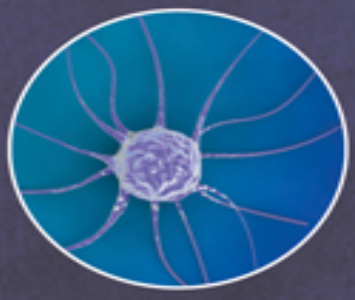

Depression and Cancer

Edited by

David W. Kissane

Mario Maj

Norman Sartorius

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Depression and Cancer

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WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

This edition first published 2011 ©2011, John Wiley & Sons, Ltd.

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

*Registered office:*John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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Library of Congress Cataloguing-in-Publication Data

Depression and cancer/editors, David W. Kissane, Mario Maj, Norman Sartorius. p.; cm. Includes bibliographical references and index. ISBN 978-0-470-68966-0 (pbk.)

1. Cancer-Psychological aspects. 2. Depression, Mental. I. Kissane, David W. (David William) II. Maj, Mario, 1953- III. Sartorius, N.

[DNLM: 1. Depressive Disorder-etiology. 2. Neoplasms-complications. 3. Neoplasms-psychology. WM 171]
RC262.D47 2011 616.99'40019—dc22

2010029174

A catalogue record for this book is available from the British Library.

This book is published in the following electronic formats: ePDF 9780470972526; Wiley Online Library 9780470972533

First Impression 2011

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Preface

Cancer affects close to one in two men and women across their lifetime, with this risk increasing steadily with age. In many countries, cancer competes with heart disease to become the leading cause of death, while being arguably the major cause of health morbidity, given the many losses, including disfigurement, disability and impairment, associated with the disease and its treatment. Psychological reactions to these losses are many, ranging from demoralization and passivity to anger and memory problems. In addition, depressive disorders are often comorbid with cancer. The likelihood of general practitioners and oncologists seeing patients with depression in the context of their care for people with cancer is extremely high.

The diagnosis of cancer is perceived by many to be their death sentence. The related existential threat initiates substantial suffering, all the moreso if pain is persistent, hopes are dashed, fears fueled, grief intensified and the person feels alone. Such suffering results in much dismay and despair. Whatever the therapy – surgery, radiation, chemotherapy, hormones, vaccines or targeted molecular treatments – the burden of the immediate, long-term and late effects of these regimens adds to the inherent distress. Metaphors of waging war and battlefields fortify against the images of an insidious and uncontrollable spread of disease. In some societies, the word ‘cancer’ remains unspeakable; for others, its prognosis is never acknowledged. The psychological hurdles to adaptation are formidable.

While its diagnosis readily precipitates a mid-life crisis, cancer recurrence induces deep angst as the prospect of cure fades. The very meaning of existence may be called into question. Worldwide, cancer accounts for nearly 14per cent of all deaths, but this rises to 25 per cent in Western societies. No family escapes its experience. The treatment

of metastatic cancer models the journey of a chronic medical illness for diseases like breast cancer, whereas for others, like pancreatic malignancy, the focus is essentially palliative and on quality of life. The challenge of holistic care has spawned the birth of a new discipline, named psycho-oncology, drawing its practitioners from psychiatry, psychology, social work and a range of related mental healthcare providers to deliver psychosocial care to cancer patients and their families. In many countries, they work alongside hospice and palliative care practitioners in providing care during the end-of-life; in others, they reach into genetic counseling services, transplant programs, smoking cessation clinics, cancer prevention and screening units, and, of course, cancer survivorship programs. Consultation-liaison psychiatry services almost always have key involvement with oncology and palliative care programs. For all of these psycho-oncology services, the treatment of cancer patients who develop depressive disorders becomes the bedrock of care.

Currently, the USA estimates that over 12 million cancer survivors exist in its society. New hurdles to adjustment are recognized as these patients transition into survivorship. For some, this is the first time that the busyness of a therapeutic schedule eases and the chance to accept their new reality emerges. For others, coping with the morbidity of their treatment challenges their body image, self-worth, sexuality, fertility, fitness or functionality. Whether living with an amputated limb, lymphedema necessitating daily arm compression, xerostomia only ameliorated by the constant sipping of water, or the need for multiple reconstructive surgeries to sustain cosmesis, the rehabilitative challenges after primary cancer treatment are substantial. As we reflect on the life-cycle of the cancer journey, its cumulative experience of grief, transition and

loss, the many challenges to optimal adaptation and quality of life become apparent.

Against this background of the ubiquitous burden of a malignant diagnosis and its treatment, this book focuses upon the relationship between cancer and depression. Major human suffering results from this association, suffering that we can effectively assuage. We begin with an appraisal of its prevalence by Mary Jane Massie and colleagues to make explicit the size of this problem. With cancer's additional dimension of existential threat, both major and sub threshold depressive states enlarge this burden of illness, bringing clinical challenges of definition and recognition to the fore.

The subjective experience of depression in oncology patients results from the interplay of complex gene-environment interactions, involving the biology of the brain with the biology of the cancer and the adaptation of the person. Not only does cancer and its treatment interact often with the hypothalamic-pituitary-adrenal system, but cancers also produce a variety of circulating proteins or cytokines that cross the blood-brain barrier and interact with the mood regulating circuits of the limbic system. Dominique Musselman and her research colleagues elucidate the contribution of these cytokine cas-cades. Adetailed chapteron the pharmacologic treatment of depression by Luigi Grassi and colleagues pays careful attention to the potential for drug-drug interactions, which arise frequently in cancer care.

The psychosocial challenges of cancer to each person's coping necessitates adaptation through grief and mourning, coming to terms with loss and change, and then moving forward with life. Whenever depression interferes with these processes, its form can span sub-threshold to clinical presentations. Furthermore, the existential realm adds death anxiety, aloneness, loss of meaning and control to

this equation, bringing states of demoralization into tension with depression. David Clarke focuses on this in a chapter on psychological adaptation to cancer, while later David Kissane, Gary Rodin and colleagues present the broad range of psychotherapeutic modalities that can be added to our pharmacologic armamentarium to improve outcomes.

Screening to increase recognition of depression has proven necessary in oncological care because of the unfortunate tendency for clinicians from every discipline to blur the sadness of the predicament with the prevailing mental health reality. Steven Passik covers the range of available measures to screen for depression and the service issues associated with their clinical application.

William Breitbart and colleagues describe the increased rate of suicide among cancer patients in their chapter on the desire for hastened death. Requests for physician-assisted suicide can be a cry for help and clinicians need considerable experience to tease out the many confounding influences that predispose to, precipitate and perpetuate affective disorders.

Depression is a recognised risk factor for shortened survival from cancer, this outcome being partly mediated through patients' adherence to anti-cancer treatments. Unrecognized depression could bring increased morbidity to bear through this mechanism. Meta-analyses by Robin DiMatteo and Kelly Haskard-Zolnierek about the impact of depression on treatment compliance in medical illness make explicit the inherent issues here.

Finally, the social cost of depression is pronounced, and this burden is felt as muchin cancer care as with other medical illness. The roles of culture and socioeconomic status are pertinent. Noteworthy social disparities exist in cancer survival. The health beliefs occurring in African Americans, Asians, Hispanics or Europeans affect cancer outcomes, asdoes their socioeconomic status. Irrespective

of access to cancer care, including in Scandinavian societies where health insurance is universal, those living in poor socioeconomic circumstances die earlier. Using Denmark's national medical record system, Chris-toffer Johansen and colleagues conclude our book by providing methodologically sound evidence that stress, depression, personality and major life events do not cause the onset of cancer. However, untreated depression and social disparity impact cancer survival, making the treatment of affective disorders a paramount public health concern for every society.

This volume ondepression and cancer is partofa WPA series on the comorbidity of mood disorders with various medical illnesses, including heart disease and diabetes. We are grateful to our authors who have given generously of their time and scholarship, to our publishers at Wiley-Blackwell, and to the WPA, through which we hope that the care of depressed patients will steadily improve. Cancer brings a huge social burden; untreated depression adds enormously to any suffering; we have many tools to ameliorate this and improve patients' wellbe-ing. Let us help those who become weary of life to renew its vigour and joy, with appreciation for life's value, meaning and purpose, despite the diagnosis of cancer.

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CHAPTER 1

The Prevalence of Depression in People with Cancer

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Depression is amongst the main causes of disability worldwide, leading to personal suffering and increased mortality. The US National Comorbidity Survey revealed a 12-month prevalence of major depressive disorder of 6%, with a lifetime prevalence of 16%, while high comorbidity exists with anxiety disorders, substance use disorders and impulse control disorders [1]. In any twelve-month period, more than half the patients with major depressive disorder are diagnosed with an additional anxiety disorder. Patients with comorbid depression and anxiety disorders experience more severe symptoms, have longer time to recovery, use more healthcare resources and have poorer outcome than

do those with a single disorder [2]. Seed at et al. [3] found that, across cohorts from 15 countries, women developed depression almost twice as frequently as men.

When comorbid with medical illness, depression increases the symptom burden and functional impairment, and worsens medical outcomes [4]. Early studies of depression in the medically ill used patient self-report and varied measures, with a heterogeneous mix of hospitalized medical and surgical patients, and reported prevalence rates ranging from 20 to 30% [5]. In 1987, a retrospective review of 263 000 patients from 327 hospitals found that 24% of those receiving a psychiatric consultation were depressed [6]. However, Snyder et al. [7], using both clinical interview and DSM-III-R criteria reported less depression (6%), but more adjustment disorder with depressed mood (14%), in 944 medically ill patients referred for psychiatric consultation.

Wells et al. [8] examined Epidemiological Catchments Area Study data regarding mental disorders amongst persons with at least one of eight chronic medical conditions. Six-month and lifetime prevalence rates of mental disorders were increased in those with versus without medical illness (25 and 42% versus 17 and 33%). Thirteen per cent of the chronically medically ill had a lifetime diagnosis of affective disorder versus 8% of those free from medical illness.

Lifetime rates of depression in patients with neurological conditions range from 30 to 50% [9]. Prevalence rates of depression in patients with other medical or systemic illnesses show a variable picture, with the highest rates observed with endocrine disturbances such as Cushing’s disease and surprisingly low rates documented in end-stage renal disease.

PREVALENCE OF DEPRESSION IN CANCER PATIENTS

Using DSM-III criteria through a structured clinical interview, the Psychosocial Collaborative Oncology Group (PSYCOG) was one of the first groups to carefully determine the prevalence of mental disorders in 215 randomly selected hospitalized and ambulatory adult cancer patients in three cancer centers [10]. Forty-seven per cent of the patients evaluated had clinically apparently psychiatric disorders. Of these patients, over two-thirds (68%) had adjustment disorders with depressed oranxious mood, 13% had a major depression, 8%had an organic mental disorder, 7% had a personality disorder, and 4% had a preexisting anxiety disorder. The authors concluded that nearly 90% of the mental disorders observed were reactions too manifestations of disease or treatment. Personality and anxiety disorders can complicate cancer treatment, and were described as antecedent to the cancer diagnosis. This epidemiologically sound study has remained the gold standard for many years.

Many research groups have assessed depression in cancer patients along the years [10–69], and the reported prevalence varies quite widely (major depression 3 to 38%; depression spectrum syndromes 1.5 to 52%). The following databases were searched to retrieve references published between 1965 and 2009: PubMed, Embase, CINAHL (nursing), PsycINFO, Scopus, Science Citation Index/Social Sciences Citation Index, Cochrane Evidence Based Medicine database. The searches were limited to English language references and to studies with more than 100 subjects, where this information was indicated. Table 1.1 shows the 60 studies with more than 100 patients that provided information about the number of patients interviewed and cancer type(s), evaluation methods, and per cent with depression or affective syndromes. Most authors reported patient gender and hospitalization status. The reported prevalence varies significantly because of varying

conceptualizations of depression, different criteria used to define depression, differences in methodological approaches to the measurement of depression, and different populations studied.

In early, typically cross-sectional studies, the rate of depression was usually reported for adults with mixed types and stages of cancer. Depression was reported by severity (borderline, mild, moderate, severe, and extreme), or by a symptom such as depressed mood, or by some of these diagnostic categories: major depression, minor depression, depressive disorder, adjustment disorder with depressed mood, or dysthymia, limiting our ability to compare studies. Although many research groups reported the gender and age (usually older) of study subjects, findings usually were not reported by demographic variables, and racial minorities were always underrepresented.

Table 1.1 Representative studies of the prevalence of depression in cancer patients (adapted from Massie [5])TraitAnxietyInventory.

Study	N	Patients	Method	Percent depressed	Specific findings
Fras *et al.* [11]	110	Pancreatic and colon cancer	Semi-structured interview; MMPI	50% (pancreas); 13% (colon)	76% psychiatric symptoms in those with pancreatic cancer; psychiatric symptoms appeared before other symptoms in patients with pancreatic cancer
Morris *et al.* [12]	160	Breast biopsy and mastectomy patients; British cohort	Interview; HRSD	22% depression in mastectomy	Mastectomy patients had persistent depression (22%) at 2 yr compared to benign biopsy patients (8%)
Maguire *et al.* [13]	201	117 ambulatory breast cancer patients; 89 benign disease; British cohort	Clinical interview	26% moderate or severe depression after mastectomy	Control benign patients had 12% depression
Silberfarb *et al.* [14]	146	Hospitalization status not indicated; 34% primary disease; 36% recurrent; 30% advanced, all breast cancer; US cohort	Structured interview; open-ended questions; modified psychiatric status scale	10% depression in primary cancer diagnosis; 15% in recurrent; 4.5% in advanced cancer	Physical disability did not relate to emotional disturbances; first recurrence of breast cancer most disturbing time; advanced patients had the least depression
Derogatis *et al.* [10]	215	Half hospitalized, half ambulatory; all sites and all stages, randomly selected; US cohort	DSM-III criteria; SCL-90; RDS; GAIS; Karnofsky Rating Scale	6% major depression 12% adjustment disorder with depressed mood; 13% adjustment disorder with mixed emotional features	Excluded severely ill (Karnofsky < 50); 47% received DSM-III diagnosis; 68% of these diagnoses were adjustment disorder
Farber *et al.* [15]	141	Ambulatory; primarily breast cancer	SCL-90	19% severe; 21% moderate; 14% mild	A comparison of males and females with clinical and global scales of the SCL-90 showed no significant differences
Hughes [16]	134	Lung cancer	Structured clinical interview	16% depressed	Most of the depressed patients were depressed before physical symptoms began
Lansky *et al.* [17]	500	85% ambulatory; 43% survivors with no evidence of disease; 34% early stage	DSM-III, organic brain syndrome section of the PDI; HRSD, Zung SDS; visual pain analogue line	5.3% (using HRSD and SDS); 4.5% (using DSM-III criteria)	
Holland *et al.* [18]	218	Ambulatory; 107 advanced pancreatic, 111 advanced gastric; US cohort	POMS	21 median POMS gastric; 38 median POMS pancreatic scores	Pancreatic cancer patients had higher depression than gastric cancer amongst men only
Devlen *et al.* [19]	120	Ambulatory; Hodgkin's disease and non-Hodgkin's lymphoma	Semi-structured interview	8% depressed in year after treatment	Prospective study with interviews at baseline, 2, 6, and 12 mo after diagnosis

Study	N	Patients	Method	Percent depressed	Specific findings
Lasry *et al.* [20]	123	Hospitalized breast cancer	CES-D	50% mastectomy; 50% lumpectomy with radiation; 41% lumpectomy	Depression varied with treatment
Stefanek *et al.* [21]	126	Ambulatory; mixed; US cohort	BSI	33% depressed; 9% severe; 24% moderate	20% high psychiatric distress in general
Pettingale *et al.* [22]	168	Hospitalized early breast cancer and lymphoma; all stages; British cohort	Interview; STAI; Wakefield	Major depression not cited	In lymphoma patients, the more advanced the disease, the higher the depression. No correlation with disease state and depression in breast cancer
Grassi *et al.* [23]	196	Hospitalized and ambulatory; recent diagnosis of cancer; mixed, 18–70 yr; Italian cohort	HRSD; IBQ; interview	24–38% depressed depending on threshold used	38% depression with HRSD cutoff of 17; 24% with HRSD of 21
Hardman *et al.* [24]	126	Hospitalized; mixed; British cohort	Structured interview GHQ	3% pure depression; 23% mixed anxiety and depression	Psychiatric symptoms related to feeling moderately or severely ill and previous psychiatric illness, but not with awareness of having cancer
Fallowfield *et al.* [25]	269	Stage I and II breast cancer assessed 2 wk, 3 mo, 12 mo after surgery; British cohort	Interview	21% mastectomy; 19% lumpectomy	Less depression in mastectomy and lumpectomy patients given treatment choice
Kathol *et al.* [26]	152	Mixed; US cohort	DSM-III and DSM-III-R criteria; RDC; Endicott substitution criteria; HRSD; BDI	25–38% major depression, depending on diagnostic system; 19% (depressive symptoms)	Authors concluded that self- and observer-rated scales are sufficient to screen at risk patients but not to diagnose
Colon *et al.* [27]	100	Hospitalized acute leukaemia; US cohort	DSM-III-R criteria	1% major depression; 2% organic affective syndrome; 8% adjustment disorder	Illness status, depressed mood and perceived social support independently affected outcome; depressed patients had poorer outcome
Hopwood *et al.* [28]	222	Ambulatory; advanced breast cancer; British cohort	HADS; RSCL	9% depression and 9% anxiety using HADS; 22% affective disorder using RSCL	HADS and RSCL detected different groups of cases; one third of depressed patients persisted for 1–3 mo

Study	N	Patients	Method	Percent depressed	Specific findings
Goldberg *et al.* [29]	320	Newly diagnosed, hospitalized for breast cancer surgery	Modified RSCL; pre-operative, 6 and 12 mo post-operatively	32% depressed malignant; 24% depressed benign biopsy	At 1 yr depression had decreased (21% depressed) in both groups
Maraste *et al.* [30]	133	Ambulatory; adjuvant radiotherapy; breast cancer	HADS	1.5% depressed; 14% anxiety	Age and surgery-related anxiety; anxiety in ages 50–59 was 44% in mastectomy vs. 4% in conservative surgery
Sneed *et al.* [31]	133	Hospitalized; newly diagnosed; mixed sites and stages	BSI; HIS-GWB	Major depression not cited	Women with gynaecological and breast cancer had less depression, anxiety, hostility, somatization, psychological distress than men and women with other cancers
Carroll *et al.* [32]	809	Various cancer sites; US cohort	HADS	17.7% anxiety disorder 9.9 % depressive disorder	
Cathcart *et al.* [33]	257	Ambulatory; women with node negative breast cancer; 155 women received tamoxifen; 102 received no tamoxifen	Clinical interview	15% in tamoxifen treated group; 3% in those not receiving tamoxifen	4.5% of 155 women receiving tamoxifen had to discontinue it secondary to depression
Pinder *et al.* [34]	139	86 hospitalized, 53 ambulatory advanced breast cancer; British cohort	HADS interview	13% depressed; 25% anxiety or depression	Depression more prevalent in low socioeconomic class, i poor performance states, and closer proximity to death
Sneeuw *et al.* [35]	556	Ambulatory stage I and II breast cancer; interviewed at least 1.5 yr after treatment	DSM-III criteria; DIS; CES-D; SCL-25	4.5% depressed; 6.3% generalized anxiety disorder; 8.8% phobic disorder	Depressive symptoms a one and a half years afte treatment and longer; n significant differences i patients who had mastectomy vs. conservative treatment
Kelsen *et al.* [36]	130	Pancreatic cancer; US cohort	BDI; BHS; MPAC; FLIC	38% depressed (scores $\geq$ 15 BDI)	
Aass *et al.* [37]	716	Various cancer sites; Norwegian cohort	HADS, EORTC QLQ033, HOC Questionnaire	9% depression; 15% anxiety	
Berard *et al.* [38]	456	Breast; head and neck; lymphoma	HADS; BDI; Structured psychiatric Interview	14% depression overall; 8% depression (overlap with both scales)	
Kissane *et al.* [39]	303	Early stage breast cancer; Australian cohort	MILP; HADS; EORTC-QLQ	45% DSM psychiatric disorder; 42% depression and/or anxiety; 27.1% minor depression; 9.6% major depression	8.6% DSM anxiety disorder

Study	N	Patients	Method	Percent depressed	Specific findings
Montazeri *et al.* [40]	129	Lung cancer; Scottish cohort	HADS (administered at baseline and follow-up); QLQ	*Baseline:* 6% borderline anxiety; 10% severe anxiety; 11% borderline depression; 12% severe depression *Follow-up:* 11% borderline anxiety; 10% severe anxiety; 22% borderline depression; 32% severe depression	
Hammerlid *et al.* [41]	357	Head and neck cancer; Swedish & Norwegian cohort	HADS (administered at 6 different times)	19%–71% probable anxiety; 18%–51% probable depression	
Bodurka-Bevers *et al.* [42]	246	Epithelial ovarian cancer	CES-D; state anxiety sub-scale of STAI; QOL	21% CES-D depression; 29% anxiety	
Chen *et al.* [43]	203	Solid and liquid tumours; Taiwanese cohort	HADS	12% anxiety; 20% depression	
DeLeeuw *et al.* [44]	197	Head and neck cancer	Social Provisions Scale; CES-D; EORTC QOL C30 + 3	29% possible depression (before treatment); 28% possible depression (after 6 mo)	
Hopwood *et al.* [45]	987	526 small cell lung cancer; 461 non-small cell lung cancer; British cohort	HADS, Quality of Life Form	33% depression, self-reported; 21% depression and anxiety	Higher prevalence for small cell lung cancer patients
Kugaya *et al.* [46]	107	Head and neck cancer; newly diagnosed; Japanese cohort	Clinical interview with DSM-III; SCID; HADS	13.1% adjustment disorder 3.7% major depression 15.9% past history of major depression 33.6% alcohol dependence	6.5% alcohol abuse 32.7% nicotine dependence
Pascoe *et al.* [47]	504	Various cancer sites; Australian cohort	HADS	11.5% anxiety 7.1% depression	
Skarstein *et al.* [48]	568	Various cancer sites; European	HADS; EORTC QLQC33	9% depression, 13% anxious, 17% psychiatric distress, 5% depression and anxiety	HADS more accurate for depression; EORTC-QLQ good for anxiety, but underdiagnosed depression
Akechi *et al.* [49]	148	Post operative ambulatory breast cancer; Japanese cohort	HADS	23% psychiatric morbidity; 5% depression	
Akechi *et al.* [50]	129	Non-small cell lung cancer; Japanese cohort	Clinical Interview, DSM-III	4.7% major depression; 13.9% adjustment disorders	

Study	N	Patients	Method	Percent depressed	Specific findings
Ciaramella *et al.* [51]	100	Various cancer sites	Interview; SCID; Endicott HAMD	49% all DSM depressive disorders with SCID; 29% depression with Endicott;	28% depression with both diagnostic criteria
DeLeeuw *et al.* [52]	197 initially; 123 at the end of 3 yr	Head and neck cancer	CES-D; EORTC QQL C30 + 3	42% depression between 6 mo and 3 yr after treatment	
Sharpe *et al.* [53]	3938 screened 570 interviewed	Various cancer sites; breast cancer over-represented; UK cohort	HADS – all patients SCID for HADS high scorers	23% 15 or more on HADS; 34% of HADS high scorers had major depression	8% of entire sample had major depression
Atesci *et al.* [54]	117	Various cancer sites	SCID, HADS, GHQ	13.7% major depression	
Kissane *et al.* [55]	503	Breast cancer (303 early stage; 200 advanced); Australian cohort	MILP, HADS	37% DSM depressed (major depression, dysthymia, adjustment disorder) early stage; 31% advanced disease	Early stage: 9.6% major depression, 27.1% minor depression; Metastatic: 6.5% major depression, 24.5% minor depression
Nan *et al.* [56]	108	Mixed digestive tract cancers	Zung SDS	50% SDS index >50	
Litofsky *et al.* [57]	598	High-grade gliomas	SF-36 Mental Health scores	93% patient-reported depressive symptoms; 15% physician-reported depression in postoperative period;	Patient-reported depressive symptoms persisted at 3 and 6 mo; physician-reported depression increased to 22% at 3 and 6 mo
Thomas *et al.* [58]	236	Various cancer sites; Indian cohort	HADS	20% depressed (8% definite cases)	
Montazeri *et al.* [59]	177	Breast cancer	HADS	29% severe depression	
Wedding *et al.* [60]	213	Various cancer sites	BDI	8% major depression; 19% mild to moderate depressive symptoms	
Steel *et al.* [61]	101	Hepatobiliary	CES-D	37% at diagnosis	
Lueboontha-vatchai. [62]	300	Breast cancer; Thai cohort	Thai HADS	9% depressive disorder; 16.7% depressive symptoms	
Arnold *et al.* [63]	363	Primary brain tumours	Modified Brief PHQ	41% depression 48% generalized anxiety disorder	
Wedding *et al.* [64]	175	Various cancer sites	BDI	16.6% mild to moderate depression; 9.1% major depression	