**  
- Financial distress was reported as more severe than physical distress, distress about physical functioning, social/family distress, and emotional distress by 45 (30%), 46 (31%), 64 (43%), and 55 (37%) of patients, respectively (was significantly | Quality score: 9  
**Strengths:**  
- This study examined and compared financial distress in two cohorts with different income levels. This design provides insights that FT does not only affect people with lower income levels.  
- This study measured symptom burden |
Barbaret et al., 2017

**Purpose:** Examine frequency and severity of financial distress and its association with quality of life and symptoms among patients with advanced cancer

**Setting:** Teaching Hospital, CCC

**Timeframe:** March 2013 - June 2014

**N = 143**

**Cancer type:** Lung (25%), Breast (25%), Colorectal (25%), Prostate (25%)

**Disease Stage:** Metastatic (85%), relapse (4%), locally advanced (8%), other (2%)

**Treatment:** Surgery (52%), CTX (92%), XRT (56%), targeted (6%)

**Time since diagnosis (d):** Had financial distress: 1,979 (4,997), had no financial distress: 1,619 (1,814)

**Mean Age:** 58 y.o.

**Male:** 49%

**Income level (annual):** <$15,000 Euro (38%), >$15,000 Euro (62%)

**Education level:** college (27%), completed high school (15%), did not complete high school (59%)

**Health insurance at diagnosis:** NR

**Health insurance at the time of study:** NR

**Employment status:** NR

**Financial toxicity measures:**
- Financial distress was assessed using a self-rated numeric scale from 0 to 10 (0 = absent, 10 = worst). Patients were considered to have FD if they rated 1 or above on the 0-10 scale. High FD was defined as rating 4 or above
- Four self-rated items on “subjective financial burden”, “financial concerns”, “financial difficulties”, “financial worries” and using a numeric rating scale (0= absent, 10 = worst).

**Symptom burden and other relevant measures:**
- ESAS, HADS, FACT-G

**Analysis:**
- Student t-test, Chi-square (Man n-Whitney or Fisher test), Pearson or Spearman correlation ANOVA/Wilcoxon

**Key findings:**
- Patients with FD had higher HADS-D (8 versus 6 p = 0.007) and HADS-A (9 versus 7, p = 0.009) scores.
- FD was linked to increased total ESAS score (p = 0.005) and spiritual suffering (p = 0.045).

**Quality score:** 10

**Strengths:**
- This study measured symptom burden including physical symptoms (ESAS).

**Weaknesses:**
- Use of non-validated scale to assess financial toxicity
- Relatively small sample size, limited to bivariate analyses

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de Souza et al., 2017

**Setting:** Cancer centres at the University of Chicago Medicine and the NorthShore University Health System.

**Timeframe:** May 2013 to February 2015.

**N=233**

**Cancer type:** NR

**Disease Stage:** Stage IV solid tumours

**Treatment:** NR

**Time since diagnosis (y):** <1 (39%), >1 (61%)

**Median age (range):** 59 (27-88)

**Male:** 41.6%

**Income level:** Median household income (range) of poverty level = 376.6% (0-7,964%)

**Financial toxicity measures:**
- COST

**Symptom burden and other relevant measures:**
- Brief POMS, FACT-G, EORTC-C30

**Analysis:**
- Multivariable linear regression analyses

**Key findings:**
- FT (as measured by COST) was correlated with income (correlation coefficient [r] = 0.28, P<.001), psychosocial distress (r = -0.26, P<.001), and HRQOL, as measured by the FACT-G (r = 0.42, P<.001) and by the EORTC QOL instruments (r = 0.33, P<.001).

**Strengths:**
- This study is the first to validate an instrument to measure FT as a construct.

**Weaknesses:**
- Sample was drawn from tertiary referral centres where all participants
toxicity correlated with HRQOL.

**Education level:** < college (15.5%), some college or technical training (37.3%), completed college and above (47.2%)

**Health insurance at diagnosis:** NR

**Health insurance at the time of study:** Private or employer-based (61.8%), Medicare (31.3%), Medicaid (5.6%), COBRA coverage (1.3%)

**Employment status:** Working (33.5%), Unemployed (9%), Retired (32.6%), On short-term/long-term disability (19.3%), other (5.1%)

- Independent factors significantly associated with FT were: race (p<.04), employment status (p<.001), income (p=.003), number of inpatient admissions (p=.01), and psychological distress (p=.49).

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- Independent factors significantly associated with FT were: race (p<.04), employment status (p<.001), income (p=.003), number of inpatient admissions (p=.01), and psychological distress (p=.49).

**Quality score:** 11

**Strengths:**
- This study focused only on haematological cancer.

**Weaknesses:**
- Use of non-validated measures of FT
- Relatively low response rate (35%) which creates a potential for response bias

**Kale and Carroll, 2016**

**United States**

**N= 1,380**

**Purpose:** Determine the prevalence and assess predictors of cancer related financial burden and examine the association

**Setting:** 2011 Medical Expenditure Panel Survey (MEPS) data

**Timeframe:** 2011

**Cancer type:** Breast (17%), Prostate (12%), Colorectal (4%), Melanoma (6%), other (61%)

**Disease Stage:** NR

**Treatment:** NR

**Time since diagnosis (y):** ≥5 (65%), <1 (6%), 1 - <3 (15%), 3-5 (14%)

**Age:** <65 (72%), ≥65 (28%)

**Male:** 44%

**Financial toxicity measures:**
- The Cancer Self-Administered Questionnaire (CSAQ):
  1. You or anyone in family had to borrow money or go into debt.  
     a. How much money was borrowed or how much debt was incurred?
  b. Have you or a family member ever filed for bankruptcy?
  2. Have you or a family member made any other financial sacrifices?
  3. Ever worried about paying large medical bills?
  4. Unable to cover cost of medical care visits?

**Quality score:** 9

**Strengths:**
- Relatively large sample size (>1,000)

**Weaknesses:**
- The dataset did not include cancer stage and treatment type and did...
between financial burden and HRQOL and psychological health

<table>
<thead>
<tr>
<th>Income/poverty level</th>
<th>high (46%), medium (29), low (12%), poor (13%) – (did not define)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education level</td>
<td>&lt; high school (11%), high school (28%), college (45%), &gt; college (16%)</td>
</tr>
<tr>
<td>Health insurance at diagnosis</td>
<td>92%</td>
</tr>
<tr>
<td>Health insurance at the time of study</td>
<td>96%</td>
</tr>
<tr>
<td>Employment status</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Participants were judged to have a financial burden if they answered “Yes” to one of the above questions
- Authors also examined the number of financial problems (range, 0-4) as a proxy for the extent of financial burden: (1) borrowed money, (2) declare bankruptcy, (3) worried about paying large medical bills, (4) Unable to cover cost of medical care visits

**Symptom burden and other relevant measures:**
- Depressed mood- Patient Health Questionnaire-2
- Psychological distress- Index of Kessler
- Worries related to cancer recurrence - 3 question survey (how often survivors worry about cancer getting worse or coming back, (2) how often they worry about cancer recurrence affecting their responsibilities at home or work, (3) what they believe about their changes of cancer recurrence or the disease getting worse within the next 10 years?

**Analysis:**
- Chi-square, student t-tests, binary logistic regression, and multivariable linear regression

**Key findings:**
- Multivariable level: Compared to those without financial burden, Survivors with financial burden (yes/no):
  - had increased odds of depressed mood (odds ratio, 1.95).
  - [The odds for depressed mood were 3.41 times higher for survivors reporting ≥3 financial problems], and
  - were more likely to worry about cancer recurrence (odds ratio, 3.54).
- Survivors reporting ≥3 financial problems had 2.56 times higher odds of psychological distress compared to those without.

- not control for these factors.
- Recall bias could be present because the majority of participants were diagnosed over 5 years ago.
Meeker et al., 2016  
**United States**  
N=120  
**Purpose:** Assess and characterise the relationships among financial distress, emotional symptoms, and overall distress in insured patients with cancer.  
**Setting:** Insured patients within a CCC  
**Timeframe:** September 2013 to April 2014  
**Cancer type:** Genitourinary (38%), Gastrointestinal (24%), Gynaecologic (13%), Sarcoma (8%), Other (17%)  
**Median age (range):** 62 (22-87)  
**Disease Stage:** NR  
**Treatment:** Surgery (68%), CTX (67%), XRT (39%), targeted therapy (16%), HRT (1%)  
**Time since diagnosis (y):** <1 (37%), 1-3 (22%), 3-5 (17%), >5 (25%)  
**Male:** 48%  
**Income level:** >100K (23%), 75-100K (13%), 50K-≤75K (20%), 25K-≤50K (20%), <25K (16%), Missing (8%)  
**Education level:** <high school (7), high school (33%), trade school/some college (27%), degree (21%), advanced degree (11%), missing (1%)  
**Health insurance at diagnosis:** 100%  
**Health insurance at the time of study:** 100%  
**Employment status:** retired (41%), used for wages (26%), unable to walk (19%), out of work (5%), other (6%), missing (3%)  

**Financial toxicity measures:**  
- The InCharge Financial Distress/Financial Well-being Scale  
**Symptom burden and other relevant measures:**  
- Overall distress was measured using the National Comprehensive Cancer Network Distress Thermometer.  
- Emotional distress was measured using the self-reported 6-item questionnaire (part of the Problems List).  

**Analysis:**  
- Structural equation modelling  
**Key findings:**  
- A 1-unit increase in the financial distress scale (which indicates improved financial well-being) leads to a 0.3-unit decrease in the emotional distress scale (which indicates less emotional distress) (p=.008).  
- A 1-unit increase in the emotional distress scale leads to a 0.58-unit increase in overall distress (which indicates increased overall distress) (p<.001).  
- A 1-unit increase in the financial distress scale (which indicates improved financial well-being) leads to a 0.553-unit decrease in overall distress.  
- After controlling for demographic variables, the total effect was that a 1-unit increase in the financial distress scale (which indicates improved financial well-being) leads to a 0.727 unit decrease in overall distress.  
- **Conclusion:** The total effect can be divided into two routes: pathways A and B (emotional distress mediates the association between financial distress and overall distress) and pathway C (financial distress directly increases overall distress).  

**Quality score:** 11  
**Strengths:**  
- This is the only one study that investigated the mediating effects of emotional distress between financial distress and overall distress.  

**Weaknesses:**  
- The instrument used to measure both overall and emotional distress is a screening tool (i.e., the distress thermometer problem checklist), which is not a validated measure of emotional and overall distress.  
- This study only included insured patients receiving care at a CCC.
Lathan et al., 2016

United States

N=5,343

Purpose: Measure the association between patient financial strain and symptom burden, and quality of life for patients newly diagnosed with lung or colorectal cancer

Setting: Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium.


Cancer type: Colorectal (54%), Lung (46%)

Treatment: NR

Male: 56%

Health insurance at diagnosis: NR

Health insurance at the time of study: 94%

Employment status: NR

Lung cancer (n=2,434)

Disease Stage: I (30%), II (9%), III (28%), IV (28%)

Time since diagnosis (mths): baseline (median): 4.2, follow up interview (median) 12.4

Age: <59 (27%), 60-69 (32%), 70-79 (30%), ≥80 (10%)

Income level: <20K (34%), 20-<40K (31%), 40-<50K (16%), ≥60K (18%)

Education level: <high school (21%), high school (62%), college degree or higher (18%)

Colorectal cancer (n=2,909)

Disease Stage: I (30%), II (9%), III (28%), IV (28%)

Time since diagnosis (mths): baseline (median): 4.2, follow up interview (median) 12.4

Age: <59 (27%), 60-69 (32%), 70-79 (30%), ≥80 (10%)

Income level: <20K (34%), 20-<40K (31%), 40-<50K (16%), ≥60K (18%)

Education level: <high school (21%), high school (62%), college degree or higher (18%)

Financial toxicity measures:

- Patients (or their surrogates) asked an interview question, “If you lost all of your current sources of income (for example, your pay check, Social Security or pension, public assistance) and had to live off of your savings, how long could you continue to live at your current address and standard of living?” Response options were: less than 1 month, 1-2 months, 3-6 months, 7-12 months, more than 1 year, and do not know

Symptom burden and other relevant measures:

- BPI, EORTC-C30 and EQ5D

Analysis:

- Univariable and multivariable linear regression and Univariable and multivariable ordinal logistic regression (Spearman’s rank correlation coefficient was used to examine the potential for collinearity

Key findings:

- At 4 months after diagnosis: relative to patients with more than 12 months of financial reserves, those with limited financial reserves reported significantly increased pain (adjusted mean difference, 5.03 [95% CI, 3.29 to 7.22] and 3.45 [95% CI, 1.25 to 5.66], respectively, for lung and colorectal), greater symptom burden (5.25 [95% CI, 3.29 to .22] and 5.31 [95% CI, 3.58 to 7.04]), and poorer QOL (4.70 [95% CI, 3.61 to 6.82] and 5.22 [95% CI, 3.61 to 6.82]).

- At 12 months (since diagnosis), financial strain was an independent predictor of pain and depression (results not reported).

Quality score: 9

Strengths:

- Large sample size - >5000, this is the only included study that measured financial reserves

Weaknesses:

- N/A
**Fenn et al., 2014**

**United States**

**Setting:** 2010 National Health Interview (NHIS) Survey  
**Timeframe:** 2010  
**Cancer type:** Multiple cancer type  
**Disease Stage:** NR  
**Treatment:** NR  
**Time since diagnosis (y):** NR  
**Purpose:** Examine the relationship between the financial problems caused by cancer and quality of life  
**N=2,108**

**Analysis:**  
- Bivariate analysis and binary logistic regression model  

**Key findings:**  
- Patients who had a higher level of cancer related financial problems were more likely to worry that the cancer may return all the time (43%) when compared to patients with lower financial burden (28.1%) (p < .001).  

**Quality score:** 6

**Strengths:**  
- Relatively larger sample size >2,000  
- This study is the only longitudinal study that provide insights about changes in outcome measures over 12 months.  

**Weaknesses:**  
- This study did collect participant characteristics, but did not report them.  

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**Note.** ANOVA = Analysis of variance, BMT = Bone Marrow Transplantation, BPI = Brief Pain Inventory, CCC = Comprehensive Cancer Center, COST = Comprehensive Score for financial Toxicity, CTX = Chemotherapy, DASS = Depression Anxiety Stress Scale, ECOG = Eastern Cooperative Oncology Group Performance Status, EORTC = European Organisation for Research and Treatment of Cancer, FACT-G = Functional Assessment of Cancer Therapy-G, ESAS = Edmonton Symptom Assessment System, EORTC = European Organisation for Research and Treatment of Cancer, FD = Financial Distress, GPH = General Public Hospital, HADS = Hospital Anxiety and Depression Scale, HRQOL = Health-related Quality of Life, HRT = Hormonal Therapy, IQR = Interquartile Range, MSPSS = Multidimensional Scale of Perceived Social Support, NHL = Non-Hodgkin Lymphoma, NR = not reported, POMS = Profile of Mood States, Q = quartile, QoL = Quality of Life, SF12 = Short-Form Health Survey, USD = United States Dollars, XRT = Radiotherapy.

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### Table 3. Findings of relationships between symptom burden and financial toxicity (by types of measures)

1. Monetary measures
<table>
<thead>
<tr>
<th></th>
<th>Physical</th>
<th>Psychological and spiritual</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
<td>Dyspnoea</td>
<td>Physical symptoms other than pain</td>
</tr>
<tr>
<td>Sharp et al. 2013 (^1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Note.** “+” = findings indicate a positive correlation, “-” = findings indicate a negative correlation, “N” = findings indicate no correlation, and “NA” = did not assess

\(^1\) Monetary measures were used but only descriptive analysis was conducted.

2. Objective measures

<table>
<thead>
<tr>
<th></th>
<th>Physical</th>
<th>Psychological and spiritual</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
<td>Dyspnoea</td>
<td>Physical symptoms other than pain</td>
</tr>
<tr>
<td>De Souza et al. 2017 (^2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hall et al. 2016 (^2)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
### 3. Subjective measures

<table>
<thead>
<tr>
<th>Study</th>
<th>Physical</th>
<th>Psychological and spiritual</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
<td>Dyspnoea</td>
<td>Physical symptoms other than pain</td>
</tr>
<tr>
<td><strong>Sharp et al. 2013</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Delgado-Guay et al. 2015</strong></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Barbaret et al. 2017</strong></td>
<td>Measured, but not reported</td>
<td>Measured, but not reported</td>
<td>Measured, but not reported</td>
</tr>
</tbody>
</table>

**Note.** “+” = findings indicate a positive correlation, “-” = findings indicate a negative correlation, “N” = findings indicate no correlation, and “NA” = did not assess

1 Measure of FT used has both objective and subjective components.

2 Used multiple (7) measures to indicate FT.

3 Inconsistent direction of correlation for different indicators of FT: positive correlation with decreased income but negative correlation with taking time off work.
<table>
<thead>
<tr>
<th>Study</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>+</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Souza et al. 2017</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(Weak)</td>
<td>NA</td>
</tr>
<tr>
<td>Meeker et al. 2016</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Lathan et al. 2016</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>(Weak)</td>
<td>NA</td>
<td>(Weak)</td>
<td>NA</td>
<td></td>
<td>(Weak)</td>
</tr>
<tr>
<td>Fenn et al. 2014</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Note.** “+” = findings indicate a positive correlation, “-” = findings indicate a negative correlation, “N” = findings indicate no correlation, and “NA” = did not assess

1 Used 2 indicators of FT

2 Findings showed higher odds of anxiety, depression and distress in both patients who have more and less concerns of their financial situation after being diagnosed with cancer, compared to those who report unchanged levels of concern.

3 Both depression and anxiety were measured with two tools: ESAS and HADS.

4 Did not report measures of strength of association.

5 Measure of FT used has both objective and subjective components.

6 Findings for two separate disease cohorts (lung and colorectal cancer) were reported; however findings were generally consistent.
### Supplementary Data. Quality Assessments of the Included Studies

<table>
<thead>
<tr>
<th></th>
<th>Sharp, Carsin &amp; Timmons, 2013</th>
<th>Delgado-Guay et al., 2015</th>
<th>Barbaret et al., 2017</th>
<th>de Souza et al., 2017</th>
<th>Hall et al., 2016</th>
<th>Kale and Carroll, 2016</th>
<th>Meeker et al., 2016</th>
<th>Lathan et al., 2016</th>
<th>Fenn et al., 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the study explain how the patient sample was selected?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Was the inclusion/exclusion criteria clearly formulated?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Was the socio-demographic and medical data described (e.g. age, race, employment status, educational status, tumour stage and diagnosis etc.) in the study?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Is the type of (cancer) treatment described?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Are the results of study compared between two or more groups (e.g. healthy population, groups with different cancer treatment or age, comparison with time at diagnosis etc.)?</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the mean/median or standard deviation/range of time since diagnosis and treatment given?</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Were the participation and response rates of the participants described and if so were they more than 75%?</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was information about patient/disease characteristics presented?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Was a standardized or valid quality of life/symptom measure (i.e. questionnaire, scale) used?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Are mean, median, standard deviations or percentages reported for the most important outcome measures?</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Was an attempt made to find a set of determinants with the highest prognostic value?</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Did the patient sign an informed consent form before study participation?</td>
<td>0</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
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<td>9</td>
<td>10</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

**Note.** 1 = Yes; 0 = No. Each Yes score is assessed 1 point. Studies with ≥10 points = high quality, Studies with 7 to 9 points = moderate quality, Studies with ≤ 6 points = low quality