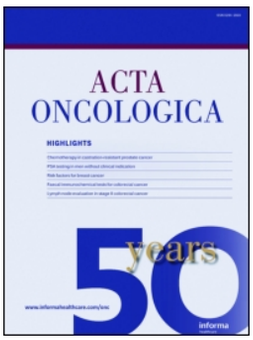

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review

R. Caruso, M. G. Nanni, M. Riba, S. Sabato, A. J. Mitchell, E. Croce & L. Grassi

To cite this article: R. Caruso, M. G. Nanni, M. Riba, S. Sabato, A. J. Mitchell, E. Croce & L. Grassi (2017): Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review, Acta Oncologica, DOI: 10.1080/0284186X.2016.1266090

To link to this article: http://dx.doi.org/10.1080/0284186X.2016.1266090

Published online: 31 Jan 2017.

ACTA ONCOLOGICA, 2017
http://dx.doi.org/10.1080/0284186X.2016.1266090

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS

Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review

R. Caruso[a,b], M. G. Nanni[a,b], M. Riba[c,d], S. Sabato[a], A. J. Mitchell[e], E. Croce[a] and L. Grassi[a,b]

[a]Institute of Psychiatry, Department of Biomedical and Specialty Surgical Sciences, University of Ferrara, Ferrara, Italy; [b]University Hospital Psychiatry Unit, Integrated Department of Mental Health and Addictive Disorders, S. Anna University Hospital and Health Authorities, Ferrara, Italy; [c]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA and University of Michigan Comprehensive Cancer Center, Ann, Arbor, MI, USA; [d]Psycho-oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [e]Department of Psycho-oncology, University of Leicester and Leicestershire Partnership Trust, Leicester, UK

ABSTRACT

Background: Although depression and mood-related disorders are common in persons with cancer, these conditions remain frequently overlooked in clinical practice. Negative consequences of depressive disorder spectrum have been reported (e.g. suicidal ideation, increase physical complications and somatic symptoms, negative influence on prognosis), indicating the need for routine screening, assessment and management.

Methods: A search of the major databases (Medline, Embase, PsycLIT, PsycINFO, and the Cochrane Library) was conducted on the reviews and meta-analyses available in order to summarize relevant data concerning depressive disorders spectrum in terms of prevalence, risk factors, and screening and assessment among patients with cancer across the trajectory of the disease.

Results: The data show a prevalence of depression and depressive disorders between 5% and 60% according to the different diagnostic criteria, the tools used in the studies (e.g. semi-structured psychiatric interview and psychometric questionnaires), as well as the stage and type of cancer. Furthermore, despite the significant health care resources devoted to cancer care and the importance of addressing depressive symptoms, assessment and management of depressive spectrum disorders in cancer patients remains suboptimal.

Conclusions: Routine screening and adequate assessment of depressive spectrum disorders is necessary in patients with cancer in order to effectively manage the multifaceted and complex consequences on cancer care.

ARTICLE HISTORY
Received 25 August 2016
Accepted 15 November 2016

According to the World Health Organization (WHO), depression is expected to be the leading cause of disability by 2030 and it is the most significant contributor to the overall global burden of disease [1,2]. In patients with medical illness, the burden of depression is even more serious. The WHO World Health Survey (WHS), involving 245 404 participants from 60 countries in all regions of the world, showed that between 9.3% and 23% of participants with one or more chronic physical diseases had comorbid depression and that depression had the largest effect on worsening mean health scores and on increasing disability compared with the other chronic conditions [3].

In the specific context of cancer, depression is also common [4]. This problem is extremely important as a number of studies have shown an association between depressive spectrum disorders and negative consequences on quality of life, adherence to treatments, subjective perception of physical symptoms and, possibly, prognosis [5–7]. Yet depression in cancer patients still remains not infrequently undetected in clinical practice [8,9]. Recent guidelines and recommendations have been developed in order to help all health cancer care professionals, including oncologists, primary care physicians, nurses, radiotherapists, address the problem of depression in cancer in a timely manner [10–15].

On this basis by examining the reviews and meta-analyses published in the last 15 years, the present paper has the following aims: 1) to summarize the relevant data concerning the prevalence of depressive spectrum disorders among cancer patients; 2) to define the most significant risk factors and 3) to summarize relevant data regarding screening and assessment.

Methods

Eligibility criteria

A search was made of the major databases over the last 15 years [Embase/Medline (PsycLIT, PsycINFO, the Cochrane Library)] from January 2001 to June 2016. Inclusion criteria were previous reviews and meta-analyses summarizing the

CONTACT Luigi Grassi luigi.grassi@unife.it Clinica Psichiatrica, Università di Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy

results from observation studies and randomized clinical trials (RCT) related to the prevalence, risk factors, screening and assessment for depressive spectrum disorders among cancer patients. Studies that investigated the specific prevalence of depression in patients with cancer in full journal articles were included. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, books, book chapters or research not published in the English language were excluded. For some topics where there were no reviews or meta-analysis available, we examined the most recent primary observational studies and RCTs.

Identifying research evidence

We searched the electronic databases for articles that met the previously discussed criteria using pre-specified MESH terms that included Cancer (EXP)' OR 'Cancer' AND 'Depression (EXP)' or 'major depression (EXP)' or 'Depressive disorders (EXP' or 'mood disorders (EXP)' or 'demoralization (EXP) or 'adjustment disorders with depressed mood (EXP)'. To supplement the electronic searches, we also conducted searches of the reference lists of previous reviews and meta-analyses as well as systematic searches of the content lists of key journals to identify any additional reviews or meta-analyses missed by the electronic search.

Data extraction

The following specific information relating to data collection and results was extracted individually, when possible, from each identified review or meta-analysis and entered into a predesigned spreadsheet: depression and all the other possible depressive spectrum disorders prevalence (%); disease stage and type; stage of treatment (pretreatment, on-treatment or post-treatment); instruments used to assess depression (questionnaires or interviews); risk factors.

Results

After searching and screening the literature, we obtained a total of 21 reviews and meta-analyses. Those that were not complete, not informative enough and not examining the prevalence of depression and its related issues in a comprehensive way were excluded from analysis, although cited in the paper and reported in the references section. Eleven more detailed reviews/meta-analyses were retained, of which nine regarding heterogeneous samples of cancer patients and two regarding specific cancer sites. A summary of the main topics discussed in these reviews in terms of general epidemiology data, prevalence according to stage and type of cancer, and risk factor for depression, are reported in Table 1.

General epidemiological prevalence

In a recent review of 211 studies of cancer patients, in different contexts (outpatient clinics, hospital, palliative care settings), in different stages (early diagnosis, recurrence, survivorship or advanced stages), an extreme variability of prevalence was found, with pooled mean prevalence of depression in cancer patients ranging from 8% to 24% [16]. Those differences can be been explained as related to the heterogeneous samples of patients and the different type of the assessment instruments (e.g. questionnaires vs. interviews) [16]. Also the quality criteria of assessment methods represents a limitation about prevalence studies, as underlined by Walker et al. [17], who, among 66 relevant papers, identified only 15 studies meeting satisfactory criteria (i.e. random or consecutive sampling, $\geq$70% response rate, sample size $\geq$100) with again prevalence of depression ranging from 5% to 49%. Similar findings were reported in a further review of 31 studies involving 9248 cancer patients, in whom the prevalence of depression was 10.8%, with a range of 3.7–49.0% [18].

The general epidemiological prevalence data, however, indicate values of depressive disorders that are two to three times higher than those of the general population [19,20], and similar to what are found in patients with other physical illness [21]. As examples of single studies, Rasic et al. [22] reported a 15.5% 12-month prevalence of major depression after cancer diagnosis versus 5.4% in healthy controls (36 984 people aged 15–54 years in the Canadian Community Health Survey) and Dalton et al. [23] by assessing linked data from 608 591 adults with cancer in the Danish Cancer Registry, reported a relative risk for depression of 1.16–3.08 in the first year after diagnosis, which seemed to increase at 10-year follow-up. Similar results were found in a culturally relevant meta-analysis of 17 Chinese studies which showed a 7.85-fold increased risk of depression among 3497 cancer patients when compared with a control group (54.6% vs. 18.37%) [24].

Importantly, depression may have different clinical characteristics, with prevalence changing also in relation with the diagnosis of the type of depression. A meta-analysis of 70 studies conducted by Mitchell et al. [25], with 10 071 individuals across 14 countries in oncological and hematological settings, found a prevalence of depressive disorders of 16.3%, of which Diagnostic and Statistical Manual of Mental Disorders (DSM)-defined major depression of 14.9%, DSM-defined minor depression of 19.2%, dysthymia of 2.7%, adjustment disorder of 19.4%, and general mood disorder of 38.2%. More recently, demoralization, as a clinically significant syndrome which is part of depressive spectrum disorders, but at the same time separate from major depression and not classified in the usual International Classification of Diseases (ICD) or DSM psychiatric systems, has been examined in cancer settings. A few recent systematic reviews on this topic are available [26–28], indicating that demoralization, which is characterized mainly by existential distress, hopelessness, pessimism, loss of meaning and purpose in life, can be diagnosable in about 25–30% of patients and it is related to poorer quality of life, suicidal ideation and loss of dignity [29,30].

Prevalence of depression and phase of treatment

In some meta-analysis, especially those related to specific cancer sites, information about studies examining the

Table 1. Main reviews/meta-analysis relative to depressive spectrum disorders in cancer.

Authors	Type of study	Sample	Results
Mitchell et al. [72]	Meta-analysis	56 diagnostic validity studies 10 009 patients	Case finding: 1 stem question, 2 stem questions and the BDI-II = Level 2 evidence (2a, 2b and 2c respectively) (grade B recommendation). Screening: 2 stem questions Level 1b evidence; BDI-II Level 2c evidence
Mitchell et al. [44]	Review and meta-analysis	43 studies 51 381 cancer survivors 217 630 healthy controls	Prevalence of depression 11.6% in cancer and 10.2% in healthy controls
Mitchell et al. [25]		24 studies, 4007 patients in palliative care settings 70 studies, 10 071 patients in oncological/ hematological settings	DSM = 16.5%; ICD = 14.3% major depression 9·6% minor depression; 15.4% adjustment disorder All types of depression = 24.6%; all types of mood disorder = 29%). DSM or ICD 16.3% 14.9% major depression; 19.2% minor depression; 19.4% adjustment disorder; 2.7% dysthymia All types of depression 20.7%; depression or adjustment disorder = 31.6%; any mood disorder = 38.2%
Walker et al. [17]	Review	66 relevant studies, only 15 (23%) met quality criteria	Prevalence of depression: 5–16% in outpatients; 4–14% in inpatients; 4–11% in mixed out/inpatient; 7–49% in palliative care. Expert interviewers (psychiatrists or clinical psychologists)=lower prevalence estimates
Krebber et al. [16]	Meta-analysis	211 studies (during or after treatment)	HADS-depression subscale (HADS-D) $\geq$ 8, HADS-D $\geq$11, Center for Epidemiologic Studies $\geq$16, and (semi-)structured diagnostic interviews were used to define depression in 66, 53, 35 and 49 studies, respectively. Respective mean prevalence of depression was 17% (95% CI 16–19%), 8% (95% CI 7–9%), 24% (95% CI 21–26%), and 13% (95% CI 11–15%) ($p < 0.001$). Prevalence of depression ranged from 3% in patients with lung cancer to 31% in patients with cancer of the digestive tract, on the basis of diagnostic interviews. Prevalence of depression was highest during treatment 14% (95% CI 11–17%), measured by diagnostic interviews, and 27% (95% CI 25–30%), measured by self-report instruments. In the first year after diagnosis, prevalence of depression measured with diagnostic interviews and self-report instruments were 9% (95% CI 7–11%) and 21% (95% CI 19–24%), respectively, and they were 8% (95% CI 5–12%) and 15% (95% CI 13–17%) $\geq$ 1 year after diagnosis
Robinson et al. [27]	Review	25 studies (33 articles); 4545 patients	Demoralization is prevalent in patients with progressive disease or cancer and clinically significant in 13–18%
Hotopf et al. [12]	Review	46 eligible studies on prevalence of depression; 4 studies on case finding	HADS: 29% median prevalence of 'definite depression' (score on the depression subscale >10) Psychiatric interviews: MDD = 5–26% (median 15%)
Mitchell et al. [94]	Meta-analysis	50 analyses testing HADS- depression subscale	In the identification of depression the HADS-T, HADS-D and HADS-A had a pooled sensitivity and specificity of 82.0%, 77.0%; 71.6%, 82.6% and 80.5%, 77.8%, respectively. All versions performed poorly in case finding but well in a screening capacity
Yang et al. [24]	Review and meta-analysis	17 eligible studies; 3497 Chinese adults with cancer	Depression = 54.90% in cancer patents vs. 17.50% in healthy subjects (OR = 7.85, 95% CI 5.56–11.07)

DSM: Diagnostic and Statistical Manual of Mental Disorders; HADS: Hospital Anxiety and Depression Scale; ICD: International Classification of Diseases; MDD: Major Depressive Disorder.

prevalence of depression according to the treatment phase is also provided.

In a meta-analysis of 27 studies resulting in a pooled sample size of 4494 patients with prostate cancer, for example Watts et al. [31], found that depression was 17.27% (CI 15.06–19.72%) in pretreatment (13 studies), 14.70% (CI 11.92–17.99%) in patients currently undergoing treatment (nine studies), and 18.44% (CI 15.18–22.22%) among those who had completed treatment (13 studies). Meta-analysis or reviews of studies conducted among breast cancer patients tend to agree in indicating that women who have received chemotherapy have a higher prevalence of depression than those who have not, that those in the first year after diagnosis of breast cancer are at higher risk for depression, that compared to patients who do not receive adjuvant therapy, patients on adjuvant chemotherapy have higher levels of depression, and that adverse symptoms of chemotherapy are associated with increased depression and decreased health-related quality of life [32].

Table 2. Main risk factors for depression in cancer patients.

Individual factors
- Family history of mood disorders [92]
- Personal psychiatric history (mood disorders, alcohol or drug addiction) [92]
- Personality traits (Type D, external locus of control, emotional repression, poor coping mechanisms, such as hopelessness-helplessness traits) [66–68]

Interpersonal and social risk factors:
- History of stressful life events (especially losses) [92]
- Loneliness (single, divorced, separated, widowed) [65]
- Social isolation [65]
- Low socio-economic status [5,7]
- Lack of social support [92]

Biological factors
- Type of cancer (e.g. lung, pancreas, head and neck, brain) [16,33,37,39]
- Advanced stage or metastatic disease [17,41,42]
- Uncontrolled physical symptoms (e.g. pain, nausea, vomiting, fatigue) [4]
- Inflammation factors (IL-interleukin 2; IL-6, TNF-α, and proinflammatory cytokines) [53,57]
- Treatment-related factors [5,7]
  - Immunological therapy (interferon-α)
  - Drugs [corticosteroids, methyldopa, β-blockers, antibiotics, clonidine, angiotensin-converting enzyme (ACE) inhibitors]
  - Anticonvulsants (phenytoin, levetiracetam)
  - Chemotherapy agents (vinblastine, vincristine, procarbazine, ciproterone)

Prevalence of depression and cancer site

Differences in the prevalence of depressive spectrum disorders have been also demonstrated according to cancer site. A meta-analysis of 211 studies [16] showed a rate ranging from 3% (lung cancer) to 28% (brain cancer), as measured by diagnostic interviews; and from 7% (skin cancer) to 31% (gastrointestinal cancer), as measured by self-report instruments. In a large scale analysis of more than 21 000 cancer patients screened for depression using the Hospital Anxiety Depression Scale (HADS), Walker et al. [33], found the highest prevalence of major depression in patients with lung cancer (13.1%) followed by gynecological (10.9%), breast (9.3%), colorectal (7%), and genitourinary cancer (5.6%). Further specific reviews and meta-analyses have been conducted on cancer patients specifically grouped for site, such as breast [34–36], head and neck [37,38], prostate [31], pancreas [39] and gastrointestinal cancer [40], generally confirming the aforementioned prevalence findings, although, again, other variables (e.g. type of instruments used, patients in treatment or off treatment, stage) tend to influence the data.

Prevalence of depression and cancer stage

Cancer stage can have an influence on the prevalence of depression with psychological differences existing between local or loco/regional stages with good prognosis and more advanced disease. It is, however, a fact that reviews and meta-analysis tend to examine mixed samples of in- and outpatients, with non-advanced and advanced stages. For example, in the cited meta-analysis conducted by Mitchell et al. [25] patients were recruited from both outpatient and inpatient settings, as well as breast surgery units, hematological settings and mixed oncological settings, with also some heterogeneity in terms of site and with insufficient data in terms of cancer types and cancer duration.

Some information is available regarding patients in *more advanced stages* of cancer, where the estimation of depressive spectrum disorders is often complicated by the symptoms related to cancer (e.g. weakness and fatigue, pain, nausea, respiratory problems) that make the diagnosis more difficult. However, a review of about 50 studies found a 29% median prevalence of depression in this population (albeit with mixed assessment methods). When confined to semi-structured or clinical interviews the prevalence of major depression tends to vary from 5% to 26% [41]. In a meta-analysis relative to 24 studies, involving 4007 cancer patients across seven countries in palliative care settings [25], a DSM or ICD diagnosis of any mood disorder regarded 29% of the patients, with different prevalence of the single depressive disorders. In a recent meta-analysis of 15 good-quality psychiatric interview-based studies [17], the prevalence of depression was reported to vary from 7% to 49% in palliative care patients. The data of a further systematic review of 59 studies carried in several settings (e.g. hospital departments, oncology departments, hospice/palliative care units and outpatient services) showed a 2–56% prevalence of depression [42].

Many recent data are now available as regards *survivorship* usually defined as patient living with cancer several years beyond their initial diagnosis. This is a key area since the number of cancer survivors worldwide has been steadily increasing. However, studies tend to use different criteria for survivorship, indicating both a short period after diagnosis and treatment (e.g. $\geq$1 year) or longer periods (e.g. $\geq$2 years) or other criteria (e.g. a person living with cancer from the time of diagnosis to the time of death), which influence the correctness of the single reports. In any case, depressive disorders, as assessed by psychometric scales, at least over one year form diagnosis, were found to affect 9.4–66.1% (overall percentage of 39.9%) of breast cancer patients, while the range of severe symptoms of depression varied from 3.0% to 41.7% (overall percentage of 21.2%) [35]. When these prevalence figures were compared with the general female population, the percentage of women with severe symptoms of depression was higher in four studies and equal in four studies, with a tendency to a reduction of depression over the ensuing years [43]. This was confirmed in

Table 3. Common assessment methods for depressive spectrum disorders in cancer settings.

Tools	Characteristics	Clinical use	Notes
Interviews			
Structured Clinical Interview for DSM - SCID	Clinician Version and Standard research version to be used in research and clinical settings	Designed to be administered by a clinician or trained mental health professional	Assessment of current psychiatric patients, lifetime psychiatric diagnoses in medical patients, family members, community samples
World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI)	Comprehensive, fully structured interview	Designed to be used by trained lay interviewers	Assessment of mental disorders according to the definitions and criteria of ICD-10 and DSM-IV in epidemiological and cross-cultural studies and for clinical and research purposes
Diagnostic Criteria for Psychosomatic Research (DCPR)	Clinical interview	Set of 12 psychosocial syndromes demoralization, disease phobia, health anxiety thanatophobia, illness denial, persistent somatization, functional somatic symptoms secondary to a psychiatric disorder, conversion symptoms, anniversary reaction, irritable mood, type A behavior, and alexithymia	Research evidence accumulated in several clinical settings (cardiology, oncology, gastroenterology, endocrinology, primary care, consultation psychiatry, nutrition, and community)
Short psychometric questionnaires			
Hospital Anxiety Depression scale (HADS)	14 items (7 for anxiety; 7 for depression) plus total score	Score HADS-D: 0–7 = normal; 8–10 = borderline case; 11–21 = case; HADS Total ≥15 Adjustment Disorders; ≥19 MDD	In oncology best thresholds for screening =15 for the HADS total (sensitivity 0.87; specificity 0.88), =7 for the HADS-D subscale (sensitivity 0.86; specificity 0.81 disorders [96]). Caution in any case in using thresholds [97] and in use for screening rather than case finding
Center for Epidemiologic Studies Depression Scale (CESD)	20 items 0–3 Likert scale	Scores ≥16: risk for clinical depression; ≥22: clinically relevant depression; ≥25: MDD	CESD-R (Revised version) also available, reflecting DSM5 diagnosis of MDD [98]
Beck depression Inventory II (BDI-II)	21 questions, each answer being scored on a scale value of 0–3	Score 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression Sensitivity: 81%; Specificity: 92%	
Profile of Mood States (POMS)	65 adjectives (5–point scale):	6 factors (Anger-Hostility; Confusion-Bewilderment; Depression-Dejection; Fatigue-Inertia; Tension-Anxiety; Vigor-Activity)	Short version available for cancer settings [99]
Patient Health Questionnaire PHQ-9	9 items (scored 0– 3, range 0–27) covering DSM criteria for MDD	Score 5–9: mild depression; 10–14 moderate depression; 15–19 moderately severe depression; 20–27 severe depression	Score ≥8: sensitivity 93%, specificity 81% PPV 25%, NPV 99% in cancer settings [100]
Demoralization scale (DS) Demoralization scale II (DS-II)	24 items on a 5-point Likert scale 16 items on a 3-point Likert scale	Scores ≥30 high demoralization Scores 0–3: low demoralization; 4–10 middle demoralization; ≥11 high demoralization	DS and DS-II validation studies in progress in cancer settings (e.g. Germany, Italy, Spain)
Subjective Incompetence Scale (SI)	12 items on a 0–3 Likert scale	Studies on threshold scores in progress	SI validation studies in progress in cancer settings

a meta-analysis of studies examining depression among 51 381 cancer survivors, as assessed at least two years after diagnosis (mean 4.35 years, SD 1.67), and 217 630 healthy controls, with data showing a prevalence of depression of 11.6% and 10.2%, respectively [44].

Risk factors for depressive spectrum disorders in cancer

The knowledge of risk factors for depressive spectrum disorders is important in terms of possible prevention and early identification.

A first group of variables is related to *general predisposing factors for depression*, which includes both non-biological and biological variables. Among the former a family or individual history of depression, has been associated with an earlier age of onset of disease and a longer length of illness [45], while female gender and poor social support have also been confirmed to be predictive of depression in the general population [46]. Among the latter, gene-stress susceptibility factors, alterations of the stress response mechanisms [e.g. in particular the noradrenergic and serotoninergic systems and the hypothalamic-pituitary-adrenal axis (HPA)], antibodies mechanisms (e.g. anti-ribosomal-P and anti-N-methyl-D-aspartate receptor antibodies) and inflammation (e.g. cytokines, interleukin-1, interleukin-6, tumor necrosis factor-alpha), interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function and synaptic plasticity [47,48], and contribute to a brain-arousal profile indicative of risk for depression [49–51]. In cancer patients, as in many other medical illnesses involving the mechanisms of neuroinflammation [52], these aspects are particularly important, given the role of the chronic stress response, the disease itself and treatment in the modulation of the HPA and the immune system [53–57].

Some *specific cancer factors* have been in fact recognized, including drugs and several anti-cancer treatment that have

been shown to have 'depressogenic' properties (e.g. corticosteroids, chemotherapy agents, hormones) [58]. Reviews of studies investigating the associations between chemotherapy, immunotherapy, radiotherapy, hormone therapy and depression confirm the higher prevalence of depressive spectrum disorders in patients in active treatment with respect to those that are not in treatment. A recent report indicates that the decrease or transient ablation of hippocampal neurogenesis and the onset of inflammatory responses in the brain are the mechanisms that emerge as candidates potentially underlying depressive symptoms among cancer patients undergoing classic treatments, such as chemo- and radiotherapy [59] (Table 2 for more details). A further biological factor to be mentioned regards the role of the polymorphism of the serotonin transporter-linked region (5-HTTLPR) that in psychiatry has been suggested to predict the development of depression after stress [60]. No specific support was found on this association, alone or in conjunction with life events, in the few existing studies relative to head and neck cancer [61], breast cancer [62,63] and colon cancer patients, including a recent meta-analysis [64].

Psychosocial and personality factors have been also examined with respect to the risk of depressive spectrum disorders. A recent meta-analysis [65] of 41 longitudinal studies in breast cancer patients confirmed that anxiety traits, poor coping strategies, poor perceived social support and early levels of psychological distress after diagnosis influenced later depressive symptoms. A review of studies concerning a specific personality trait, alexithymia (i.e. inability to identify, be aware of and describe one's own emotions) has been inconclusive on the possible association of this construct and depression in cancer patients [66]. In contrast, although no review or meta-analysis are available, studies on Type D (distressed) personality (i.e. the tendency to experience negative emotions, or negative affectivity, and to inhibit self-expression in social interaction, or social inhibition) showed that cancer patients with high levels of Type D had poorer mental health status, even after adjustment for confounding background variables, in some types of cancer [67–69].

Screening and assessment

The literature concerning screening and assessment of depressive spectrum disorders in oncology has grown significantly in the last 10 years (Table 3) [70]. In a first analysis that examined ultra-short tests (e.g. one item asking 'Are you depressed?') to detect mood disorders in cancer patients, Mitchell [71] found that the pooled ability of ultra-short methods to detect depression was modest with better rule out than rule in accuracy (sensitivity 78.4%, specificity 66.8%, positive predictive value 34.2%, and negative predictive value 93.4%). In a further meta-analysis, the same authors [72] identified 56 diagnostic validity studies involving more than 10,000 patients and showed that for case finding (defined as confirmation of a true positive case) one stem question (i.e. 'Are you depressed?'), two stem questions (i.e. 'Are you depressed?' and 'Have you lost interest in things?), and a 12-item questionnaire, the Beck Depression Inventory (BDI-II), were not adequate enough (Level 2 evidence), while for screening (defined as confirmation of a true negative individual), they worked better (Level 1b evidence or Level 2c evidence). The data confirm that irrespective of the methods (psychometric tools or simple questions), these tools perform well at excluding depression in the non-depressed, but perform poorly at confirming depression [73]. The same conclusion regards the Distress Thermometer (which measures the subjective perception of emotional distress on a 0–10 visual analog scale), that, even if it is largely used and it is available in a number of validated translations, it is only partially helpful at the cutoff $\geq$7 to exclude depression in the non-depressed, but not to confirm depression [74].

A more recent meta-review of 11 reviews, representing 372 primary studies in oncology [75], examined more than 50 depression instruments used in adults with, or recovering from, any type of cancer. The HADS (a 14-item questionnaire, 7 for anxiety and 7 for depression) was the most thoroughly evaluated measure. The limitations are that it has a moderate accuracy and relatively low acceptability for front line clinicians due to its length and scoring system. It has been recommended in advanced cancer or palliative care by some groups, and several cutoff points to detect depression have been reported in different studies, making difficult to compare the findings. The BDI was more generalizable across cancer types and disease stages, with good indices for screening and case finding, while the Center for Epidemiologic Studies Depression Scale (CES-D) (a 20-item scale) was the best-weighted measure in terms of responsiveness. In a further review, it has been underlined that multisymptom assessment instruments (i.e. those assessing both anxiety, depression, fatigue and other symptoms) are less specific, although more informative in terms of the problems patients may report [76].

In palliative care patients, a review examining an extensive electronic database identified 202 studies in which 106 different assessment methods were used, particularly the HADS, while the full range of the DSM (fourth edition) diagnostic criteria were seldom employed, and few studies classified depression by referring to a diagnostic system or by using cutoff scores [77]. There is a concern that somatic symptoms of cancer might invalidate the use of standard self-report depression scales. Although fatigue (and possibly psychomotor change) probably has less diagnostic weight in advanced cancer patients overall use of conventional scales seems to be supported [78].

With regard to demoralization, some tools have been proposed in clinical practice in cancer care, such as the Demoralization module within a clinically oriented interview (Diagnostic Criteria for Psychosomatic Research) [16,79]. Also, psychometric tools have been recently devised, including the Subjective Incompetence Scale [80], and the Demoralization scale (24-item Version-I and a shorter 16-item Version-II) [81–83].

Discussion

Our initial finding from our review of the main reviews and meta-analyses available is that depressive spectrum disorders

are a common mental health complication of cancer. Their prevalence results are at least 2–3 times higher than those of the general population, although wide differences have been reported between studies, with estimations of depressive spectrum disorders varying extremely in cancer settings.

Many factors are responsible for this variability, including the characteristics of instruments used to assess depression (e.g. psychometric tools and type of tool, ultra-short, short or standard tools; clinical interview), the type of the single depressive conditions, the type and stage of cancer, and the phase of treatment.

As a further result of our report, the type of psychiatric diagnosis of depression, such as major depression, adjustment disorders, sub-syndromal depressive conditions and demoralization syndrome should also be taken into consideration, as they are different conditions in terms of clinical characteristics, outcome and treatment.

A third finding from this review is that a higher prevalence of depression has been reported among patients both early in the course of illness and in the following phases. Further a high rate of distress and depression exists in advanced stages of illness (particularly in the very late stages). However, survivorship is not exempt from mood disorders and given the large number of patients in the survivorship phase the overall burden of depression should also be considered in this phase. This highlights the need to avoid abandoning long survivors even if in remission as many will still suffer from depressive spectrum disorders.

With respect to risk factors, the main predisposing variables implicated in the onset of depression in the general population (e.g. family and individual history of depression, poor social support, gene-stress variability, inflammation mechanisms) are also reported among cancer patients, with the further important roles exerted by both biological cancer- or treatment-related mechanisms (e.g. cytokine and inflammation mechanisms, depression-inducing drugs) and psychological (e.g. coping, personality) factors, that should also be taken into account. However, psychosocial variables related to the risk of depression (e.g. some personality traits, coping mechanisms, occurrence of life events), are not routinely assessed in clinical practice. For example, it has been observed that in palliative care, while some variables characterizing the sample populations are usually reported (e.g. age, gender and stage of cancer), other significant depression-related variables (e.g. antidepressant use, previous depressive episodes) are rarely accounted for [42].

Regarding screening and assessment, as a further result of our study, the large majority of investigations have indicated that some tools (e.g. BDI-II, CES-D) are more sensitive and specific than others and can be of help in cancer settings. However, as a recommendation, all tools should form part of an integrated approach involving both clinical assessment and follow-up, as psychological tools cannot be used alone to diagnose depression, but they may be considered as a first-stage screen to rule out cases of depression [84]. Different instruments in fact vary widely in their brevity, acceptability and coverage. Indeed, there is no overall consistency in which symptoms are covered by which depression instrument (see http://www.psycho-oncology.info/compare.htm). In general, the acceptability of short and ultra-short measures is high but some questions remain over their accuracy. Instruments may or may not help clinicians characterize specific subtypes of depression (e.g. DSM5 or ICD10) and this will be reflected in the prevalence figures of studies using these tools.

As a common conclusion of all reviews and meta-analyses examined in the present paper, assessment, diagnosis and treatment of depression should be a key priority for any clinical oncology team working with cancer patents across the disease trajectory and survivorship to optimize their quality of life and clinical treatment outcomes. This directly involves the need for more training of physicians and health care professionals in the risk factors for depressive disorders and in screening and assessing cancer patients during the illness trajectory. This should be a common and routine practice for patients with cancer [85,86], and physical illness in general [87]. In fact, training and application of local, regional or national guidelines to treat depression in cancer care have significant benefits in terms of outcome and cost-effectiveness. This has been for example confirmed in a recent series of studies within the Depression Care for People with Cancer (DCPC) program in the Symptom Management Research Trials (SMaRT) Oncology series of RCTs, carried out in Scotland [88–91].

Further studies should reinforce the investigation of early markers of depression (thus of patients at risk for developing depression). Studies should also attempt further characterization of clinical conditions and relevance of specific depressive symptoms within the spectrum of depressive disorders, their consequences on the patients' social, psychological and biological dimensions, as well as, training of health cancer care professionals on depression. Lastly, there is a need to ensure adequate services are available for patients with depression in oncology. Recognition of prevalence with screening is not sufficient on its own [92]. These are only the first steps, and they should be followed by appropriate acceptable treatment and follow-up to ensure the long-term burden of depression is minimized [93].

Disclosure statement

All authors declare that they have no conflict of interest.

Funding

This paper was supported by the University of Ferrara Research Funding (FAR). The authors would like to express their gratitude to Unitalsi Triveneta and the Italian Medical Board/Association – Section of Ferrara for their unrestricted research grant and support in memory of Francesco Tomasi, MD, and the Associazione per Supporto Psico-Oncologico (ASPO) for their unrestricted clinical research grant for the improvement of psychosocial care in oncology.

ORCID

L. Grassi http://orcid.org/0000-0002-1050-4494

References

[1] World Health Organization (WHO): Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. EB130/9, WHO, Geneva, 2011.

[2] Lépine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat. 2011;7:3–7.
[3] Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007 Sep 8;370:851–858.
[4] Pasquini M, Biondi M. Depression in cancer patients: a critical review. Clin Pract Epidemiol Ment Health. 2007;3:2.
[5] Smith H. Depression in cancer patients: Pathogenesis, implications and treatment. Oncology Letters. 2015;9:1509–1514.
[6] Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer. 2009;115:5349–5361.
[7] Dauchy S, Dolbeault S, Reich M. Depression in cancer patients. EJC Suppl. 2013;11:205–215.
[8] Passik SD, Dugan W, McDonald MV, et al. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol. 1998;16:1594–1600.
[9] Kissane DW. Unrecognised and untreated depression in cancer care. Lancet Psychiatry. 2014;1:32.
[10] Block SD. Assessing and managing depression in the terminally ill patient. ACP-ASIM End-of-Life Care Consensus Panel. American College of Physicians - American Society of Internal Medicine. Ann Intern Med. 2000;132:209–218.
[11] Howell D, Keshavarz H, Esplen MJ, et al. on behalf of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer. A Pan Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer, Toronto: Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology, July 2015.
[12] Rayner L, Price A, Hotopf M, et al. The development of evidence-based European guidelines on the management of depression in palliative cancer care. Eur J Cancer. 2011;47: 702–712.
[13] Rubin G, Berendsen A, Crawford SM, et al. The expanding role of primary care in cancer control. Lancet Oncol. 2015;16:1231–1272.
[14] Butow P, Price MA, Shaw JM, et al. Clinical pathway for the screening, assessment and management of anxiety and depression in adult cancer patients: Australian guidelines. Psychooncology. 2015;24:987–1001.
[15] Andersen BL, DeRubeis RJ, Berman BS, et al. American Society of Clinical Oncology.: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol. 2014 May 20;32:1605–1619.
[16] Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology. 2014;23:121–130.
[17] Walker J, Holm Hansen C, Martin P, et al. Prevalence of depression in adults with cancer: a systematic review. Ann Oncol. 2013;24:895–900.
[18] Ng CG, Boks MP, Zainal NZ, et al. The prevalence and pharmacotherapy of depression in cancer patients. J Affect Disord. 2011;131:1–7.
[19] Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr. 2004;32:57–71.
[20] Pirl WF. Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. J Natl Cancer Inst Monogr. 2004;32:32–39.
[21] National Institute for Health and Care Excellence (NICE): Depression in adults with a chronic physical health problem: recognition and management (CG91), NICE 2009. Clinical guideline Published: 28 October 2009 nice.org.uk/guidance/cg91.
[22] Rasic DT, Belik SL, Bolton JM, et al. Cancer, mental disorders, suicidal ideation and attempts in a large community sample. Psycho-Oncology. 2008;17:660–667.
[23] Dalton SO, Laursen TM, Ross L, et al. Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-based study of cancer patients in Denmark from 1973 to 2003. J Clin Oncol. 2009;27:1440–1445.
[24] Yang Y-L, Liu L, Wang Y, et al. The prevalence of depression and anxiety among Chinese adults with cancer: a systematic review and meta-analysis. BMC Cancer. 2013;13:393.
[25] Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12:160–174.
[26] Tecuta L, Tomba E, Grandi S, et al. Demoralization: a systematic review on its clinical characterization. Psychol Med. 2015; 45:673–691.
[27] Robinson S, Kissane DW, Brooker J, et al. A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: a decade of research. J Pain Symptom Manage. 2015;49:595–610.
[28] Tang PL, Wang HH, Chou FH. A systematic review and meta-analysis of demoralization and depression in patients with cancer. Psychosomatics. 2015;56:634–643.
[29] Grassi L, Biancosino B, Marmai L, et al. Psychological factors affecting oncology conditions. Adv Psychosom Med. 2007; 28:57–71.
[30] Grassi L, Nanni MG. Demoralization syndrome: New insights in psychosocial cancer care. Cancer. 2016;122:2130–2133.
[31] Watts S, Leydon G, Birch B, et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open. 2014;4:e003901.
[32] Jesse R, Fann JR, Anne M, et al. Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry. 2008;30:112–126.
[33] Walker J, Hansen CH, Martin P, et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. Lancet Psychiatry. 2014;1:343–350.
[34] Caplette-Gingras A, Savard J. Depression in women with metastatic breast cancer: a review of the literature. Palliat Support Care. 2008;6:377–387.
[35] Mass SW, Roorda C, Berendsen AJ, et al. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. Maturitas. 2015;82:100–108.
[36] Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat. 2008;110:9–17.
[37] Lydiatt WM, Moran J, Burke WJ. A review of depression in the head and neck cancer patient. Clin Adv Hematol Oncol. 2009;7:397–403.
[38] Barber B, Dergousoff J, Slater L, et al. Depression and Survival in Patients With Head and Neck Cancer: A Systematic Review. JAMA Otolaryngol Head Neck Surg. 2016;142:284–288.
[39] Boyd AD, Riba M. Depression and pancreatic cancer. J Natl Compr Canc Netw. 2007;5:113–116.
[40] Jansen L, Koch L, Brenner H, et al. Quality of life among long-term (≥5 years) colorectal cancer survivors-systematic review. Eur J Cancer. 2010;46:2879–2888.
[41] Hotopf M, Chidgey J, Addington-Hall J, et al. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. Palliat Med. 2002;16:81–97.
[42] Janberidze E, Hjermstad MJ, Haugen DF, EURO IMPACT, et al. How are patient populations characterized in studies investigating depression in advanced cancer? Results from a systematic literature review. J Pain Symptom Manage. 2014;48:678–698.
[43] Zainal NZ, Nik-Jaafar NR, Baharudin A, et al. Prevalence of depression in breast cancer survivors: a systematic review of observational studies. Asian Pacific J Cancer Prev. 2013;4:2649–2656.
[44] Mitchell AJ, Ferguson DW, Gill J, et al. Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis. Lancet Oncol. 2013;14:721–732.

[45] Prendes-Alvarez S, Nemeroff CB. Personalized Medicine: Prediction of Disease Vulnerability in Mood Disorders. Neurosci Lett. 2016;13. DOI: 10.1016/j.neulet.2016.09.049.
[46] Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. J Affect Disord. 2014;169:15–20.
[47] Postal M, Appenzeller S. The importance of cytokines and autoantibodies in depression. Autoimmunity Reviews. 2015;14:30–35.
[48] Young JJ, Bruno D, Pomara N. A review of the relationship between proinflammatory cytokines and major depressive disorder. Journal of Affective Disorders. 2014;169:15–20.
[49] Kupferberg A, Bicks L, Hasler G. Social functioning in major depressive disorder. Neurosci Biobehav Rev. 2016;69:313–332.
[50] Belzung C, Willner P, Philippot P. Depression: from psychopathology to pathophysiology. Curr Opin Neurobiol. 2015;30:24–30.
[51] Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry. 2015;20:32.
[52] Benatti C, Blom JM, Rigillo G, et al. Disease-Induced Neuroinflammation and Depression. CNS Neurol Disord Drug Targets. 2016;15:414–433.
[53] Reich M. Depression and cancer: recent data on clinical issues, research challenges and treatment approaches. Curr Opin Oncol. 2008;20:353–359.
[54] Spiegel Giesel-Davis Depression and Cancer: Mechanisms and Disease Progression. Biol Psychiatry. 2003;54:269–282.
[55] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5:617–625.
[56] Aldea M, Craciun L, Tomuleasa C, et al. Glucocorticoids and inflammation: a double-headed sword in depression? How do neuroendocrine and inflammatory pathways interact during stress to contribute to the pathogenesis of depression? j BUON. 2014;19:5–14.
[57] Myers JS. Proinflammatory cytokines and sickness behavior: implications for depression and cancer-related symptoms. Oncol Nurs Forum. 2008;35:802–807.
[58] Celano CM, Freudenreich O, Fernandez-Robles C, et al. Depressogenic effects of medications: a review. Dialogues Clin Neurosci. 2011;13:109–125.
[59] Pereira Dias G, Hollywood R, Bevilaqua MC, et al. Consequences of cancer treatments on adult hippocampal neurogenesis: implications for cognitive function and depressive symptoms. Neuro-oncology. 2014;16:476–492.
[60] Gressier F, Calati R, Serretti A. 5-HTTLPR and gender differences in affective disorders: A systematic review. J Affect Disord. 2016;190:193–207.
[61] Gilbert J, Haman KL, Dietrich MS, et al. Depression in patients with head and neck cancer and a functional genetic polymorphism of the serotonin transporter gene. Head Neck. 2012; 34:359–364.
[62] Grassi L, Rossi E, Cobianchi M, et al. Depression and serotonin transporter (5-HTTLPR) polymorphism in breast cancer patients. J Affect Disord. 2010;124:346–350.
[63] Kim KR, Chung HC, Lee E, et al. Body image, sexual function and depression in Korean patients with breast cancer: modification by 5-HTT polymorphism. Support Care Cancer. 2012;20:2177–2182.
[64] Suppli NP, Bukh JD, Moffitt TE, et al. 5-HTTLPR and use of antidepressants after colorectal cancer including a meta-analysis of 5-HTTLPR and depression after cancer. Transl Psychiatry. 2015;5:e631.
[65] Brandão T, Schulz MS, Matos PM. Psychological adjustment after breast cancer: A systematic review of longitudinal studies. Psychooncology. 2016;20: doi: 10.1002/pon.4230.
[66] De Vries AM, Forni V, Voellinger R, et al. Alexithymia in cancer patients: review of the literature. Psychother Psychosom. 2012; 81:79–86.
[67] Mols F, Thong MS, van de Poll-Franse LV, et al. Type D (distressed) personality is associated with poor quality of life and mental health among 3080 cancer survivors. J Affect Disord. 2012;136:26–34.
[68] Husson O, Vissers PA, Denollet J, et al. The role of personality in the course of health-related quality of life and disease-specific health status among colorectal cancer survivors: A prospective population-based study from the PROFILES registry. Acta Oncol. 2015;54:669–677.
[69] Zhang JK, Fang LL, Zhang DW, et al. Type D Personality in Gastric Cancer Survivors: Association With Poor Quality of Life, Overall Survival, and Mental Health. J Pain Symptom Manage. 2016;52:81–91.
[70] Grassi L, Caruso R, Sabato S, The UniFe Psychiatry Working Group Coauthors, et al. Psychosocial screening and assessment in oncology and palliative care settings. Front Psychol. 2015;5:1485.
[71] Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol. 2007;25:4670–4681.
[72] Mitchell AJ, Meader N, Davies E, et al. Meta-analysis of screening and case finding tools for depression in cancer: evidence based recommendations for clinical practice on behalf of the Depression in Cancer Care consensus group. J Affect Disord. 2012;140:149–160.
[73] Mitchell AJ. Are one or two simple questions sufficient to detect depression in cancer and palliative care? A Bayesian meta-analysis. Br J Cancer. 2008;98:1934–1943.
[74] Donovan KA, Grassi L, McGinty HL, et al. Validation of the distress thermometer worldwide: state of the science. Psychooncology. 2014;23:241–250.
[75] Wakefield CE, Butow PN, Aaronson NA, International Psycho-Oncology Society Research Committee, et al. Patient-reported depression measures in cancer: a meta-review. Lancet Psychiatry. 2015;2:635–647.
[76] Aktas A, Walsh D, Kirkova J. The psychometric properties of cancer multisymptom assessment instruments: a clinical review. Support Care Cancer. 2015;23:2189–2202.
[77] Wasteson E, Brenne E, Higginson IJ, European Palliative Care Research Collaborative (EPCRC), et al. Depression assessment and classification in palliative cancer patients: a systematic literature review. Palliat Med. 2009;23:739–753.
[78] Mitchell AJ, Lord K, Symonds P. Which symptoms are indicative of DSMIV depression in cancer settings? An analysis of the diagnostic significance of somatic and non-somatic symptoms. J Affect Disord. 2012;138:137–148.
[79] Fava GA, Freyberger HJ, Bech P, et al. Diagnostic criteria for use in psychosomatic research. Psychother Psychosom. 1995;63:1–8.
[80] Cockram CA, Doros G, de Figueiredo JM. Diagnosis and measurement of subjective incompetence: the clinical hallmark of demoralization. Psychother Psychosom. 2009;78:342–345.
[81] Kissane DW, Wein S, Love A, et al. The Demoralization Scale: a report of its development and preliminary validation. J Palliat Care. 2004;20:269–276.
[82] Robinson S, Kissane DW, Brooker J, et al. Refinement and revalidation of the demoralization scale: The DS-II-internal validity. Cancer. 2016;122:2251–2259.
[83] Robinson S, Kissane DW, Brooker J, et al. Refinement and revalidation of the demoralization scale: The DS-II-external validity. Cancer. 2016;122:2260–2267.
[84] Rayner L, Loge JH, Wasteson E, EPCRC, European Palliative Care Research Collaborative, et al. The detection of depression in palliative care. Curr Opin Support Palliat Care. 2009;3:55–60.
[85] Bidstrup PE, Johansen C, Mitchell AJ. Screening for cancer-related distress: Summary of evidence from tools to programmes. Acta Oncologica. 2011;50:194–204.
[86] Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10 lessons from 40 years of primary-care research. Psychooncology. 2011;20:572–584.
[87] Meader N, Mitchell AJ, Chew-Graham C, et al. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. Br J Gen Pract. 2011;61:e808–e820.

[88] Strong V, Waters R, Hibberd C, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet. 2008;372:40–48.

[89] Walker J, Sharpe M. Depression care for people with cancer: a collaborative care intervention. Gen Hosp Psychiatry. 2009;31: 436–441.

[90] Sharpe M, Walker J, Holm Hansen C, SMaRT (Symptom Management Research Trials), et al. Oncology-2 Team. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. Lancet. 2014 Sep 20;384:1099–1108.

[91] Duarte A, Walker J, Walker S, et al. Cost-effectiveness of integrated collaborative care for comorbid major depression in patients with cancer. J Psychosom Res. 2015;79:465–470.

[92] Grassi L, Nanni MG, Caruso R. Emotional distress in cancer: screening policy, clinical limitations and educational needs. J Med Person. 2010;8:51–59.

[93] Grassi L, Caruso R, Hammelef K, et al. Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. Int Rev Psychiatry. 2014;26:44–62.

[94] Grassi L, Malacarne P, Maestri A, et al. Depression, psychosocial variables and occurrence of life events among patients with cancer. J Affect Disord. 1997;44:21–30.

[95] Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. J Affect Disord. 2010;126:335–348.

[96] Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support Care Cancer. 2011; 19:1899–1908.

[97] Carey M, Noble N, Sanson-Fisher R, et al. Identifying psychological morbidity among people with cancer using the Hospital Anxiety and Depression Scale: time to revisit first principles?. Psychooncology. 2012;21:229–238.

[98] Eaton WW, Smith C, Ybarra M, et al. : Center for Epidemiologic Studies Depression Scale: review and revision (CESD and CESD-R), in: M.E. Maruish (Ed.), The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, Instruments for Adults (3rd ed.), 3, Lawrence Erlbaum, Mahwah, NJ, 2004, pp. 363–377.

[99] Baker F, Denniston M, Zabora J, et al. A POMS short form for cancer patients: psychometric and structural evaluation. Psychooncology. 2002;11:273–281.

[100] Thekkumpurath P, Walker J, Butcher I, et al. Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer. 2011;117:218–227.