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Psychological problems among cancer patients in relation to healthcare and societal costs: A systematic review

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Abstract

Objective: This study systematically reviewed the association of psychological problems among cancer patients with healthcare and societal resource use and costs.

Methods: PubMed, PsycINFO, and Embase were searched (until 31 January 2021) for studies on psychological symptoms (anxiety, depression, distress, fear of recurrence) or psychiatric disorders (anxiety, depression, adjustment) and healthcare use (e.g., mental, inpatient healthcare), economic losses by patients and family, economic losses in other sectors (e.g., absence from work), and costs. The search, data extraction, and quality assessment were performed by two authors.

Results: Of the 4157 identified records, 49 articles were included (psychological symptoms ($n = 34$), psychiatric disorders ($n = 14$), both ($n = 1$)) which focused on healthcare use ($n = 36$), economic losses by patients and family ($n = 5$), economic losses in other sectors ($n = 8$) and/or costs ($n = 13$). In total, for 12 of the 94 associations strong evidence was found. Psychological symptoms and psychiatric disorders were positively associated with increased healthcare use (mental, primary, inpatient, outpatient healthcare), losses in other sectors (absence from work), and costs (inpatient, outpatient, total healthcare costs). Moderate evidence was found for a positive association between (any) psychiatric disorder and depression disorder with inpatient healthcare and medication use, respectively.

Conclusions: Psychological problems in cancer patients are associated with increased healthcare use, healthcare costs and economic losses. Further research is needed on psychological problems in relation to understudied healthcare use or costs categories, productivity losses, and informal care costs.

KEYWORDS
cancer, costs, healthcare use, oncology, psychiatric disorder, psychological symptom, work productivity

1 | BACKGROUND

Psychological problems such as symptoms of anxiety, symptoms of depression, psychological distress and fear of cancer recurrence are commonly reported in cancer patients.[1-3] In case of severe problems a psychiatric disorder may be present. Approximately 11-19% of all cancer patients have a major depression disorder, anxiety disorder or adjustment disorder.[4] These psychological problems may, besides influencing a patients' health-related quality of life,[5] also have economic consequences.[6]

As previously hypothesized by Carlson and Bultz,[6] cancer patients with psychological problems may not only have increased mental healthcare use, they may also make more use of other domains of healthcare such as general practitioner (GP) visits or hospitalization. Patients with psychological problems are less likely to adhere to cancer treatment or lifestyle recommendations, which may affect their treatment effectiveness and in turn may increase healthcare use.[7] Also, cancer patients with psychological problems are at higher risk of developing comorbidities (e.g., diabetes and cardiovascular disease),[8,9] which may result in higher healthcare use. Besides higher healthcare use, psychological problems may also impact on economic losses by patients and their family themselves (e.g., out of pocket purchases or received informal care)[6] and economic losses in other sectors for example productivity losses due to absence from work (i.e., sick leave) or decreased work productivity.[10,11] Psychological problems among cancer patients are thus hypothesized to result in high economic costs from both a healthcare and societal perspective.

It is important to gain detailed insight into these economic consequences of psychological problems among cancer patients, as healthcare costs and other societal costs of cancer are already high,[12] and decisions have to be made on allocation of limited healthcare resources. Recently a systematic review (2018)[13] on 10 studies up to December 2017 investigated the relation between psychiatric disorders and healthcare costs among cancer patients. This systematic review revealed that psychiatric disorders are associated with increased healthcare use and costs across all phases of the cancer trajectory. This systematic review was, however, limited to studies from the United States and did not include studies on psychological symptoms or studies that investigated economic losses of patients, their family or other sectors (e.g., productivity losses). In addition, two systematic reviews investigated factors associated with return to work after cancer diagnosis among cancer patients.[14,15] However these two reviews did not specifically focus on the economic consequences of the association between psychological problems and return-to-work (i.e., the actual time absent from work).

No systematic review has, so far, focused on the association between psychological problems (including both psychological symptoms and psychiatric disorders) and all potentially related healthcare and societal resource use and costs among cancer patients. Therefore, the aim of this study was to systematically review associations between psychological problems (anxiety, depression, fear of cancer recurrence, distress, adjustment to cancer) and healthcare and societal related resource use and costs among cancer patients. Results are relevant both from the perspective of cancer patients and their families, as well as their employers (productivity), and the healthcare system with respect to reimbursement of psychological treatment for cancer patients.

2 | METHODS

2.1 | Literature search

Preferred reporting items for systematic reviews and meta-analyses guidelines were used to conduct and describe this systematic review.[16] A comprehensive search was conducted in PubMed, Embase, and PsycINFO from inception up to 31 January 2021. Our search strategy included combinations of keywords, MeSH terms and synonyms which were adapted for each database search, related to three main topics: (1) cancer patients, (2) psychological problems (i.e., psychological symptoms including anxiety symptoms, depressive symptoms, distress and fear of cancer recurrence and psychiatric disorders including anxiety disorder, depression disorder and adjustment disorder) and (3) the use or costs of healthcare or societal resources (e.g., visits to the GP, medication use, inpatient costs, informal care costs, productivity losses).

A detailed description of the search strategy is available in Appendix 1. An information specialist from the medical library provided advice on the literature search. Additionally, reference lists from included articles were manually searched and authors were asked for additional studies.

2.2 | Study inclusion and exclusion criteria

Research studies were included if:

(1) they investigated the association between psychological symptoms (i.e., symptoms of anxiety or depression, distress, or fear of cancer recurrence) or a psychiatric disorder (i.e., anxiety disorder, depression disorder or adjustment disorder) and the use or costs of healthcare or societal resources;
(2) they included adult cancer patients (age ≥ 18 years) only; and
(3) full text was available in English or Dutch.

Research studies were excluded if they:

(1) presented descriptive statistics on the use or costs of healthcare or societal resources in a certain cancer population without investigating its association with (level of) psychological problems;
(2) measured work ability or work performance instead of lost working hours;

(3) measured return-to-work (yes/no) without insight on time absent from work;

(4) measured return-to-work among cancer patients who were not of working age (i.e., included both patients of working age and those who were retired) or

(5) were reviews

No limits were set for year of publication.

2.3 | Selection process and quality assessment

After removing duplicates, two independent reviewers (F. E. Van Beek and L. M. A. Wijnhoven) screened all identified records based on title and abstract. Records that were not relevant based on the screening were excluded. Subsequently, the full-text article of potentially relevant records were screened for eligibility using the inclusion and exclusion criteria. In case of disagreement, the full-text article was discussed by the two reviewers, and when needed a third author (F. Jansen) was involved to meet consensus.

The quality of the included study was assessed with an 11-item quality assessment scoring list based on Hayden et al.[17] and Drummond et al.[18,19] This list compromises four domains: study population, study attrition, data collection and data analysis. Each item was scored positive ("1") or negative ("0"). In case information to evaluate an item was lacking, that item was scored negative as well. In case an item was not applicable, that item was scored as "not applicable (N/A)." A total score was calculated by summing the item scores, resulting in a score ranging from 0 (lowest quality) to 11 (highest quality). The quality assessment was conducted independently by two reviewers (F. E. Van Beek and L. M. A. Wijnhoven). In case of disagreement, the item was discussed by the two reviewers, and when needed a third author (F. Jansen) to meet consensus. In line with previous studies,[20,21] the article was rated "high quality" when an article was assigned at least 70% of the total score.

2.4 | Data extraction

All studies eligible for inclusion were read thoroughly to extract data. For the data extraction a standardized collection form was used including: general information (first author, publication year, country), study design, study population (number of patients included, cancer site, relevant inclusion and exclusion criteria), psychological outcome and its measurement, use/costs outcomes and its measurement, and results (e.g., odds ratio, risk ratio, differences in mean). Based on the Dutch cost guideline of the National Healthcare Institute,[22] the use/cost outcome were, categorized into (1) healthcare use (e.g., medical specialist visits, length of hospital stay, medication use), (2) economic losses by patients and family (e.g., time expenses for providing informal care, travel costs, out of pocket payments) and (3) economic losses in other sectors (e.g., absenteeism from work). In addition, a fourth category was added in which healthcare use, losses by patients and family, and/or losses in other sectors were valued in monetary units. Based on the associations found in the literature, the four categories were further divided into subcategories including healthcare use (i.e., mental healthcare, supportive nonmental healthcare, primary care, oncology-related healthcare, inpatient care, outpatient care, medication, and other healthcare use), economic losses by patient and family (i.e., complementary and alternatively medicine use (CAM), healthcare use of spouses, and lost work productivity of spouses), economic losses in other sectors (i.e., return-to-

1. Healthcare use[a]
- Mental healthcare
- Supportive non-mental healthcare
- Primary care
- Oncology-related healthcare
- Inpatient care
- Outpatient care
- Medication
- Other healthcare use

2. Economic losses by patient and family
- complementary and alternatively medicine use
- Healthcare use of spouses
- Lost work productivity of spouses

3. Economic losses in other sectors
- Return to work

4. Healthcare use, losses by patients and family and losses in other sectors measured in monetary units
- Mental healthcare
- Inpatient
- Outpatient
- Medication
- Total healthcare
- Absenteeism and presenteeism (costs)
- Out of pocket costs
- Other costs

FIGURE 1 Categorization of healthcare and societal resource use and costs. [a]For the subcategorization, we were dependent on the description provided in the individual studies. Healthcare resource utilization was only categorized in the subcategory "oncology-related healthcare" if this matched the definition used in the corresponding article. In all the other cases, the investigated association was categorized in a broader subcategory, for example, "outpatient care"

work) and losses in monetary units (i.e., mental healthcare, inpatient, outpatient, medication, total healthcare, absenteeism and present-isms (costs), out of pocket costs, and other costs) (Figure 1).

2.5 | Statistical methods and level of scientific evidence

We used a best-evidence synthesis to estimate the level of evidence for the investigated associations between psychological problems and healthcare use, economic losses by patients and family, economic losses in other sectors, and total costs, as used in previous studies.[20,21,23] The levels of evidence were (1) strong if an association was consistently supported by at least two high quality studies, (2) moderate if an association was consistently supported by at least one high-quality study and at least one low-quality study or if a factor was consistently supported by at least two low-quality studies, and (3) inconclusive, if an association was supported by only one study, results were inconsistent or did not show an indication for a positive or negative association.

3 | RESULTS

3.1 | Identification and selection of studies

In total 4157 articles were yielded by PubMed, Embase and PsycINFO. Of these studies 272 were selected for full text review (Figure 2). In total 49 studies[24–71] fulfilled the eligibility criteria and were included in this systematic review. The majority of the studies focused on healthcare use (n = 36)[24,25,27–29,31,33–35,37–39,41–48, 51,53,54,56–62,64,67,69–72] followed by studies on costs in monetary units (n = 13),[26,29,34,36,38,42–44,48,53,55,57,61] economic losses in other sectors (n = 8)[30,32,40,49,63,65,66,68] and economic losses by patients and family (n = 6).[28,29,50,52,64,69] Thirteen studies[28,29,34,38,42–44, 48,53,57,61,69] focused on two or more of these categories (e.g., healthcare use and costs in monetary units), resulting in a total sum greater than 49 studies. In Tables 1–4 the characteristics of the included studies are presented according to healthcare use (Table 1), economic losses by patients and family (Table 2), economic losses in other sectors (Table 3) and costs in monetary units (Table 4).
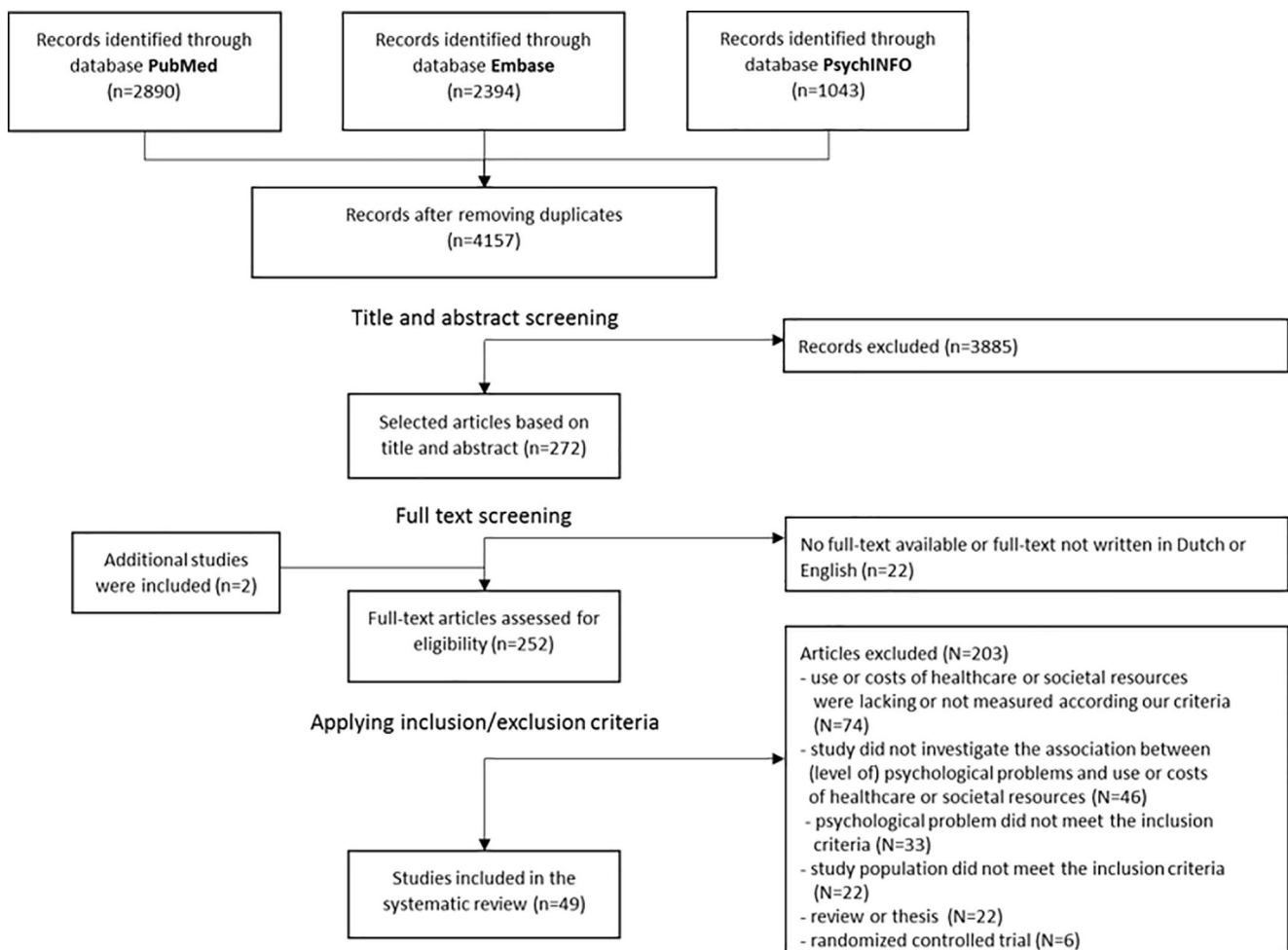

FIGURE 2 PRISMA flow diagram

TABLE 1 Overview of articles on the relation between psychological problems and healthcare use among cancer patients

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
Mixed cancers							
Cagle, 2020, USA	Prospective cohort	Mixed cancers (467)	+ Died between 2012 and 2014 + Older than 50 years	**Depression** ssCES-D	Hospice use (yes/no)	Interviews with the person most familiar with the decedent	Not significant Depression and hospice use
Champagne, 2018, Canada[b]	Longitudinal (follow-up at 0, 2, 10, 14, and 18 months)	Mixed cancers (955)	+ Age between 18 and 80 + First cancer diagnosis nonmetastatic to be scheduled to receive a surgery − Severe psychiatric disorder − Diagnosed or treated for sleeping disorder	**FCR** FCRI-SF ($\geq$13)	Medical professional: Specialist physician, general practitioner, nurse, pharmacist, homeopath/ osteopath, massage therapist Psychosocial professional: social worker psychologist, psychiatrist, physiotherapist Psychotropic medication: Anxiolytics/hypnotics, antidepressants (yes/ no)	Study-specific questionnaire	Significant FCR and medical professionals ($F = 4.09$, $p = 0.04$) FCR and psychosocial professionals ($F = 5.23$, $p < 0.00001$) FCR and anxiolytics/hypnotics ($F = 9.88$, $p = 0.0017$) FCR and antidepressants ($F = 5.23$, $p = 0.0499$)
Compen, 2018, Netherlands[b]	Cross-sectional	Mixed cancers (245)	+ HADS $\geq$ 11 + Stable 3 months psychotropic medication + Current active anticancer treatmen − Severe psychiatric morbidity − Previous mindfulness intervention	**Anxiety, depression and adjustment disorder, psychological distress** HADS, SCID-I	Mental healthcare: social workers, psychologists, and psychiatrists Primary healthcare: GP, occupational physicians, and physical and occupational therapists Somatic healthcare: medical outpatient clinics, ED, day healthcare units, and overnight hospital stays	TiC-P	Significant Depression disorder and mental healthcare (IRR = 1.71 (1.11–2.62)) ($p < 0.01$) Adjustment disorder and mental healthcare (IRR = 1.77 (1.00–3.10)) ($p < 0.05$) Distress and mental healthcare (IRR = 1.09 (1.06–1.12)) ($p < 0.01$) depressive symptoms and mental health (IRR = 1.14 (1.09–1.19)) ($p < 0.01$) Anxiety symptoms and mental health (IRR = 1.12 (1.07–1.18)) ($p < 0.01$) Depressive symptoms and primary healthcare use (IRR = 1.04 (1.00–1.08)) ($p < 0.05$) Not significant Depression, anxiety, adjustment disorder with primary and somatic healthcare use Distress and anxiety with and primary and somatic care Depressive symptoms and somatic healthcare use
Faller, 2017, Germany	Cross-sectional	Mixed cancers (4020)	+ Age between 18 and 75 + Evidence of a malignant tumor	**Anxiety, depressive symptoms, distress** DT ($\geq$5), PHQ ($\geq$9), GAD-7 ($\geq$10)	Utilization of psychological care (yes/no), counseling support (yes/no)	Study-specific questionnaire	Not significant Distress and utilization psychological care (OR = 1.01 (0.95–1.06)) Depression and utilization psychological care (OR = 1.03 (1.00–1.07)) Anxiety and utilization psychological care (OR = 1.06 (1.02–1.10))

(Continues)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
Hamilton, 2019, USA	Prospective cohort	Mixed cancers (893)	+ Having a cancer-related medical appointment + During treatment, standard clinical care	Distress DT (>6)	Service use: social work, psychologist, nutritionist, or chaplain, psychological service use on any inpatient hospitalization	Electronic medical record from the past 12 months (yes/no) (frequency visits)	Significant Distress (continue) and service use (B = 0.03) (p = 0.007) Distress (yes/no) and service use (B = 0.21) (p = 0.004) Distress (>6, continue) and social work (p = 0.001) Distress (>6, continue) and dietetics utilization (p = 0.004) Not significant Distress (>6, continue) and chaplaincy service and psychology service
Jacobsen, 2016, USA	Part of longitudinal (cross-sectional)	Advanced mixed cancer patients (123)	+ Older than 20 years + Identified informal care giver + Diagnosis of advanced cancer (presence of distant metastases and failure of first-line chemotherapy)	Major depressive disorder SCID	Mental health service use	Study-specific questionnaire	Significant Depression and mental health service use (OR = 16.07 (1.68–153.77))
Jeffery, 2012, USA[b]	Cross-sectional	Mixed cancers (11,014)	+ At least one healthcare service record in fiscal year 2006 + 18 years or older + Survived at least 2 years after their initial cancer treatment − Nonmelanoma skin cancer	Depression Medical record (ICD-9)	Service use: inpatient stays, lengths of inpatient stays, number of outpatient visits (number) Medication: prescriptions (number)	Medical record	Significant Depression (yes/no) mean number of stays (0.41 (0.9) vs. 0.12 (0.44)) Depression (yes/no) mean number of bed days (3.15 (14.39) vs. 0.64 (4.3)) Depression (yes/no) mean number outpatient visits (33.66 (28.84) vs. 18.69 (18.29)) Depression and number of prescriptions (45.28 (33.73) vs. 24.46 (23.51)) All p-values < 0.05
Lo, 2013, Canada	Retrospective, observational (1 year before measurement of depression, 1 year after depression diagnosis)	Mixed cancer patients (680)	+ 18 years or older + Confirmed diagnosis of stage 4 gastrointestinal, breast, gynecologic, or genitourinary cancer, or stage IIIA, IIIB, or IV lung cancer + 451 (173–1036) (median) days since diagnosis + Cognitive impairment documented + Carcinoid or neuroendocrine tumors	Depression Back Depression Inventory II (≥20)	Physician visits: primary care mental health, primary care nonmental health and oncology	Administrative databases	Significant Look-back period (1 year before measurement of depression) Depression and primary nonmental healthcare (RR = 1.21 (1.00–1.50)) (p = 0.005) Look-forward (1 year after measurement of depression) Depression and primary care mental health visits (RR = 2.35 (118–4.66)) (p = 0.015) Depression and oncology visits (RR = −0.78 (0.65–0.94)) (p = 0.008)) (negative association) Not significant Look-back period (1 year before measurement of depression) Depression and primary care mental health visits, oncology visits Look forward period (1 year after measurement of depression) Depression and primary nonmental health visits
Mausbach, 2017, USA	Retrospective cross-sectional	Mixed cancer (5055)	None	Depression Medical record (ICD-9)	Nonmental healthcare visits (number), ED visits, inpatients healthcare use	Medical record (the total number of contacts was calculated as the sum of use categories)	Significant Depression and healthcare visits (RR = 1.76 (1.61–1.93)) (p = 0.001) Depression and ED visits (OR = 2.45 (1.97–3.04)) (p = 0.001)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
					(hospitalization and 30-days rehospitalization)		Depression and hospitalization (OR = 1.81 (1.49–2.20)) (p < 0.001) Depression and 30-days rehospitalization (OR = 2.03 (1.48–2.79)) (p < 0.001)
Mausbach, 2020, California[b]	Retrospective cohort	Mixed cancers (13,426)	+ Diagnosis of cancer in 2014 + 18 years or older + At least one healthcare claim within 1 year of cancer diagnosis	**Anxiety, depression** (electronic medical record)	Healthcare use (ED visits, inpatient hospitalization)	Electronic medical record	Significant Depression and ED visits (B(SE) = 0.817 (0.074)) (p < 0.001) Depression and hospitalization (B(SE) = 0.584)) (0.076) (p < 0.001) Anxiety and ED visits (B(SE) = 0.851 (0.073)) (p < 0.001) Anxiety and hospitalization (B(SE) = 0.704 (0.074)) (p < 0.00)
Pan, 2015, USA[b]	Cross-sectional	Mixed cancer patients (4766)	+ Older than 21 years + Reported with cancer in 2006–2009	**Depression** Medical record (ICD-9)	Inpatient (yes/no), outpatient (yes/no), ED (yes/no), prescription drug (yes/no), and other healthcare services (yes/no)	Study-specific questionnaire	Significant Depression and ED visits (AOR = 1.46 (1.17–1.82)) (p < 0.001) Not significant Depression and inpatient use and other service use
Rana, 2019, Australia	Cross-sectional	Mixed cancers (517)	+ Older than 15 years + Diagnosed with any type of cancer	**Distress** K-10 (four categories: 1 = no, 2 = mild, 3 = moderate, 4 = severe distress)	Doctor visits (yes/no), hospital admissions (>1)	Study-specific questionnaire	Significant Distress a little (compared to never distress) and doctor visits (OR = 1.88 (1.02–3.47)) (p = 0.04) Distress and doctor visits (B = 0.144 (0.110–0.178)) (p = 0.00) Not significant Distress sometimes and most times compared to never and doctor visits Distress most times, sometimes, a little compared to never and hospital admissions Distress and hospital admissions
Sarker, 2015, Germany	Cross-sectional	Mixed cancers (335)	+ 18 years or older + A malignant tumor (all tumor entities and disease stages) + 12 (21.3–228) (mean, SD range) months after cancer diagnosis, − Presence of psychical, psychological and/or cognitive impairments	**FCR and anxiety** FoP-Q-SF (high FCR >34), GAD-7 (categorical)	Psychological support services, medical support services, complementary support services, spiritual and religious support services, and other support services (yes/no)	Self-report over 1 year	Not significant FCR and anxiety with psychological support services, medical support services, spiritual and religious support services, and other support services
Trevino, 2019, USA	Cross-sectional	Mixed cancer (1211)	+ 75 years or older with cancer undergoing surgery + Who were referred to the geriatric services for preoperative evaluation + Underwent elective surgery with a	**Distress, depression** DT ((I>4), GDS (≥1))	Mental healthcare use (social work, psychology, and/or psychiatry clinicians and the patient and/or family	Electronic medical record	Significant Distress and mental healthcare use (OR = 1.72 (1.16–2.56)) (p = .007) Not significant Depression and mental healthcare use (OR = 1.10 (0.73–1.64)) (p = 0.65)

(Continues)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
			length of stay of >3 days, and received at least 30 days of postoperative follow-up		during the postoperative stay)		
Lebel, 2013, Canada	Cross-sectional	Breast, prostate, colon, or lung cancer (231)	+ 18 years or older + Diagnosed in the past 10 years + 7.2 (2.4) (mean, SD) years since diagnosis	FCR FCRI (severity subscale >13)	Outpatient clinic, medical specialist, another healthcare provider, ER, admitted to hospital over the past 6 months (visits) and medication taken in the past week)	CBMTG healthcare utilization questionnaire	Significant FCR and outpatient visits ($B = 0.16$) ($p = 0.025$) FCR and ER visits ($B = 0.14$) ($p = 0.047$) Not significant FCR and MS visits, medication use, mental healthcare visits and number of overnight visits
Breast cancer							
Fox, 2013, USA[b]	Retrospective	Breast cancer (40,202)	+ 18 years or older + Diagnosis of invasive breast cancer + Procedure for mastectomy – Breast conserving surgery	**Psychiatric disorder:** depression, **GAD,** adjustment disorder, panic disorder Medical record (ICD-9)	Prolonged hospitalization (>3 days)	NIS reports (electronic medical record)	Significant Psychiatric disorder and prolonged hospitalization (OR = 1.40 (1.32–1.49))
Keyzer-Dekker, 2012, Netherlands	Cross-sectional	Benign or malignant breast disease (151)	+ Referral after mammogram + Palpable lump abnormality on a screening mammogram – Medical history with breast cancer or psychiatric disease – Advanced breast cancer	**Anxiety and depression** STAI, CES-D (cut-off not mentioned)	Medical specialist and GP (visits), and use of psychosocial healthcare, that is, psychologist, welfare worker, self-help groups (yes/no) (number visits)	Self-report questions concerning use during first year after diagnosis	Significant Anxiety (low/high level) and psychosocial healthcare use ($p = 0.004$) Not significant Anxiety and medical specialist and GP visits Depression and psychosocial healthcare use and MS and GP visits
Oleske, 2004, USA	Cross-sectional (retrospective)	Breast cancer (123)	+ Women between 21 and 65 and who were expected to survive at least 3 years + At least 1 year after treatment + Mean time since diagnosis, 3.6 years	**Symptoms of depression** CES-D (≥16)	Any type of hospitalization overnight for any reason	Survey of 27 items about the frequency of visits in the past year	Significant Depressive symptoms and hospitalization (OR = 1.09 (1.03–1.16)) ($p = 0.041$)
Otto, 2018, USA	Cross-sectional	Early breast cancer survivors (300)	+ 18 years or older + Diagnosed within the past 7 years + Completed any planned surgeries, chemotherapy, or radiation therapy – Recurrence of breast cancer	**FCR** FCRI	Frequency of office visits, phone calls oncology medical providers and primary care, sought out mental health (yes/no), psychotropic medication (yes/no)	Self-report over the past 3 months	Significant FCR and oncology visits (RR = 1.53 (1.16–2.01)) ($p = 0.002$) FCR and phone calls (RR = 2.08 (122–3.54)) ($p = 0.007$) FCR and primary care provider visits (R = 1.31, (1.06–1.61)) ($p = 0.013$) Not significant FCR and primary care phone calls, mental health treatment and psychotropic

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
Thewes, 2012, Australia	Cross-sectional	Early breast cancer (218)	+ Age between 18 and 45 + Early breast cancer (stage 0–2) + Diagnosed at least 1 year ago + Completed hospital-based treatment, no history of recurrent disease or new primary cancer + 50 months (mean) after diagnosis	FCR FCRI (severity subscale >13) (subscale 0–36)	GP and oncologist visits, other healthcare usage (professional counselling, participation in support groups and membership of consumer advocacy groups (yes/no)	Self-report over the past 12 months	Significant FCR and GP visits (yes/no) (9.9 (2.3 to 17.4)) (p = 0.01) FRC and mammograms (once or more per year/no) (−18.2 (−29.1 to −7.3)) (p = 0.001) **(negative association)** FCR and other screening practices (yes/no) (−10.9 (−20.7 to −1.2)) (0.003) **(negative association)** FCR and current counseling (19.4 (4.8 to 33.9)) (p = 0.009) FCR and support group (10.9 (0.2 to 21.6)) (p = 0.05)
Vachon, 2020, USA	Cross-sectional	Breast cancer (1127)	+ 45 years or younger or age between 55 and 70 years + Initial cancer diagnosis at stages I–IIIa + 3 till 8 years post initial treatment at time enrollment study + Been treated with an adjuvant chemotherapy regimen − No cancer recurrence	FCR Concerns About Recurrence Scale Total Worries Index	Cancer-related healthcare use (routine follow-up, visiting healthcare provider, ER), no cancer-related healthcare use (visiting healthcare provider, ER)	Study-specific questionnaire about healthcare use past 12 months	Significant FCR and routine follow-up care cancer (IRR = 1.003, SE = 0.01, p = 0.02) Not significant FCR and ER (related to cancer, ER (not related to cancer), healthcare provider visits (related to cancer), annual healthcare provider visits (not related to cancer)
Other single tumor types							
Arts, 2018, Netherlands	Cross-sectional	Lymphoma and chronic lymphocytic leukemia (1444)	+ 18 years or older + Cancer survivors − No terminal care	Psychological distress HADS (≥13)	Receiving psychological care (yes/no), ≥ 3 GP contact (yes/no), ≥4 medical specialist visit (yes/no)	Study-specific questionnaire (recall period of 12 months)	Significant Distress and receiving psychological care (OR = 2.19 (1.62–2.98)) (p < 0.05)) Distress and contacting GP (OR = 2.06 (1.57–2.69)) (p < 0.05)) Distress and medical specialist visit (OR = 1.80 (1.36–2.38)) (p < 0.05))
Bhattarai; 2013, UK	Retrospective cohort	Colorectal cancer	+ Age between 30 and 100 + Registered at a contributing practice	Depression Medical records	GP consults, prescriptions, outpatient and inpatient	Medical records (1 year)	Significant Depression and prescription, inpatient and outpatient (women) Depression and prescription, inpatient and outpatient. (men) Not significant Depression and GP consultations (women)
Doll, 2016, USA	Longitudinal (follow-up at 1, 3, 6 months)	Gynecologic cancer (185)	+ Age older than 18 + Newly diagnosed gynecologic cancer and planned surgical management. − Active chemo or radiotherapy treatment	Anxiety PROMIS anxiety	Unplanned clinic or ER encounter within 30 days after surgery) (yes/no)	Hospital electronic medical record (30 days)	Not significant Healthcare use (+) group had higher anxiety scores than healthcare use (-) group (58.3 vs. 53.8) (p = 0.06)

(Continues)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
Godby, 2020, USA	Cross-sectional	Gastrointestinal cancer (355)	+ 18 years or older + Patients who were chemotherapy naïve	Depressive symptoms PROMIS (≥60)	ER visits and hospitalization prior year (yes/no), daily medication use past 7 days (yes/no)	Cancer & Aging Resilience Evaluation survey	Significant Depressive symptoms and daily medication use (OR = 2.51 (1.21–5.20)) Not significant Depressive symptoms and ER visits and hospitalization
Holla, 2016, Netherlands	Cross-sectional	Colorectal cancer (3957)	+ Older than 18 years + Undergone surgery with or without radiotherapy or chemotherapy − Cognitive impairments	Anxious and depressive mood HADS	Supportive care (dietician, oncological nurse, physical therapist, psychologist, completion rehabilitation program) (yes/no), number of visits from GP and medical doctor (number of visits)	Study-specific questionnaire	Significant Anxiety and dietary care (OR = 1.09 (1.06–1.12)) ($p < 0.01$) Anxiety and oncological nursing care (OR = 1.07 (1.04–1.11)) ($p < 0.01$) Anxiety and physical therapy (OR=(1.06 (1.03–1.09)) ($p < 0.01$) Anxiety and psychological care (OR = 1.18 (1.13–1.22)) ($p < 0.01$) Anxiety and rehabilitation program (OR = 1.08 (1.05–1.12)) ($p < 0.01$) Depression and dietary care (OR = 1.10 (1.07–1.13)) ($p < 0.01$) Depression and oncological nursing care (OR = 1.06 (1.03–1.10)) ($p < 0.01$) Depression and physical therapy (OR = 1.06 (1.03–1.09)) ($p < 0.01$) Depression and psychological care (OR = 1.15 (1.11–1.20)) ($p < 0.01$) Depression and rehabilitation program (OR = 1.06 (1.02–1.10)) ($p < 0.01$)
Jayadevappa, 2012, USA[b]	Longitudinal 1 year prior to diagnosis, and 5 years post-diagnosis	Prostate cancer (50,147)	+ Older than 66 years + 1 year prior to diagnosis, and 5 years post-diagnosis, in case the patient died, 1 year prior to dead was called terminal phase	Depression Medical record (ICD-9)	Inpatient (length of stay, number of admissions, surgical and diagnostic procedures), out-patient (laboratory testing and ER visits), durable medical equipment, home health services, skilled nursing facility use and hospice care)	SEER-Medicare linked data (1 year prior to diagnosis, and 5 years post-diagnosis)	Significant Depression in treatment phase and ER visits (OR = 3.46 (3.21–3.74)) Depression in post-treatment phase and ER visits (OR = 1.64 (1.54–1.78)) Depression in treatment phase and hospitalization (OR = 2.76 (2.63–2.88)) Depression in post-treatment phase and hospitalization (OR = 1.34 (1.29–1.39)) Depression in treatment phase and outpatient visits (OR = 1.80 (1.76–1.85)) Depression in post-treatment phase and outpatient visits (OR = 1.52 (1.50–1.80)) All compared to no depression
Jeffery, 2019, USA[b]	Retrospective cross-sectional	Head and neck cancer (2944)	+ Age between 18 and 64 + Had a primary diagnosis of head	Anxiety, depression and adjustment	Annual number of ambulatory visits, hospital admission,	ICD-9 codes	Significant Depression and ambulatory visits (WX2 = 2765.48) ($p < 0.0001$)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
			and neck cancer + Sex of the patients was known + The rank of the military sponsor was enlisted or officer + Healthcare was delivered within the United States	disorder Military data repository ICD-9	and hospital bed days		Anxiety and ambulatory visits (WX2 = 1948.34) ($p < 0.0001$) Adjustment disorder and ambulatory visits (WX2 = 2597.13) ($p < 0.0001$) Depression and number hospital admissions (WX2 = 38.43) ($p < 0.0001$) Anxiety and number hospital admissions (WX2 = 38.87) ($p < 0.0001$) Adjustment disorder and number hospital admissions (WX2 = 8.97) ($p < 0.0027$) Depression and number of hospital bed days (WX2 = 876.28) ($p < 0.0001$) Anxiety and number of hospital bed days (WX2 = 932.81) ($p < 0.0001$) Adjustment disorder and number of hospital bed days (WX2 = 43.25) ($p < 0.0001$)
Laurence, 2017, USA	Retrospective	Head and neck cancer (36,420)	+ 50 years and older − Cancers of the lip, salivary glands, nasopharynx, and thyroid	Depression Medical record (ICD-9-M)	ED visit (ended in admission vs. discharge)	Data from Nationwide Emergency Department sample (2008) (ICD-codes)	Significant *Head and neck cancer* Depression and hospital admission men (PR = 1.28 (1.21-1.36)) ($p < 0.001$) Depression and hospital admission women (PR = 1.31 (1.20-1.42)) ($p < 0.001$) *Larynx/Hypopharynx* Depression and hospital admission men (PR = 1.21 (1.21-1.30)) ($p < 0.001$) Depression and hospital admission women (PR = 1.27 (1.16-1.40)) ($p < 0.001$) *Oropharynx* Depression and hospital admission men (PR = 1.14 (1.06-1.24)) ($p < 0.001$) *Oral cavity* Depression and hospital admission men (PR = 1.56 (1.25-1.94)) ($p < 0.001$) Not significant *Oropharynx* Depression and hospital admission women (PR = 1.08 (0.92-1.27)) ($p = 0.330$) *Oral cavity* Depression and hospital admission women (PR = 1.29 (0.98-1.70)) ($p = 0.330$)
Lee, 2018, Taiwan[b]	Population-based cohort study retrospectively	Hepatocellular carcinoma (223 matched with non-disorder (anxiety and depression) group)	+ Treated between 1996 and 2010 + 18 years or older + History of HHC enrolment in registry for catastrophic illness patient database	Anxiety/depression Medical record (ICD-9)	Physician visits and lengths of stay hospital	Administrative claims for reimbursement from the Taiwan Bureau of National Health insurance	Significant Usage 1 year after diagnosis Anxiety/depression and physician visits (diff. = 48.2 (0.3)) ($p < 0.001$) Anxiety/depression and length of stay (diff. = 9.0 (0.4)) ($p < 0.001$) Usage 5 years after diagnosis

(Continues)

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
			− Patient with anxiety or depression before diagnosis				Anxiety/depression and physician visits (diff. = 91.4 (0.5)) ($p < 0.001$) Anxiety/depression and length of stay (diff. = 15.9 (1.1)) ($p < 0.001$)
McDermott, 2018, USA	Cross-sectional	Advanced non-small-cell lung cancer (13,827)	+ Older than 67 years + Diagnosed with stage IIIB or IV in 2007–2011 and claims spanning 2007–2013	Depression ICD-9 (diagnosis-time depression/post-diagnosis depression)	Hospice use >3 days and >90 days, >1 inpatient, in-hospital death, >1 ED visits, >1 hospitalizations, or ICU admission in the last 30 days of life, or chemotherapy receipt in the last 14 days of life	Electronic medical record	Significant Post-diagnosis depression and ICU admission (OR = 1.18 (1.01–1.37)) Not significant Diagnosis-time depression and inpatient admission, ICU admission, in-hospital death, ED visits and chemotherapy in last 14 days Post-diagnosis depression and inpatient admission, in-hospital death, ED visits and chemotherapy in last 14 days
Mosher, 2013, USA	Cross-sectional	Lung cancer (165)	+ 18 years or older have/had cancer treatment + 18 (22) months (mean, SD) after cancer diagnosis + Not too ill to participate in the study	Anxiety and depressive symptoms HADS (≥9, ≥8)	Mental health services, including psychotherapy/counseling/psychotropic medication and support groups, spiritual leader	Patient-reported questionnaire	Not significant Depression and anxiety and mental health use and help of spiritual leader
Niazi, 2018, USA[b]	Cross-sectional	Multiple myeloma (36,007)	+ Diagnosed between 1991 and 2010 with multiple myeloma + Full medical coverage	Depression ICD-9 (yes/no)	Inpatient, outpatient, ambulatory claims	SEER-Medicare (use and costs within the first 6 months after the diagnosis)	Significant Depression and undergoing inpatient (OR = 1.41, (1.31–1.53)) Depression and ED (OR = 1.37 (1.28–1.47)) Depression and ambulatory care. (OR = 1.22 (1.14–1.30)) all $p < 0.001$
Nipp, 2017, USA	Unclear	Mixed cancer (1036)	+ Older than 18 years and palliative + Advanced cancer + Not treated with curative intent − Excluded patients with leukemia and those who were admitted for stem cell transplantation − Patients with elective or planned hospital admissions	Depression, anxiety and distress PHQ-4 (>3 per subscale) (continues for distress)	Hospital length of stay, unplanned hospital admissions	Medical record	Significant Anxiety and time readmission within 90 days (HR = 1.059 (1.001–1.119)) ($p = 0.045$). Not significant Depression and anxiety and hospital length of stay. Depression and time to readmission within 90 days
Schuurhuize, 2019, Netherlands	Longitudinal (baseline, after 10, 24, and 48 weeks of treatments)	Metastatic colorectal cancer (349)	+ Diagnosis of metastatic colorectal cancer and started first line systemic treatment	Distress HADS (≥13), DT (≥5)	Psychosocial service utilization (yes/no)	TiC-P	Not significant Depression and psychosocial service utilization Distress and psychosocial service utilization
X, Han, 2015, USA[b]	Cross-sectional	Mixed cancers (3309)	+ History with cancer + Older than 18 years − Nonmelanoma skin cancer	Psychological distress K6 (≥13)	Medical provider visits, number of hospital outpatient visits, number of inpatient discharges, number of emergency department visits,	Survey and contacting medical providers	Significant among mixed cancer Distress (no/yes), hospital outpatient visits 35.3% versus 43.3% ($p = 0.0153$) Distress (no/yes), hospital inpatient discharge 16.0% versus 43.3% ($p = 0.0005$) Distress (no/yes), emergency visits 17.5% versus 35.3% ($p < 0.0001$) Distress (no/yes), dental visits 53.1% versus 27.1%

TABLE 1 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare use	Measurement healthcare use	Results[a]
					dental visits, number of prescribed medicines		($p < 0.0001$) **(negative)** Distress (no/yes), home healthcare visits 5.8% versus 16.2% ($p < 0.0001$) Distress (no/yes), medicine prescriptions 90.6% versus 95.5% ($p = 0.0011$) Significant among breast cancer Distress (no/yes), hospital inpatient discharge 11.7% versus 27.0% ($p = 0.0184$) Distress (no/yes), emergency visits 13.9% versus 29.4% ($p = 0.0153$) Distress (no/yes), dental visits 60.3% versus 38.0% ($p = 0.0083$) **(negative)** Significant among prostate cancer Distress (no/yes), office-based visits 95.7% versus 99.3% ($p = 0.0195$) Distress (no/yes), emergency visits 16.5% versus 41.9% ($p = 0.0351$) Distress (no/yes), medication prescriptions 94.3% versus 99.3% ($p = 0.0135$) Significant among colorectal cancer Distress (no/yes), dental visits 47.8% versus 12.2% ($p = 0.0025$) Not significant among mixed cancer Distress and office-based visits Not significant among breast cancer Distress and office-based visits, hospital outpatient visits, home healthcare visits and medication prescriptions Not significant among prostate cancer Distress and hospital outpatient visits, inpatient visits, home healthcare visits and dental visits Not significant among colorectal Distress and hospital outpatient visits, inpatient visits, home healthcare visits emergency visits and medication prescription

Abbreviations: CBMTG, Canadian Blood and Marrow Transplant group; CES-D, Center for Epidemiologic Studies Depression Scale; Diff, difference; DT, distress thermometer; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ED, emergency department; ER, emergency room; FCR, fear of cancer recurrence; FCRI-SF, Fear of Cancer Recurrence Inventory-short form; FOP-Q-SF, Fear of Progression Questionnaire – Short Form; GAD, generalized anxiety disorder; GAD-7, generalized anxiety disorder-7; GDS, Geriatric Depression Scale; GP, General practitioner; HADS, Hospital Anxiety and Depression Scale; HHC, hepatocellular carcinoma; ICD-9-CM, International Classification of Diseases; ICU, intensive care; IRR, incidence rate ratios; K6, Kessler-6; MS, Medical specialist; NIS, Nationwide Inpatient Sample; OR, odds ratio; PHQ, Patient Health Questionnaire; PR, prevalence ratio; PROMIS, Patient-Reported Outcomes Measurement Information System; SCID, Structured Clinical Interview for DSM-IV; SF, short form; STAI, State-Trait Anxiety Inventory; TIC-P, The Trimbos/iMTA questionnaire for costs associated with psychiatric illnesses.

[a]Significant results in this column indicate a positive association between psychological problems and healthcare use, unless otherwise specified.

[b]Article is also presented in Tables 2, 3 or 4.

TABLE 2 Overview of articles which included psychological problems in relation to economic losses by patients and family

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Losses of patients and family	Measurement healthcare use	Results[a]
Champagne, 2018, Canada[b]	Longitudinal (follow-up at 0, 2, 10, 14 and 18 months)	Mixed cancers (955)	+ Age between 18 and 80 + First cancer diagnosis nonmetastatic to be scheduled to receive a surgery − Severe psychiatric disorder − Diagnosed or treated for sleeping disorder	**FCR** FCRI-SF (($>=$13))	CAM: homeopath/osteopath, massage therapist, chiropractor, acupuncturist, and other	Study-specific questionnaire	Not significant FCR and CAM ($F = 1.25$, $p = 0.264$)
Thewes, 2012, Australia[b]	Cross-sectional	Early breast cancer (218)	+ Age between 18 and 45 + Early breast cancer (stage 0–2) + Diagnosed at least 1 year ago + Completed hospital-based treatment, no history of recurrent disease or new primary cancer + 50 months (mean) after diagnosis	**FCR** FCRI (severity subscale >13) (subscale 0–36)	CAM: professional counselling, massage, physiotherapy, lymphedema therapy, chiropractics, medications for anxiety, or depression, medication for sexual dysfunction, naturopathy, herbs, homeopathy, Reiki, acupuncture, meditation, yoga, hydrotherapy, hypnosis, Chinese medicine, reflexology, prayer or spiritual healing	Self-report over the past 12 months	Significant FCR and number of CAM used (1.8 (0.2–3.5)) ($p = 0.03$) Not significant FCR and CAM use (yes/no)
Manne, 2015, USA	Cross-sectional	Early-stage breast cancer (143 patients and spouses)	+ Patients had breast cancer surgery + 18 years or older + Spouses worked for the past month	**Cancer-specific distress** (Impact of Event Scale)	Healthcare use by spouses: Visits of different types of physicians in the past year (e.g., internist, cardiologist, urologist, radiologist, surgeon, oncologist, and neurologist) Losses of work productivity and absenteeism of the spouses	HPQ, questionnaire	Significant Patient cancer distress and healthcare use spouses (correlation = −0.23) (<0.05) **(negative)** Patient cancer distress and losses of work productivity of spouses (correlation = 0.18) ($p < 0.05$) Patient cancer distress and spouses absenteeism (correlation = 0.18) ($p < 0.05$)

TABLE 2 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Losses of patients and family	Measurement healthcare use	Results[a]
Compen, 2018, Netherlands[b]	Cross-sectional	Mixed cancers (245)	+ HADS ≥ 11 + Stable 3 months psychotropic medication + Current active anti-cancer treatment – Severe psychiatric morbidity – Previous mindfulness intervention	**Anxiety, depression and adjustment disorder psychological distress** HADS, SCID-I	CAM: homeopaths, acupuncturists, traditional Chinese medicine, and massage therapists	TiC-P	Significant Distress and complementary healthcare (IRR = 1.03 (1.00–1.06)) ($p < 0.05$) Anxiety symptoms and complementary healthcare ((IRR = 1.06 (1.01–1.11)) ($p < 0.05$) Not significant Depression, anxiety and adjustment disorder and depressive symptoms with complementary healthcare use
Litzelman, 2020, USA	Cross-sectional	Spouses of mixed cancer patients (1882) and mixed cancer patients (1882)	– Nonmelanoma skin cancer – Patients with missing data – If spousal reported cancer diagnosis	**Distress, depressive mood** K6 ((≥3 5), PHQ-2 (≥3) >5)	Mental healthcare use of spouses (antidepressant, antianxiety medication, psychotherapy visit) (any/none)	Medical Expenditure Panel Survey	Significant Elevated depressed mood and mental healthcare use spouses (OR = 0.59 (0.36–0.96) **(negative)** Not significant Elevated distress and mental healthcare use spouses
Sarker, 2015, Germany	Cross-sectional	Mixed cancers (335)	+ 18 years or older + A malignant tumor (all tumor entities and disease stages) + 12 (21.3–22.8) (mean, SD range) months after cancer diagnosis, – Presence of psychical, psychological and/or cognitive impairments	**FCR and anxiety** FoP-Q-SF (high FCR >34), GAD-7 (categorical)	CAM (yes/no)	Self-report over 1 year	Not significant FCR and CAM use

Abbreviations: CAM, complementary and alternatively medicine; FCR, fear of cancer recurrence; FCRI-SF, Fear of Cancer Recurrence Inventory-Short Form; FOP-Q-SF, Fear of Progression Questionnaire – Short Form; HPQ, World Health Organization Health and Work Performance Questionnaire; IRR, incidence rate ratios; PHQ, Patient Health Questionnaire; SCID, Structured Clinical Interview for DSM-IV; SF, short form; TIC-P, The Trimbos/iMTA questionnaire for costs associated with psychiatric illnesses.

[a]Significant results in this column indicate a positive association between psychological problems and losses of patients and family, unless otherwise specified.

[b]Article is also presented in Tables 1, 3 or 4.

TABLE 3 Overview of articles which included psychological problems in relation to economic losses in other sectors

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome	Work productivity	Measurement instrument work productivity	Results[a]
Den Bakker, 2019, Netherlands	Cross-sectional (retrospective registry based cohort)	Colorectal cancer (317)	+ 18 years or older + Treated with curative intent − Diagnosis of recurrent colorectal cancer − Another cancer diagnosis during sick leave	**Emotional distress**	RTW (1 and 2 years after diagnosis)	Study-specific questionnaire	Significant Distress and RTW after 1 year (OR = 0.47 (0.25–0.89)) (p = 0.020) Distress and RTW after 2 years (OR = 0.39 (0.22–0.67)) (p = 0.001)
Dumas, 2020, France	Prospective cohort (baseline at diagnosis, \3–6 months after treatment and 2 years after diagnosis)	Breast cancer (1874)	+ Diagnosed stages I–III + Younger than 57 years − History of cancer within the past 5 years − Women without information about work situation − Not employed at diagnosis − Not treated with curative intent	**Anxiety and depression** HADS (non-case: 0–7, doubtful case: 8–10, case: 11–21)	RTW (2 years after diagnosis)	Study-specific question	Significant/not significant Depression (case/non-case) and RTW (OR = 2.29 (1.34–3.91)) Anxiety (case/non-case) and RTW (OR = 1.47 (1.02–2.11)) Anxiety (doubtful case/non-case) and RTW (OR = 1.71 (1.26–2.32)) Not significant Depression (doubtful case/non-case) and RTW
Horsboel, 2015, Denmark	Longitudinal (1 year follow-up)	Hematological malignancy (105)	+ Age between 19 and 59 + 6–9 months diagnosed prior to inclusion + Employed at inclusion	**Anxiety and depressive symptoms** HADS (>8 and > 11)	RTW (1 year after diagnosis and long sickness absence)	Register for evaluation of marginalization (DREAM).	Not significant Anxiety and depression and RTW
Landeiro, 2018, Brazil	Longitudinal (6, 12, 24 months after diagnosis)	Breast cancer (121)	+ Age between 18 and 57 + <5 months post-diagnosis + Employed at diagnosis − Pregnancy − A Previous cancer diagnosis − Not insured	**Depression**	RTW (2 years after diagnosis)	Study-specific questionnaire	Significant Depression and reduced RTW (OR = 0.07 (0.01–0.63)) (p = 0.017)
Rosbjerg, 2020, Denmark	Longitudinal (followed \15 months after baseline)	Mixed cancer (114)	+ Age between 18 and 62 + All treatment intentions + Initiating chemotherapy last 24 months + Employed at time of diagnosis + Time since diagnosis (69,5 days (mean))	**Depression** Back's Depression Inventory (no depression (0–13), moderate depression (20–28), severe depression (29–63))	RTW (follow-up till 15 months after baseline)	DREAM database	Significant Symptoms of depression and RTW (HR = 0.58 (0.32–107) (p = 0.082)

TABLE 3 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome	Work productivity	Measurement instrument work productivity	Results[a]
Schmidt, 2019, Germany	Retrospective study	Breast cancer (135)	+ Completed the 5 years follow-up after surgery + Been employed at time of diagnosis − Patients who were during follow-up no longer disease free or not at working age (≥65)	**Depressive symptoms** CES-D	Impaired RTW (1 and 5 years after breast surgery)	Study-specific questionnaire	Significant Depressive symptoms at end of surgery and RTW 1 year after surgery (OR = 2.9 (1.1–8.0)) Not significant Depressive symptoms 1.5 years after surgery and RTW 5 years after surgery
Schonfeld, 1972, USA	Longitudinal	Mixed cancer (42)	+ Good or excellent prognosis for 5 years survival + Fulltime working before diagnosis − No malignancies	**Anxiety levels** IPAT anxiety scale questionnaire	RTW (9 months after first interview)	Interview	Significant Anxiety (higher) and RTW (p = 0.02), anxiety score: Working 20.2 versus not working 28.8
Spelten, 2003, Netherlands	Longitudinal	Mixed cancers (214)	+ Age between 18 and 60 + Treatment with curative intent + Paid employment at time of diagnosis + Within 4–6 months following their first day of sick leave	**Depression** CES-D	RTW (6, 12 and 18 months after first sick leave)	Self-report	Significant Depression quartiles and RTW (HR = 0.81 (0.66–0.99))

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; ICD-9-CM, International Classification of Diseases; IPAT, Intensive Care Psychological Assessment Tool; K6, Kessler-6; RTW, return to work; SCID, Structured Clinical Interview for DSM-IV.

[a]Significant results in this column indicate a negative association between psychological problems and return-to-work, unless otherwise specified.

TABLE 4 Overview of articles which included psychological problems in relation to costs in monetary units

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
Compen, 2018, Netherlands[b]	Cross-sectional	Mixed cancers (245)	+ HADS ≥ 11 + Stable 3 months psychotropic medication − Severe psychiatric morbidity − Previous mindfulness intervention	**Anxiety, depression and adjustment disorder** psychological distress SCID-I, HADS	*Mental healthcare* including visits to social workers, psychologists, and psychiatrists. *Primary healthcare* including visits to GP, occupational physicians, and physical and occupational therapists. *Somatic healthcare* including visits to medical outpatient clinics, ED, day healthcare units, and overnight hospital stays, prescription medication costs. *Complementary healthcare* utilization including visits to homeopaths, acupuncturists, traditional Chinese medicine, and massage therapists	Trimbos/iMTA questionnaire for costs associated with psychiatric illnesses (TiC-P), calculated into costs using Dutch reference prices	Significant Depression disorder and mental healthcare (OR = 3.44 (1.56–7.12)) Anxiety disorder and mental healthcare (OR = 3.92 (1.58–9.73)) Distress and mental healthcare (OR = 1.09 (1.04–1.14) (B = 1.04 (1.01–1.07)) Depressive symptoms and mental healthcare (OR = 1.16 (1.07–1.25)) Anxiety symptoms and mental healthcare (OR = 1.11 (1.03–1.20)) (B = 1.11 (1.05–1.16)) Not significant Depression disorder, anxiety disorder, adjustment disorder, distress, anxiety symptoms and depressive symptoms with primary, somatic and complementary healthcare Depressive disorder, anxiety disorder, adjustment disorder and depressive symptoms with mental healthcare
Gu, 2020, USA	Retrospective cohort study	Mixed cancer (breast, lung, prostate) (710)	+ At least one inpatient and two outpatient claims or medical provider claim − Patients lost with follow-up	**Depression** study-specific questionnaire (yes/no)	Healthcare expenditures (medicine, dental, home health, hospice inpatient, nursing facilities, outpatient)	Over 24 months since year of diagnosis. Medi-care Current Beneficiary Survey (MCBS)-Medicare sponsored by the Centers for Medicare & Medicaid services (**index year 2017**)	Significant Depression (yes/no) and medical provider (B = 0.38 (0.1)) (Change $ = 11,454 (4472–19,729) (p < 0.001) Depression (yes/no) and inpatient (AOR = 2.94 (1.82–4.74)) (Change $ = 8213 (3477–13,998) (p < 0.001) Depression (yes/no) and other (B = 0.41 (0.16) (Change $ = 405 (69–870) (p < 0.05) Depression (yes/no) and Medicare (B = 0.37 (0.01) (Change $ = 8280 (3570-13,977) (p < 0.001) Depression (yes/no) and out of pocket (B = 0.28 (0.13)

TABLE 4 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
							(Change $ = 1270 [139–2720] (0.01 ≤ p < 0.05). Not significant. Depression and hospital outpatient and prescribed medicine
Pan, 2015, USA[b]	Cross-sectional	Mixed cancer patients (4766)	+ Older than 21 years + Reported with cancer in 2006–2009	**Depression** Medical record (ICD-9-CM)	Inpatient and outpatient care, emergency department visits, prescriptions, home healthcare, durable medical equipment, dental care, eye care, and others types of healthcare (1 year)	The sum of all direct actual third-party payments made to the providers for services rendered plus the out-of-pocket spending by the individual or family (**index year 2009**)	Significant. Depression and total costs ($B = 9.136$) ($p < 0.001$). Depression and outpatient costs ($B = 8.468$) ($p < 0.001$). Depression and prescription costs ($p < 0.001$)
Mausbach, 2018, California[b]	Cross-sectional	Mixed cancer patients (13,233)	+ 18 years or older + At least one healthcare claim within 1 year of the cancer diagnosis	**Depression** Medical record (ICD-9-CM)	Annual outpatient (ambulatory) office visits, ED visits, hospital visits, and mental health visits	Electronic medical records	Significant. Depression (yes/no) and total charges ($235,337 (SD = $8573) versus $110,650 (SD = $1699)) ($B = 2.13$) ($p < 0.05$). Depression (yes/no) and outpatient costs ($175,284 (SD = $6781) vs. $87,024 (SD = $1413)) ($B = 2.01$) ($<0.05$). Depression and ED costs ($11,154 (SD = $359) vs. $8152 (SD = $170)) ($B = 1.37$) ($p < 0.05$). Depression and inpatient costs ($188 895 (SD = $6251) vs. $128 272 (SD = $2512)) ($B = 1.47$) ($p < 0.05$)
Mausbach, 2020, California[b]	Retrospective cohort	Mixed cancers (13,426)	+ Diagnosis of cancer in 2014 + 18 years or older + At least one healthcare claim within 1 year of cancer diagnosis	**Anxiety, depression** Medical record (ICD-9-CM)	Healthcare costs (total annual healthcare charges, annual outpatient (ambulatory) office charges, ED charges, and inpatient hospital charges)	Provided by the UC San Diego health cost-accounting system (electronic records)	Significant. Depression and total charges ($B = 1.38$ (1.25–1.52)) ($p < 0.001$). Depression and ambulatory charges ($B = 1.44$ (1.35–1.52)) ($p = 0.001$). Depression and ED charges ($B = 1.26$ (1.13–1.40) ($p < 0.001$). Depression and inpatient hospital charges ($B = 1.21$ (1.09–1.35) ($p < 0.001$)

(Continues)

TABLE 4 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
							Anxiety and total charges (B = 1.77 (1.61–1.94)) (p < 0.001) Anxiety and ambulatory charges (B = 1.54 (1.46–1.64)) (p < 0.001) Anxiety and total charges (B = 1.29 (1.16–1.44) (p < 0.001) Anxiety and inpatient hospital charges (B = 1.31 (1.18–1.46) (p < 0.001)
Boele, 2020, Netherlands	Longitudinal (6, 12, 18, 24 weeks and 6 and 12 months follow-up)	Glioma patients (90)	+ 18 years or older + Glioma patients with I, II, III stage + CES-D score≥12 + 3.4 years (mean) time since diagnosis − Suicidal intent	**Depression** CES-D	Direct costs of healthcare utilization from appointments and medication (including oral chemotherapy, but excluding procedures such as surgery and/or radiotherapy), and indirect costs due to productivity loss in three modules: absence from paid employment; production loss without absence from paid employment; and impediments to paid or unpaid employment	Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P) including the Short-Form Health and Labor Questionnaire (SF-HLQ) **(index year 2019)**	Significant Depression and healthcare utilization costs (+€24,459 (3662–42,250) per 4 weeks with each unit increase in scores) (p = 0.001) Not significant Depression and medication costs, overall costs and productivity loss costs
Fox, 2013, USA[b]	Retrospective	Breast cancer (40,202)	+ 18 years or older + Procedure for mastectomy − Breast conserving surgery	**Psychiatric disorder (i.e., major depression, GAD, adjustment disorder, panic disorder)** Medical record (ICD-9)	Total healthcare costs	NIS reports (electronic medical record), actual charges **(index year 2008)**	Significant Psychiatric disorder and costs (p < 0.001)
Jayadevappa, 2012, USA[b]	Longitudinal (1 year prior to diagnosis, and 5 years post-diagnosis)	Prostate cancer (50,147)	+ Older than 66 years	**Depression** Medical record (ICD-9)	Direct medical costs: physicians and other health professionals, care provided in hospitals, outpatient and ER costs, inpatient medications	SEER-Medicare linked data **(index year 2009)**	Significant Treatment phase depression and costs year of diagnosis (OR = 1.52 (1.39–1.66))

TABLE 4 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
					and laboratory services costs		Post-treatment depression and cost in year 4/5 post diagnosis (OR = 1.89 (1.78–2.00))
							Not significant Post-treatment depression and costs year of diagnosis
							Treatment phase depression and costs in cost in year 4/5 post diagnosis
Jeffery, 2019, USA[b]	Cross-sectional (retrospective)	Head and neck cancer (2944)	+ Age between 18 and 64 + The rank of the military sponsor was enlisted or officer + Healthcare was delivered within the United States	**Anxiety, depression and adjustment disorder** Military data repository (ICD-9) (yes/no)	Total annual reimbursed cost adjusted to 2014 dollars	Military data repository **(index year 2014)**	Significant Depression and total costs ($B = 0.30$ (0.024–12.53)) ($p < 0.0001$) Anxiety and total costs ($B = 0.26$ (0.027–9.51)) ($p < 0.0001$) Adjustment disorder and total costs ($B = 0.23$ (0.036–6.21)) ($p < 0.0001$)
Jeffery, 2012, USA[b]	Cross-sectional	Mixed cancers (11,014)	+ At least one healthcare service record in fiscal year 2006 + 18 years or older + Survived at least 2 years after their initial cancer treatment − Nonmelanoma skin cancer	**Depression** Medical record (ICD-9)	Total costs	Total cost that were reimbursed or paid to the provider in fiscal year 2009 Costs incurred by the patient or covered by other health/ insurance were not included.	Significant Depression yes/no and mean costs per provider (7728 (13,104) versus 16,212 (30,874)) ($p < 0.05$)
Lee, 2018, Taiwan[b]	Population-based cohort study retrospectively	Hepatocellular carcinoma (223 matched with non-disorder (anxiety and depression) group)	+ Treated between 1996 and 2010 + 18 years or older + History of HHC enrolment in registry for cata-strophic illness patient database	**Anxiety and depression** Medical record (ICD-9)	Outpatient costs, inpatient costs, inpatient costs and total treatment costs (1 and 5 years after diagnosis)	Administrative claims for reimbursement from the Taiwan Bureau of National Health insurance	Significant Year 1 after diagnosis costs Anxiety/depression and inpatient cost (diff. = 1251) Anxiety/depression and outpatient cost (diff. = 1665) Anxiety/depression and treatment cost (diff. = 2969) Year 5 after diagnosis costs (Continues)

TABLE 4 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
			− Patient with anxiety or depression before diagnosis				Anxiety/depression and inpatient cost (diff. = 2079) Anxiety/depression and outpatient cost (diff. = 3345) Anxiety/depression and treatment cost (diff. = 5303) All p values are <0.001
Niazi, 2018, USA[b]	Cross-sectional	Multiple myeloma (36,007)	+ Diagnosed between 1991 and 2010 + Full medical coverage	**Depression** Medical record (ICD-9)	Total healthcare costs (within the first 6 months after the diagnosis)	SEER-Medicare (index year 2013)	Significant Depression and total costs (OR = 1.23 (1.16–1.30)) and inpatient costs (OR = 1.33 (1.24–1.42)) all $p < 0.001$. Not significant Depression and outpatient costs
Han, 2015, USA[b]	Cross-sectional	Mixed cancers (3309)	+ History with cancer + Older than 18 years − Nonmelanoma skin cancer	**Psychological distress** K6 ($\geq$13)	Medical provider visits, hospital outpatient visits, inpatient discharges, emergency department visits, dental visits, prescribed medicines and total expenditures	Survey and contacting medical providers	Significant in mixed cancers Distress (no/yes), hospital outpatient costs 35.0% versus 43.3% ($p = 0.0013$) Distress (no/yes), hospital inpatient costs 15.9% versus 27.2% ($p = 0.0006$) Distress (no/yes), emergency costs 16.3% versus 33.9% ($p < 0.0001$) Distress (no/yes), dental visit costs 52.0 versus 26.8 ($p < 0.0001$) **(negative)** Distress (no/yes), home healthcare costs 5.5 versus 16.5 ($p < 0.0001$) Distress (no/yes), medicine prescriptions costs 90.6 versus 95.5 ($p = 0.0011$) Significant in prostate cancer Distress (no/yes), office-based costs 95.7% versus 99.3% ($p = 0.0195$) Distress (no/yes), emergency costs 15.9% versus 41.9% ($p = 0.0322$) Distress (no/yes), medication prescriptions costs 94.3% versus 99.3% ($p = 0.0135$)

TABLE 4 (Continued)

First author, year, study location	Design	Tumor type (N)	In- and exclusion criteria	Psychological outcome (measurement)	Healthcare costs categories	Measurement healthcare use and cost valuation	Results[a]
							Significant in colorectal cancer Distress (no/yes), dental visits costs 46.5% versus 12.2% (p = 0.0032) Significant in breast cancer Distress (no/yes), hospital inpatient costs 11.7% versus 27.0% (p = 0.0184) Distress (no/yes), emergency costs 13.4% versus 29.4% (p = 0.0131) Distress (no/yes), dental visits costs 59.6% versus 38.0% (p = 0.0099) Not significant in mixed cancer Distress and office-based costs, total expenditures and total costs Not significant in prostate cancer Distress and hospital outpatient, inpatient, home healthcare and dental Not significant in colorectal cancer Distress and hospital outpatient, inpatient, home healthcare emergency, medication prescription and total costs Not significant in breast cancer Distress and office-based costs, hospital outpatient, home healthcare, medication prescriptions and total costs

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; Diff, difference; ED, emergency department; ER, emergency room; FCR, fear of cancer recurrence; GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HHC, hepatocellular carcinoma; ICD-9-CM, International Classification of Diseases; K6, Kessler-6; NIS, Nationwide Inpatient Sample; SCID, Structured Clinical Interview for DSM-IV.

[a]Significant results in this column indicate a positive association between psychological problems and costs, unless otherwise specified.

[b]Article is also presented in Tables 1, 2 or 3.

In summary, all studies were published between 1972 and 2020, of which 24 studies[24,26–30,32,35–37,43,48–50,53,55–57,60,62,63,65,67,70,71] were published after December 2017. Most of the studies were conducted in the United States (N = 27),[27,34–38,41–44,46,50,52–61,66,70–72] Netherlands (N = 8),[26,29,30,39,45,67,68] Germany (N = 3)[33,64,65] and Canada (N = 3).[28,47,51] Studies were most often performed among mixed cancer patients (N = 20)[27–29,33,36–38,41,44,47,50,53,54,61–64,66,68,70] and breast cancer patients (N = 11).[32,34,38,45,49,52,59,60,63,65,71] Other studies were performed across a variety of other cancer patients: colorectal (N = 5)[25,30,38,39,67] prostate cancer (N = 2)[38,42], lung cancer (N = 3),[55,56,72] hepatocellular carcinoma (N = 2),[48,57] head and neck cancer (N = 2),[43,46] Gynecologic cancer (N = 1)[31], glioma cancer (N = 1),[26] gastrointestinal cancer (N = 1),[35] hematological malignancy (N = 1)[40] and lymphoma (N = 1)[24] patients. Sample sizes ranged from 42 to 50,147 patients.

Of all 49 studies, 34 studies[24,26–28,30–33,35–40,45,47,49–52,58–60,62–69,71,72] focused on psychological symptoms, 14 studies[25,34,41–44,46,48,53–57,61] focused on a psychiatric disorders and 1 study[29] on both. Focusing on psychological symptoms, 10 studies[31–33,39,40,45,58,64,66,72] investigated symptoms of anxiety as measured using the Hospital Anxiety and Depression Scale (HADS), General Anxiety Disorder-7, State-Trait Anxiety Inventory (STAI) or PROMIS Anxiety or Patient Health Questionnaire-4 (PHQ-4), 20 studies[26,27,29,32,33,35,36,39,40,45,49–51,58,59,63,65,67,70,72] investigated symptoms of depression as measured using the HADS, PHQ-9, Center for Epidemiological Studies Depression Scale, Geriatric Depression Scale, PROMIS, Back Depression Inventory II or a study specific questionnaire, six studies[28,47,52,60,64,69,71] investigated fear of cancer recurrence measured with the Fear of Cancer Recurrence Inventory – Short Form, Concerns About Recurrence Scale or the Fear of Progression Questionnaire—Short Form (FoP-Q-SF), and 11 studies[24,30,33,37,38,50,52,58,62,67,70] investigated distress measured with the HADS, Impact of Event Scale, Distress Thermometer or Kessler Psychological Distress Scale (K10 and K6).

Of the 14 studies[25,34,41–44,46,48,53–57,61] that investigated psychiatric disorders one study used a psychiatric interview (i.e., The Structured Clinical Interview) to investigate the presence of a depression disorder. In all other studies, the psychiatric disorder was retrieved from medical files: two studies[29,43] focused on adjustment disorder, three studies[29,43,53] on anxiety disorder, 13 studies[25,29,41–44,46,53–57,61] on depression disorder, and two[34,48] on presence of any psychiatric disorders (i.e., a combination of anxiety disorder and/or depression disorder and/or adjustment disorder).

3.2 | Quality assessment

Thirty-seven of the 49 studies were of high methodological quality as demonstrated in Appendix B. Most of the studies (19/25) scored negative on the item "patients who want to participate in study (participation rate)" due to a participation rate lower than 80%, **a** missing baseline participating rate or a selective non-response. Half of the included articles (25/49) did not meet the criteria for sufficient reporting of baseline descriptives, in particular, time since diagnosis, tumor stage, and/or treatment were often not reported. Almost all studies (42/49) used multivariate analyses and included more than 100 patients (47/49).

3.3 | Psychological problems in relation to healthcare use

Table 5 provides an overview of the results regarding type of psychological problem (i.e., anxiety symptoms, depressive symptoms, distress, fear of cancer recurrence, anxiety disorder, depression disorder, adjustment disorder or any psychiatric disorder) and type of healthcare use (i.e., mental, supportive nonmental, primary, oncology-related, inpatient, outpatient, and medicine and other healthcare use). Thirty six studies[24,25,27–29,31,33–35,37–39,41–48,51,53,54,56–62,64,67,69–72] investigated 48 associations in total of which six showed a strong evidence two a moderate evidence and 40 showed inconclusive evidence.

We found strong evidence that a depression disorder was positively associated with increased mental healthcare use.[29,41] Also, there was strong evidence that fear of cancer recurrence was positively associated with more use of primary care (i.e., GP).[60,69] In addition, strong evidence was found for a positive association between depression disorder and increased inpatient healthcare use (e.g., hospitalization, inpatient healthcare use and intensive care admission) as nine studies[25,42–44,46,53,54,56] found a positive association and three studies[46,56,61] found no association. The same holds for anxiety disorder and increased inpatient healthcare use.[43,53] Anxiety disorder[43,53] and depression[25,38,42–44,53,54,57] disorder were both found to be positively associated with increased outpatient care use (i.e., emergency department visits, ambulatory visits or general outpatient care use.

Moderate evidence (one high and one low-quality study)[34,48] was found for the association between any psychiatric disorder and inpatient care use (i.e., prolonged hospitalization or increased length of hospitalization). Moderate evidence was also found for the association between depression disorder and increased medication (i.e., number of prescriptions).[25,44]

Inconclusive evidence was found for many (n = 40) of the studied associations. Remarkable, however, were the negative associations found with regard to oncology related healthcare and psychological symptoms (i.e., depressive symptoms and fear of cancer recurrence) as these were the only examples of all healthcare use associations, in which studies demonstrated that the psychological symptoms were associated with decreased healthcare use (i.e., oncology-related visits, mammography screening and other screening practices).[51,69]

TABLE 5 Psychological problems associated with healthcare use

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder[a]
Mental healthcare	N+	(1) (2) (3)	(4)[1] (2) (3)	(5) (6) (3)	(7, 8)	(3)		(9) (3)	
	N−								
	N0	(10) (11) (12)	(10) (4)[2] (5) (1, 11)	(10), (13) (14)	(15) (16) (12)				
	LoE	?	?	?	?	?		++	
Supportive nonmental healthcare	N+	(2)	(2)	(13)					
	N−								
	N0	(12)		(13)	(12)				
	LoE	?	?	?	?				
Primary care	N+		(4)[1] (3)	(6)	(16) (8)				
	N−								
	N0	(1) (3)	(4)[2] (1)	(3)		(3)	(3)	(17) (3)	
	LoE	?	?	?	++	?	?	?	
Oncology-related healthcare	N+	(2)	(2)		(16) (18)[20]				
	N−		(4)[2]		(8)				
	N0		(4)[1]		(18)[21]				
	LoE	?	?		?				
Inpatient care	N+	(20)[5]	(21)	(22)		(23)	(24) (23)	(25) (26) (24) (17) (27) (23) (19)[6] (28) (29)[17]	(30) (31)
	N−								
	N0	(20)[7] (32)	(33) (20) (34)	(35) (22)	(15)			(19)[8] (36) (29)[18]	
	LoE	?	?	?	?	?	++	++	+
Outpatient care	N+	(1)	(1)	(35)[9] (22)	(15) (7)	(23)	(24) (23)	(25) (26) (24) (36) (17) (27, 28) (23)	(31)
	N−								
	N0		(34)	(35)[10] (22)	(15) (18)			(19)	

(Continues)

TABLE 5 (Continued)

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder[a]
	LoE	?	?	?	?	?	++	++	?
Medication	N+		(34)	(22)	(7) (16)			(25) (17)	
	N−								
	N0			(22)	(15)				
	LoE	?	?	?	?			+	
Other healthcare use	N+			(13)[12] (22)[15] (22)[19]	(16)[14]				
	N−								
	N0	(3)[11]	(3)[11]	(3)[11] (22)[16]		(3)[11]	(3)[11]	(3)[11] (36)[13]	
	LoE	?	?	?	?	?	?	?	

Note: High-quality studies were printed in bold and underlined. 1, healthcare use before depression diagnosis; 2, healthcare use after depression diagnosis; 5, readmission; 6, ICU admission; 7, hospital length of stay; 8, inpatient admission; 9, a little distress compared to never; 10, sometimes and most times distress compared to never; 11, somatic healthcare use; 12, service use; 13, other service use; 14, phone calls; 15, home healthcare among mixed cancer patients; 16, home healthcare among prostate, colorectal and breast cancer; 17, men; 18, women; 19, dental healthcare among mixed and breast cancer patients; 20, routine follow-up care cancer; 21, healthcare provider visits related to cancer; (1), Keyzer-Dekker; (2), Holla; (3), Compen; (4) Lo; (5), Trevino; (6), Arts; (7), Champagne; (8), Thewes; (9), Jacobsen; (10), Faller; (11), Mosher; (12), Sarkar; (13), Hamilton; (14), Schuurhuizen, (15), Lebel; (16), Otto; (17), Bhattarai; (18), Vachon; (19), McDermott; (20), Nipp; (21), Oleske; (22), Han X; (23), Jeffery, 2019; (24), Mausbach, 2020; (25) Jeffery 2012; (26), Mausbach, 2017; (27), Jayadevappa; (28), Niazi; (29), Laurence; (30), Fox; (31), Lee; (32), Doll; (33), Cagle; (34), Godby; (35), Rana; (36), Pan X.

Abbreviations: LoE, level of evidence; N−, negative association; N+, positive association; N0, no association; +, moderate evidence positive associations; ++, strong evidence positive association; ?, inconclusive or limited evidence on association.

aCombination of anxiety disorder and/or depression disorder and/or adjustment disorder.

3.4 | Psychological problems in relation to economic losses by patients and family

Six studies[28,29,50,52,64,69] investigated in total 10 associations between psychological problems and economic losses by patients and family, namely use of CAM ($n = 4$),[28,29,64,69] healthcare use by spouses ($n = 2$)[50,52] and lost work productivity of spouses ($n = 1$)[52] (Table 6). Inconclusive evidence was found for all of the 10 investigated associations, of which eight due to the fact that only one study investigated the association. The association between fear of cancer recurrence and CAM use was investigated in three studies of which one study[69] found a positive association with increased number of CAM but no association with use of CAM (yes/no) among breast cancer patients, and two studies[28,64] found no association at all among a mixed cancer population.

3.5 | Psychological problems in relation to losses in other sectors

Eight studies[30,32,40,49,63,65,66,68] investigated in total three associations between psychological problems and losses in other sectors, all of them focused on return to work (Table 7). Strong evidence was found that symptoms of anxiety and depression were negatively associated with return to work, indicating that patients with symptoms did not or returned later to work than patients without symptoms or with less symptoms. Three studies found a negative association between anxiety symptoms and return to work at 9, 12 and 24 months after cancer diagnosis among mixed, breast and hematological cancer patients, respectively.[32,40,66] Six studies found a negative association between depressive symptoms and return-to-work at 6, 12, 15, 18 and 24 months after diagnosis also among mixed, breast and hematological cancer patients.[32,40,49,63,65,68] One study[32] among breast cancer patients compared return-to-work among three groups of patients (no symptoms of depression, moderate symptoms of depression and severe symptoms of depression), which found that patients with severe symptoms of depression did return to work later than patients with low symptoms of depression, whereas no such difference was found in comparison to patients with moderate symptoms of depression. Inconclusive evidence was found on the association between distress and return-to-work among colorectal cancer patients.[65]

3.6 | Psychological problems in relation to losses in monetary units

Thirteen studies[26,29,34,36,38,42–44,48,53,55,57,61] investigated 33 associations in total between psychological problems and costs in monetary units (i.e., mental, inpatient, outpatient medicine total healthcare, productivity losses and out of pocket costs) (Table 8), of which four showed a strong association and 29 showed inconclusive evidence. There was strong evidence that a depression disorder was positively associated with inpatient, outpatient and total healthcare costs.

Three high quality studies found a positive association between a depression disorder and inpatients costs among mixed cancer patients.[53,57,65] Three high-quality studies[53,55,61] also found a positive association between depression disorder and outpatient costs among mixed cancer patients, whereas one high quality study[57] found no association among multiple myeloma patients. Six high-quality studies[43,44,53,55,57,61] found a positive association between a depression disorder and total healthcare costs among head and neck ($N = 1$), multiple myeloma ($N = 1$) and mixed ($N = 4$) cancer patients. One additional study[42] among prostate cancer patients reported a positive association between post-treatment depression disorder and total healthcare costs in year two and three following diagnosis, whereas no such association was found in the same study with total healthcare costs in the year following diagnosis or year four and five post diagnosis. Furthermore, there was strong evidence that an anxiety disorder was positively associated with total healthcare costs[43,53] among mixed cancer patients. Inconclusive or limited evidence was found for all 29 other investigated associations.

4 | DISCUSSION

The aim of this systematic review was to investigate associations between psychological problems and healthcare and societal related resource use and costs among cancer patients. In total 49 studies were included in this systematic review which investigated 94 different associations between psychological problems and healthcare or societal resource use or costs: 48 for healthcare use, 10 for economic losses of patients and their family, three on other losses such as return to work and 33 for total costs as measured in monetary units. For 14 of these 94 associations, moderate or strong evidence was found. Fear of cancer recurrence, having an anxiety disorder, having a depression disorder and having any psychiatric disorder were associated with higher healthcare use on at least one healthcare subcategory (i.e., mental, primary, inpatient or outpatient healthcare). Anxiety symptoms and depression symptoms were associated with reduced return to work, presence of an anxiety disorder was associated with higher total healthcare costs; and presence of a depression disorder was associated with higher inpatient, outpatient and total healthcare costs. For all other 80 investigated associations inconclusive evidence was found, mostly due to limited studies or inconsistent evidence.

This study confirms the hypothesis made by Carlson and Bultz[6] that cancer patients with psychological problems may not only have increased mental healthcare use but also make more use of other domains of healthcare. We found strong evidence that fear of cancer recurrence was positively associated with increased primary healthcare use. Inconclusive evidence was found for symptoms of anxiety, symptoms of depression, distress and fear of cancer recurrence in relation to all other healthcare use categories, often due to inconsistent findings. However, strong evidence was found that both anxiety disorder and depression disorder were associated with increased inpatient and outpatient healthcare use. In addition, evidence was found for

TABLE 6 Factors associated with economic losses by patients and family

		Psychological symptoms				Psychiatric disorders		
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder
CAM	N+	(3)		(3)	(8) [1]	(3)	(3)	(3)
	N−							
	N0	(12)	(3)		(7) (8) [2] (12)	(3)	(3)	(3)
	LoE	?	?	?	?	?	?	?
Healthcare use of spouses	N+							
	N−		(37)	(38)				
	N0			(37)				
	LoE		?	?				
Lost work productivity of spouses	N+							
	N−							
	N0		(38)					
	LoE		?					

Note: High-quality studies were printed in bold and underlined. 1, complementary and alternatively medicine use (number); 2, complementary and alternatively medicine use (yes/no); (3), Compen; (7), Champagne; (8), Thewes; (12), Sarkar; (37), Litzelman; (38), Manne.

Abbreviations: CAM, complementary and alternative medicine use; LoE, level of evidence; N−, negative association; N+, positive association; N0, no association; ?, inconclusive or limited evidence on association.

TABLE 7 Factors associated with economic losses in other sectors

	Psychological symptoms			Psychiatric disorder			
	Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder
Return to work							
N+							
N−	(39) (40) (41)	(39) [1] (40) (42) (43) (44) (45) [3]	(46)				
N0		(39) [2] (45) [4]					
LoE	−−	−−	?				

Note: High-quality studies were printed in bold and underlined. 1, depression case compared to non-case; 2, Depression doubtful case compared to non-case; 3, return to work after 5 years; (39), Dumas; (40), Horsboel; (41), Schonfield; (42), Landeiro; (43), Rosbjerg; (44), Spelten; (45), Schmidt; (46), Den Bakker.

Abbreviations: N−, negative association; N+, positive association; N0, no association; LoE, level of evidence; −−, strong evidence negative association; ?, inconclusive or limited evidence on association.

an association between depression disorder and increased mental healthcare use and any type of psychiatric disorder (including anxiety and depression disorder) and inpatient care use. This discrepancy in findings between healthcare use and symptoms of anxiety and depression versus anxiety and depression disorder may be caused by a dose-response relationship; that is, anxiety or depression problems may only result in higher healthcare use when the problem exceeds a certain threshold. However, it may also be that the association between symptoms of anxiety or depression and healthcare use only exists in certain groups of cancer patients or with specific healthcare use categories. This might explain why in a previous study among 4,020 mixed cancer patients no associations were found between anxiety and depressive symptoms and increased healthcare use,[33] whereas in another study among 3957 colorectal cancer patients this association was found to be significant.[39]

In contrast to the hypothesis of Carlson and Bultz,[6] the only healthcare use category which showed, evidence (although inconclusive) of a negative association with psychological problems was oncology-related care. So far, five studies have investigated the association between symptoms of depression or fear of cancer recurrence and use of oncology related care of which two studies found lower oncology-related care use among patients with psychological symptoms.[39,51,69] In four studies, however, also evidence was also found for no or a positive association[39,51,60,71] (some studies found evidence for both a negative association and absence of an association). An explanation may be that patients with higher symptoms of depression or fear of cancer recurrence have a more avoidant coping style[73] which may limit the uptake of specific types of oncology-related care. Further research is however needed to unravel this association.

With regard to economic losses of patient and family we found inconclusive evidence for all associations, mostly due to limited studies (i.e., eight of the 10 associations were investigated by only one study). Only two studies have investigated the association between psychological problems among breast cancer and mixed cancer patients and healthcare use and productivity losses among their spouses.

With regard to economic losses in other sectors, we found strong evidence that anxiety and depressive symptoms are negatively associated with return-to-work. These results are in line with the hypothesis of Carlson and Bultz that the economic consequences of psychological problems among cancer patients are larger than the economic costs of (mental) healthcare only.[6] In our systematic review, we only included articles which measured return-to-work with insight on time absent from work. Studies that investigated the association but without a clear timeframe for returning to work were excluded as the association between psychological problems and return-to-work in these studies may have been biased by time since diagnosis.[74–76] Remarkable, however, was that no study included in our systematic review investigated the association between psychiatric disorders and return-to-work. We hypothesize, however, that in line with the results on psychological symptoms and return-to-work, psychiatric disorders are also negatively associated with return to work.

TABLE 8 Factors associated with losses in monetary units

		Psychological symptoms				Psychiatric disorder			
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder[a]
Mental healthcare	N+	(3)	(3)[1]	(3)			(3)[1]	(3)[1]	
	N−								
	N0		(3)[2]				(3)[2]	(3)[2]	
	LoE	?	?	?			?	?	
Inpatient	N+		(47)	(22)[3]			(24)	(48)(24)(28)	(31)
	N−								
	N0			(22)[4]				(28)	
	LoE		?	?			?	++	?
Outpatient	N+		(47)	(22)[5]			(24)	(36)(48)(24)	(31)
	N−								
	N0		(47)	(22)[6]				(28)	
	LoE		?	?			?	++	?
Medication	N+			(22)[7]				(36)	
	N−								
	N0			(22)[8]					
	LoF		?	?				?	
Total healthcare costs	N+		(49)			(23)	(24)(23)	(36)(48)(24)(27)[9] (23)(28)(25)	(30)
	N−								
	N0			(22)					
	LoE		?	?		?	++	(27)[9] ++	?
Absenteeism/presenteism (costs)	N+	(49)	(49)						
	N−								
	N0		?						
	LoE								

TABLE 8 (Continued)

		Psychological symptoms			Psychiatric disorder				
		Anxiety	Depression	Distress	Fear of cancer recurrence	Adjustment disorder	Anxiety disorder	Depression disorder	Any psychiatric disorder[a]
Out of pocket costs	N+		(47)						(31)[13]
	N–								
	N0	(3)[10]							
	LoE	?	?						?
Other costs	N+		(47)[11]	(22)[14] (22)[15] (22)[18]		(3)[10]	(3)[10]	(3)[10]	
	N–								
	N0		(3)[10] (49)[12]	(3)[10] (22)[16] (22)[17]					
	LoE		?	?		?	?	?	

Note: High-quality studies were printed in bold and underlined. 1, measured with beta coefficients; 2, measured with odds ratio's; 3, among mixed and breast cancer patients; 4, among prostate and colorectal cancer patients; 5, among mixed cancers patients; 6, among breast, prostate and colorectal patients; 7, among mixed and prostate cancers; 8, among breast and colorectal; 9, year of costs taking into account differed; 10, somatic and complementary healthcare costs; 11, Medicare and other costs; 12, overall costs; 13, treatment costs; 14, home and dental care costs among mixed cancer patients; 15, dental healthcare costs among colorectal and breast cancer patients; 16, home healthcare costs among colorectal, prostate, and breast cancer patients; 17, dental healthcare costs among prostate cancer patients; 18, dental healthcare costs among mixed cancer patients; (1), Keyzer-Dekker; (2), Holla; (3), Compen; (4), Lo; (5), Trevino; (6), Arts; (7), Champagne; (8), Thewes; (9), Jacobsen; (10), Faller; (11), Mosher; (12), Sarkar; (13), Hamilton; (14), Schuurhuizen; (15), Lebel; (16), Otto; (17), Bhattarai; (18), Vachon; (19), McDermott; (20), Nipp; (21), Oleske; (22), Han X; (23), Jeffery, 2019; (24), Mausbach, 2020; (25), Jeffery 2012; (26), Mausbach, 2017; (27), Jayadevappa; (28), Niazi; (29), Laurence; (30), Fox; (31), Lee; (32), Doll; (33), Cagle; (34), Godby; (35), Rana; (36), Pan X; (37), Litzelman; (38), Manne; (39), Dumas; (40), Horsboel; (41), Schonfield; (42), Landeiro; (43), Rosbjerg; (44), Spelten; (45), Schmidt; (46), Den Bakker; (47), Gu; (48), Mausbach 2018; (49), Boele.

Abbreviations: N–, negative association, N+, positive association, N0, no association, LoE, level of evidence, ?, inconclusive or limited evidence on association.

a Combination of anxiety disorder and/or depression disorder and/or adjustment disorder.

With regard to losses in monetary units, strong evidence showed that depression disorder was positively associated with more inpatient care costs, outpatient care costs and total care costs. Anxiety disorder was also found to be positively associated with more inpatient care costs. Evidence on all other 26 associations was limited or inconclusive. Further research is needed to explore these associations and take possible moderators or mediators (e.g., coping style, social support) into account. For example, studies have demonstrated that cancer patients with psychological problems are more likely to develop comorbidities and are less likely to adhere to cancer treatment or lifestyle recommendations which may result in higher costs.[7] However, comorbidities may also lead to more psychological problems. The pathway via which psychological problems affect healthcare and societal resource use and costs, or the **reverse**, is thus not yet completely understood. Further research is needed on third variables such as coping style, and social support.

5 | STUDY LIMITATIONS

A strength of this study is that it focused on different psychological symptoms and disorders as well as different types of healthcare and societal costs. Also, in contrast to a previous systematic review,[13] the methodological quality of the included studies was investigated. Furthermore, we used the Dutch guidelines to define economic outcome categories. However, we acknowledge that this framework may not be suitable for all countries, as in some countries, for example, the healthcare costs are paid directly by the patient (without insurance). In those countries healthcare resource use may need to be categorized as "economic losses by patients and their family" instead of the category on "healthcare use." A limitation is that vote counting was used to summarize the findings of the included studies. The absence of an association in some of the included studies may have been the consequence of limited power rather than an actual absence of an association. Meta-analyses can solve this problem. However, we did not perform meta-analyses, as studies were very heterogeneous in study population, psychological problem, cost category investigated, as well as measurements instruments. Our aim was to provide an overview on all economic consequences investigated in relation to psychological problems among cancer patients and a summarized direction of an association instead of the magnitude of the association. Finally, a limitation of this study is that based on the included studies we cannot draw conclusions on the causality of psychological problems and healthcare, societal resource use and costs among cancer patients as almost all studies had a cross-sectional design.

6 | CLINICAL IMPLICATIONS

Results of this systematic review indicate that the economic consequences of psychological problems among cancer patients are beyond mental healthcare costs only. Psychological problems among cancer patients also impact societal costs such as losses due to delayed return to work. This information is important to consider when building a business case for the reimbursement of psychological treatment for cancer patients. Based on the results of this systematic review we claim that treating psychological problems in general among cancer patients may not only improve psychological well-being among cancer patients but also lead to medical cost offset and improved return-to-work. Two previous reviews[77,78] and later published studies[79-81] showed evidence that psychological treatment for patients with cancer is not only effective, but may also be cost saving. Several other studies are ongoing,[82,83] including one study on the effectiveness, cost-utility and budget impact of psychological treatment among cancer patients with an adjustment disorder,[84] which, as also shown in this systematic review, is still an understudied population.

7 | CONCLUSIONS

Psychological problems in cancer patients are associated with increased healthcare use, healthcare costs and economic losses, especially for (symptoms of) anxiety and depression disorder, and fear of cancer recurrence. Future research is needed on psychological problems in relation to understudied healthcare use or costs categories, productivity losses of patients and their caregivers, and informal care costs.

CONFLICT OF INTEREST
All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
F. E. Van Beek: conceptualization; methodology; investigation; writing Original Draft. L. M. A. Wijnhoven: conceptualization; investigation; writing - Review Editing. Karen Holtmaat: writing - Review Editing. José A. E. Custers: writing - Review Editing. Judith B. Prins: writing - Review Editing. Irma M. Verdonck-de Leeuw: conceptualization; writing - Review Editing; supervision; funding Acquisition. F. Jansen: conceptualization; methodology; investigation; writing - Review Editing; supervision.

DATA AVAILABILITY STATEMENT
The data that support the findings of this systematic review are all presented in Tables 1–4.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.