Depression and cancer: An unexplored and unresolved emergent issue in elderly patients

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Abstract

Despite the high prevalence of depressive disorders in cancer patients and elderly people, the topic of depression in elderly cancer patients still remains unexplored. This emerges from a systematic review of the literature conducted to investigate issues of depression, diagnosis, pathogenesis, treatment and their complex neuroimmunobiological interactions. Indeed, it becomes apparent that depression in elderly patients with cancer may have a peculiar phenomenology. In addition, the moderate rate of major depressive disorder and the high rate of minor depressive disorder are accompanied by subthreshold forms of depression that are at risk to be underecognized and untreated. Immune dysfunction may represent a common pathogenic ground of depression, cancer and aging. This may have important implications for treatment. In the near future, we need to develop validated mood disorder diagnoses and verify antidepressant treatment efficacy for elderly cancer patients with depression in order to improve their clinical outcome and quality of life.

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1. Introduction

Cancer in the elderly has become an increasingly common problem [1]. Indeed, epidemiologic studies describe that about 60% of all malignancies occur in people aged 65 years or older [2], and if the current demographic trends continue, it can be estimated that by 2020 about 70% of all cancers will be diagnosed in those aged 65 years or older [3].

One out of two cancer patients report psychiatric disorders, especially depression [4–7]. At the same time, depression is a burdensome problem even in elderly people [8]. Thus, depression is highly prevalent both in cancer and in the elderly [9,10]. Consequently, depression appears to be a relevant problem in elderly people with cancer, but the topic of mood disorders in geriatric patients with cancer still remains unexplored and unresolved. In particular, we have to clarify the biological mechanisms explaining the high comorbidity rate between cancer and the elderly, depression and the elderly, and consequently cancer and depression in the elderly population. This insight may also open a new avenue for treatment.

The objective of this paper is to review the existing literature regarding the relationships between aging, cancer and depression, in order to propose an integrated point of view about depression and cancer in elderly patients. This purpose was pursued with a multidisciplinary approach by performing: (1) a critical analysis of currently used diagnostic criteria for mood disorders; (2) a preliminary description of depressive symptoms specific for the general elderly population and in particular for the subgroup of elderly depressed patients suffering of cancer; (3) an analysis of the current data on epidemiology and outcome of depressive disorders; (4) a summary of the biological mechanisms shared by cancer and depression in aging population, with particular emphasis on immune-mediated pathways; and finally (5) a review of published data on depression treatment.

2. Methods

2.1. Search limits

In order to clarify the status of the art in the topic of mood disorders in geriatric patients with cancer, we conducted detailed searches of the published medical literature with a review of the Medline (PubMed) databases.

Article inclusion criteria were as follows: (1) period of publication between January 1980 and January 2007; (2) subject mean age of 65 years and older; (3) articles with a specific focus on depression in elderly people. Exclusion criteria were: (1) articles not written in English; (2) articles with a primary focus on medical symptoms (e.g. sexual dysfunction; anorexia or malnutrition; dysphonia or hearing disorders, etc.), social factors (e.g. social support or social stigma), or other conditions that can be secondarily associated to depression (e.g. cognitive impairment, symptom beliefs, coping resources); (3) articles with a primary focus on outcome (quality of life or adjustment); (4) articles with a primary focus on survivorship because of the peculiar symptom-intense experience during terminal care.

For our purposes, we used various combinations of the following keywords: “elderly”, “aging”, “geriatric”, “cancer”, “depression” and “mood disorders”.

2.2. Selection process

Search terms were used to extract records limited to the issue of depression in elderly people. A paper was considered for inclusion if all the above-mentioned criteria were satisfied.

An additional search was performed to identify papers specifically focused on depression in elderly patients with cancer. In this second stage, we chose only papers strictly adherent to the keywords “depression”, “elderly” (or “aging”) and “cancer”. The criterion of “adherence to the keywords” of a paper was defined as the presence of all the above-mentioned keywords in either the text or the abstract.

Eventually, we considered cross-references and review articles reported in the different papers collected. Conceptually related articles were included as well. A paper was considered as “conceptually related” to the issue of depression in elderly patients with cancer if it contained a source of information (i.e. data, models or hypotheses) on a topic that has been reported in literature to be related to the above-mentioned keywords (e.g. immunological dysfunction).

Thus, 30,076 articles were selected by matching the keywords “depression and elderly”, 6,020 by “depression and cancer”, 2,098 by “depression and cancer and elderly”.

In particular, among these last 2098 articles picked out by the computer, only 58 papers were initially selected by I.S. and G.S. as possible candidates for the review because they met the above-mentioned criteria of search limits and selection process. Only eight of the selected papers were strictly connected with the topic of depression in elderly patients with cancer: Bernabei et al. [11]; Charlson and Peterson [12]; de Jonge et al. [13]; Labisi [14]; Labisi [15]; Llorente et al. [16]; Rao and Cohen [17]; Roth and Modi [18]. All other articles cited in the review were conceptually correlated. Such discrepancy in the amount of articles selected by the computer-search and articles considered relevant to our aims after the complete selection process suggests that this issue is often approached by a point of view not primarily mood-oriented.

3. Diagnosis of depressive disorders in psychiatry

The Diagnostic and statistical manual of mental disorders, 4th ed., text revised (DSM-IV-TR) [19], the most used diagnostic manual in psychiatry, categorizes “Depressive Disorders” within the wider section of “Mood Disorders”, which also includes bipolar disorders. The depressive disorders are distinguished from the bipolar disorders because of
the absence in subject’s history of a manic, mixed or hypomanic episode. In other words, unlike depressive disorders, bipolar disorders are characterized by two poles: depressed mood and mania (i.e. euphoria, heightened emotion and activity). The depressive disorders include major depressive disorder (MDD), dysthmic disorder (DD) and depressive disorder not otherwise specified (NOS). MDD is characterized by one or more major depressive episodes, i.e. 2 weeks or more of symptoms, present most of the day, nearly every day, of depressed mood or loss of interest accompanied by four or more additional symptoms of depression described in Table 1, which cause significant functional impairment.

DD is characterized by a longer period (at least 2 years) in which the depressed mood symptom is present for more days than not, and is accompanied by two or more of the following: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, feeling of hopelessness. Within the residual category of depressive disorder NOS, that is used when depression is present and clinically relevant but criteria for MDD or DD are not met, a category called “Minor Depressive Disorder” (MIND) is included. MIND is characterized by one or more periods in which depressive features are identical to MDD in duration but which involve fewer symptoms, at least two but less than five, of which one is sad mood or loss of interest or pleasure in activities.

In particular, MIND possibly includes those depressive syndromes that do not fulfills standard diagnostic criteria for MDD, but that appear to be of extreme relevancy in the topic of mood disorders in elderly patients and/or in patients with medical comorbidity. Indeed, though most elderly people do not fulfill diagnostic criteria for MDD or DD, they manifest clinically significant depressive symptoms that have been described in literature as minor, subsyndromal or subthreshold depression [20].

The other two categories included in the mood disorders section are based on their primary biological etiology, and are: mood disorder due to a general medical condition, and substance-induced mood disorder. In the case of a prominent and persistent disturbance in mood, which is a direct physiological consequence of a general medical condition, we can diagnose a mood disorder due to a general medical condition. The mood disturbance must be etiologically related to the general medical condition through a careful assessment of several factors, such as temporal association between the onset, the exacerbation or remission of the general medical condition and of the mood disturbance.

There are, however, forms of depression which may be present in patients with medical comorbidity but which are “Subsyndromal” or “Subthreshold”. To highlight the occurrence of these subsyndromes is very important for our purposes because they are very often observed in cancer patients. However, subthreshold depressions are below the threshold of even MIND diagnosis and therefore they may be underecognized.

In particular, subthreshold symptoms of depression have been considered in literature in different ways: as prodromes, because they have been found to predict the onset of an episode of major depression [21], or as residual symptoms after recovery from an earlier episode; finally, the subthreshold depression may constitute an independent condition [22]. This diagnostic construct has been well confirmed in the elderly population [23], and there is evidence that older patients with subsyndromal depression experience greater severity of medical illnesses [24] and greater functional disability [25] in comparison with patients without depression. Again, it is important to emphasize that despite the high rate
of subsyndromal depression in the general population, it is not considered as a specific diagnostic entity in the DSM-IV-TR. Thus, these more subtle but invalidating forms of depressive disorders are at risk of being untreated.

A further possible limitation of the DSM-IV-TR categorization in cancer patients is that it does not consider different depressive disorders in young and in elderly people, with or without medical comorbidity. Indeed, depression in the medical population as well as in elderly people could have specific clinical features.

4. Phenomenology of depression in the elderly

Studies on mood disorders in aging people are focused on unipolar depressive disorders because of the higher prevalence of depression versus bipolar disorder in the elderly [9]. Community studies indicate that 25% of elderly people report having depressive symptoms, but less than 10% meet the criteria for MDD [26]. In particular, MIND and subthreshold depression are highly prevalent in elderly people, may have consequences on patient’s functioning, and are at risk of being unrecognized [27,28]. In fact, depressive symptoms occurring in late-life often go underdiagnosed and untreated [29], in part because they are erroneously assumed to be a physiological response to aging, physical losses or other life events which are common in elderly people [30]. In addition, depression is often difficult to identify because elderly depressed patients may not manifest sad mood or prominent anhedonia, which are the core symptoms of unipolar mood disorders [10]. Another factor complicating diagnosis of mood disorders in the elderly is the heterogeneity of their clinical manifestations. Indeed, Alexopoulos and colleagues [10,31] demonstrated that elderly people who have the onset of the first depressive episode in late-life constitute a heterogeneous group of patients with higher medical burden and neurological disorders, compared to people who suffer from mood disorders with early-onset. In fact, in the former group, depression appears when aging-related changes are prominent, and the occurrence of brain abnormalities and cognitive impairment may influence the development of depression [10].

Since the prevalence of geriatric depression is much higher in the medical setting than in the community [32], and considering that unrecognized and untreated mood disorders in aging people may probably be the cause of disability and suffering for patients and caregivers, these issues appear to be of extreme relevance in the specific topic of comorbidity with cancer in old age. Indeed, late-life depression often affects individuals with other medical and/or psychosocial problems [33]. Studies have found that depression in the elderly is a risk factor for morbidity and poor quality of life [8,34–36], increased non-suicide mortality [37,38], and poor recovery after a medical illness [8,39,40]. Furthermore, depressive symptoms have been identified as predictors of poor adjustment after a somatic event [8]. Thus, there is an increased attention on the effect of depressive symptoms in several somatic illnesses, and there is an agreement on the fact that medical comorbidity is a risk factor for depression as well as vice versa [9].

5. Mood disorders in elderly patients with cancer

5.1. Epidemiology and risk factors

Despite the growing awareness in the oncological community about the size of the problem of depression in geriatric patients with somatic illnesses, there are no studies specifically focused on epidemiology of depressive disorders in elderly cancer patients. However, a recent longitudinal study by de Jonge et al. [13] analysed prevalence, persistence, and risk factors of depression in a large sample of elderly subjects suffering from one of the following somatic illnesses: cancer, myocardial infarction, congestive heart failure, or fall-related injury of the extremities. Although specific data for cancer patients have not been reported, this study is relevant for having investigated depressive symptoms in a large sample of elderly patients with several somatic illnesses. Authors found that the prevalence of depressive symptoms significantly increased after the somatic illness. In particular, 38% of the whole sample experienced significant depressive symptoms at one of the follow-up assessments. Notably, 49% of this subgroup with depression reported mild symptoms, 38% moderate symptoms and only 13% severe symptoms. Thus, almost all patients (about 87%) who reported mood changes suffered from a mild or moderate symptomatology, confirming the relevance of subsyndromal depression in elderly people with somatic illnesses, including cancer. In addition, the majority of patients (67%) had persistent depressive symptoms. This study identified several independent risk factors for developing depression, i.e. age, smoking, self-reported well-being and general health, baseline depressive symptoms, neuroticism; whereas the risk factor for the persistence of depression during time was neuroticism only. Neuroticism can be considered as a subject’s tendency to emotional instability and is a well-known risk factor of depression also in general population [41], as well as in children and adolescents [42]. Thus, authors conclude that the relationship between depressive symptoms, somatic illness, and age is mediated by the premorbid vulnerability to mood liability. Indeed, consistently with the dynamic stress-vulnerability model [43], neuroticism could be considered as a marker of psychobiological vulnerability, or “frailty”, in elderly people. Neuroticism could enhance the risk of onset of depression as well as its persistence, by the amplification of stressful effects of life events, leading to an increased and persistent depressive reaction after a somatic illness. In our opinion, this hypothesis is consistent with findings from general cancer population studies, suggesting that one of the factors modulating the relationship between cancer and depression is the individual’s management of the distress due to the illness [44–47].
5.2. Phenomenology of depressive disorders in elderly patients with cancer: the problem of comorbidity and its assessment

The elderly patient with cancer appears as a vulnerable or frail individual [48], burdened with additional difficulties, for instance in carrying out daily activities such as cleaning, cooking, shopping and self-care [18]. In addition, cognitive impairment may occur concurrently with depression in elderly cancer patients, complicating its phenomenology. Furthermore, there is preliminary evidence in literature about an association of depression and other psychological/somatic symptoms, in this population. A study by Bernabei et al. [11] investigated the relationship between depression and pain in a large sample of elderly patients with cancer, finding that aging patients with depression are more sensitive to pain due to cancer. These data are consistent with studies on non-cancer institutionalised elderly people affected by different medical conditions [49–52]. Notably, the presence of pain increases the prevalence of depression in cancer patients [53], who complain not only of more depressive disorders, but also of anxious and somatic symptoms, compared to patients without pain [54,55]. Indeed, it has been argued that anxiety disorders associated with pain in elderly cancer patients decreased after treatment with analgesics [18]. The link between pain and depression appears to be bidirectional. On the one hand, there is strong evidence that pain causes depression in cancer patients [9,53,56,57]. On the other hand, there are studies suggesting that depression and anxiety, in particular during the course of illness, reinforce pain by increasing its intensity [54,58,59].

Another symptom related to both pain and depression in cancer patients is fatigue [60], which is also reported by aging cancer patients [17]. From studies on cancer patients, it is well established that fatigue correlates significantly with level of depression [60–62], and that these two conditions share several common features. In fact, some demographic variables (i.e. younger age, female gender), medical features (i.e. prior surgery, distant metastases and cancer site), and psychological factors (i.e. increased anxiety, anger and confusion) have been found to be related to higher levels of fatigue and depression in cancer patients [63].

The relationship between depression, pain and fatigue has been reviewed by Rao and Cohen [17], focusing on its relevance for elderly patients with cancer. Although these symptoms could be distressing for aging cancer individuals, little is known about possible interactions and effects. According to the authors, diagnosis and management of depression, pain and fatigue require further research on biological age-related changes, in order to clarify how aging interacts with these symptoms to generate a distinctive condition in elderly cancer patients. Despite the high rate of comorbidity in elderly patients with cancer, studies on the relationship between depression and clinical outcome often do not take comorbidity into account, as observed by Charlson and Peterson in their review [12].

Furthermore, many somatic symptoms of depression, such as anorexia, weight loss, low energy and sleep disturbances, are similar to those of cancer itself [64], therefore they may easily be misattributed to cancer and not to depression [65]. Thus, several authors have proposed to exclude these somatic symptoms from depression diagnosis in cancer patients [66] or to substitute them with other non-somatic symptoms [67]. In particular, four major approaches have been proposed to assess mood symptoms in cancer patients [68]: (i) an inclusive approach, in which depressive symptoms are considered, even if they may be related to the physical illness; (ii) an etiologic approach, which considers symptoms of depression only if they are assessed by the interviewer not to be the result of physical illness; (iii) a substitutive approach, which substitutes psychological symptoms instead of somatic symptoms of depression and (iv) an exclusive approach, which considers only those symptoms that have been demonstrated to be more frequent in depressed than in nondepressed patients. A study by Ciaramella and Poli [64] suggests that a combination of these approaches, for instance using both the etiologic and substitutive methods, is more accurate in identifying depressed individuals with cancer. Unfortunately, such comprehensive approach is unlikely to be used in research studies, and, in particular, in the clinical practice because of several practical limitations, such as time constraints [68]. Therefore, a quick but accurate approach that allows the identification of mood disorders in cancer patients should be employed. For this purpose, even the use of biomarkers (i.e. the cortisol profile, indicating the presence of alterations in the hypothalamic-pituitary-adrenal (HPA) axis) has been suggested [69].

Thus, taking into account the described difficulties in identifying depression in the elderly patients with cancer and its peculiar phenomenology, the assessment of depressive symptoms in this population requires an overall approach in order to identify all physical, emotional, and psychological aspects of depression, as well as a specific assessment of signs of suicidality [14,15].

5.3. Suicide in elderly people with cancer

Chronic medical illnesses have been found to be associated with an increased risk for suicide in elderly people [70–72,16]. There is only one study exploring the issue of suicide in aging patients with cancer, by Llorente et al. [16]. Authors performed a population-based, retrospective study of men aged 65 years and older, residing in South Florida between 1983 and 1993, in order to determine the incidence of suicide among prostate cancer patients. Authors found that 20% of all the suicides were cancer-related. Notably, prostate cancer accounted for 15% of all the cancer-associated suicides and for 3% of all suicides in this age- and gender-specific population. The risk of committing suicide was four-fold higher in men with prostate cancer in this sample. Since the prognosis for prostate cancer is generally good, these findings appear to be surprising. However, as
argued by the authors, the treatment for this type of cancer may involve issues about sexuality, sense of maleness, and self-esteem, with deleterious consequences on mood [16]. In addition, some clinical correlates of suicide were identified, such as comorbid anxiety symptoms, depressive symptoms, pain related to cancer and marital status. Thus, authors conclude that older men with prostate cancer are at increased risk for committing suicide, especially if they manifest depression, anxiety symptoms and untreated pain. Therefore, an increased awareness of the psychiatric effects of the cancer diagnosis, and assessment and treatment of depression and pain may be important preventive measures [16].

6. Common biological basis among depression, cancer and aging

Since elderly patients with cancer are at increased risk of depression, the study of the common molecular mechanisms involved in the pathogenesis of both cancer and depression, in association with the physiologic changes due to aging, may lead to the identification of the interrelatedness of these diseases and their causal relationships, and therefore provide a valuable tool for new strategy of clinical intervention.

Despite aging cannot be considered directly responsible for the neoplastic processes, the incidence of cancer generally increases with age, even though the latter may positively or negatively influence the susceptibility to carcinogenesis in different tissues. The cellular and molecular mechanisms underscoring the link between cancer and aging have been efficaciously summarized in several reviews [73–75]. Interestingly, besides mutation burden, telomere dysfunction, impairment of DNA repair and alterations in proliferative homeostasis, several disturbances in the immune system have been consistently described in aging [76]. The immune system is aimed to defend the host from any insult (exogenous or endogenous) that may threat the body, by means of cellular and humoral effectors (cytotoxic immune cells and antibodies, respectively). The earlier and quickest mechanism of the immune reaction is the triggering of the inflammatory response and the activation of innate immunity mechanisms. This primary, nonspecific response is directed to eliminate the insulting agent, to initiate a more specific, long lasting and adaptive immune activation, and to concomitantly restore physiological homeostasis and promote tissue repair. However, in order to function properly, this network of immune mechanisms needs a tight regulation. In fact, if inflammation becomes unrestrained, for instance, it may eventually exert a large range of deleterious effects in the host. The principal orchestrators of the immune response are T lymphocytes, which differently modulate both the cellular and the humoral responses by secreting several cytokines, the hormone-like soluble mediators of the immune homeostasis. Distinctive patterns of cytokines are produced by different subsets of T helper (Th) lymphocytes with diverse functions (e.g. Th1 and Th2). Hence, Th1 are able to mainly produce interleukin (IL)-2, interferon (IFN)-γ, IL-12 and IL-18 and promote cellular immunity; while Th2 produce IL-4, IL-5, IL-6, IL-10, IL-13, and transforming growth factor (TGF)-β and favour the humoral immune response. Th1 and Th2 cytokines that are crucial in regulating the type of immune response and the extent of inflammation, can antagonize each other, and an imbalance in Th1/Th2 cytokines is often associated to several common diseases. In aging, both immunosenescence, the progressive decline in immune function resulting in an increased susceptibility to infections and cancer [77], and a generalized increase of immune-inflammatory response [78] have been described. In particular, there is evidence that immunosenescence may favour the development of cancer in cases of lymphomas and other highly immunogenic tumors [79]. Overall, both cell-mediated and humoral immune responses are affected by aging, with a downregulation of specific immunity and a nonspecific activation of pro-inflammatory pathways. In addition, a general decrease in functioning of lymphocytes characterized by a Th1 decline and a shift of adaptive humoral response to a nonspecific, natural antibody-mediated immunity is observed in aged subjects [80,81]. On the other hand, aging is also associated with a low-grade chronic inflammation. In fact, elevated circulating levels of pro-inflammatory mediators, including IL-1β, tumor necrosis factor (TNF)-α, IL-6 and IL-18 are suggested to play an important role in the process of aging [82–85]. Similar immune dysregulations are also observable in cancer, where a persistent humoral immune response exacerbates the activation of innate immune response and inflammatory pathways, which concur in promoting cancer development [86,87]. Thus, since chronic inflammation and, in particular, the release of pro-inflammatory cytokines is strongly associated with processes that contribute to the onset and progression of cancer, the association between aging and cancer seems to directly involve immune dysregulation and pro-inflammatory cytokine up-regulation.

Interestingly, immune dysregulation can also be considered as one of the factors explaining the link between depression and cancer. In fact, a predominant activation of innate immune cells has been described also in depressive disturbances. Indeed, two well-known physiologic correlates of depression are decrease in cell-mediated immune function and alterations in the activity of HPA axis, which is associated with the levels of pro-inflammatory cytokines. From research studies performed in the general population, we know that these physiologic correlates of depression may adversely affect the health status. Thus, although depression can be a secondary manifestation of cancer, it also appears possible that, from a biological point of view, a depressive state may favour the development of a cancer, as reported by Reiche et al. [88], who reviewed how stress and depression may influence the risk and the progression of cancer trough neuroendocrine-immune-mediated mechanisms. In particular, depressed subjects show a reduction of both viral and antigen specific measures of cell-mediated immunity [89–91] and a reduced ability of T cells to mount an
Antigen-specific response such as those necessary to combat viruses, bacteria and tumors [92–94]. Therefore, depressive symptoms appear to be associated with poorer cellular immune function across several domains [9]. These data have been confirmed also in cancer patients. In women with cancer, severity of depression may reduce the number of leukocytes over short periods of time [95] and depressive symptoms are predictors of both lower white blood cell counts and normal killer cell number [95,96]. Similarly, cytokine dysregulation has been largely associated with depression [97–99] and serum levels of pro-inflammatory cytokines including IL-1β, TNF-α, IL-6 and IL-18 are all elevated in depressed patients [100–102]. Indeed, several studies investigating the interactions between immunity and depressive symptoms, have suggested that a dysfunction of the innate immune system is a relevant contributor factor to the onset and maintenance of depressive disorder [103,104]. The relationship appears to be reciprocal, in the sense that immune activation may alter mood, and a depressed state may affect immune functioning [105,106]. In particular, exposure to certain cytokines such as IL-1β, leads to a complex constellation of symptoms that are similar to those of a depressive state (i.e. anhedonia, decreased sexual/social activity, sleep abnormalities, decreased feeding and motor behavior, anxiety, diminished intracranial self-stimulation) [105,107,108]. In addition, cytokine exposure leads to neuroendocrine changes analogous to those observed in individuals with depression, such as increased corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and corticosterone levels [109], alterations of the monoaminergic system [105] and decreases in brain-derived neurotrophic factor (BDNF) [110]. Another possible effect of cytokine release is the increase of HPA activity [105], suggesting a cross-sensitization between stress and cytokine production [106]. It has been hypothesized that the inflammatory response, together with the stress response, is involved in the survival of the organism and the species. Therefore, immune disturbances, such as the chronic inflammation state, may influence several aspects of the individuals’ well being and they may be linked to the pathogenesis of several common diseases, including cancer and depression [111]. Cytokines are crucial in inflammatory responses, and a disturbance at the neuroendocrine-immune interface may imply a cytokine network imbalance, leading to an excessive production of pro-inflammatory cytokines. Accordingly, further evidence of the link between depression, cancer and immune dysregulation is that cytokines can be considered reliable biomarkers for depression in cancer, as in the case of IL-6, whose plasma concentrations are significantly increased in depressed patients with cancer [69] and, interestingly, pharmacological doses of cytokines in cancer patients have an effect on maintenance of depression [112]. Thus, although more research is needed to clarify the link between such measures of immunity and clinically relevant immune function [9], there is preliminary evidence for a directional relationship between depressive symptoms and dysregulation of the immune system in cancer patients. Moreover, some immunological dysfunctions have also been described in elderly patients with depression and since both depression and aging undoubtedly affect immunity, this link appears to be quite meaningful. Hence, elderly depressed patients are characterized by a history of increased exposure to Cytomegalovirus, which could have resulted in a pro-inflammatory profile [113] and these changes, in turn, negatively affect immune response in depressed patients. Accordingly, aged subjects are at greater risk for cytokine-induced depressive symptoms [103,114], although it is also possible that the action of depressive symptomatology on the immune system causes an exacerbation of the illness.

Therefore, aging, in virtue of its ability to alter immune competence and promote inflammation, can have an impact on mechanisms by which both cancer and depression develop and progress. Aging can be thus considered as a common risk factor for both depression and cancer, as summarized in Fig. 1.

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**Fig. 1.** Bidirectional mechanisms of interaction between aging, cancer and depression. Aging is associated with altered cellular (Th1) and humoral (Th2) immune function, and pro-inflammatory cytokine up-regulation. These immune dysfunctions, mainly mediated by stress-related stimuli through neuroendocrine (HPA) modulation, appear to be a central biological process in the interaction of aging with cancer and depression. Sympathetic/parasympathetic deregulation may alter the homeostasis.
Altogether, these observations imply that the study on association of cancer and age involves both biological and clinical challenges, especially taking into account the role of depressive disorders that seem to share part of the described pathogenic mechanisms, including immune dysregulation.

7. Treatment, cancer and depression

The complexity of care in geriatric patients with cancer makes it highly challenging to determine which treatments are effective for depression in this population. Indeed, because of the above-described pathogenic mechanisms, depression in elderly patients with cancer manifests distinctive characteristics from other age groups. Consequently, an appropriate and specific therapeutic approach in the elderly should differ from other age groups.

In reality, in clinical practice, the procedure for the assessment and the treatment of depressive symptoms in elderly cancer patients are largely based on data obtained from the general medical population [115]. This is because, unfortunately, the treatment of depression among cancer patients has received insufficient attention, particularly in the old age population but also in other age-ranges [115]. However, results are encouraging because, despite the paucity of randomized placebo-controlled trials, there is preliminary evidence that depressive disorders in cancer patients can be successfully treated with antidepressants, as summarized by Williams and Dale [116].

The SSRI paroxetine has been found to be effective in reducing depressive symptoms in patients with different types of cancer [117–119]. In the Roscoe’s double-blind randomized placebo-controlled trial [117], the sample consisted of 94 females with breast cancer receiving no less than four cycles of chemotherapy and not undergoing concurrent radiation or interferon treatments. Paroxetine 20 mg/day was found to be more effective than placebo in improving depressive symptoms and reducing MDD rate during chemotherapy. In the Morrow’s single-blind randomized placebo-controlled trial [118] the sample consisted of 549 patients with a diagnosis of breast, lung, hematological, gynecological or gastrointestinal cancer, reporting fatigue at their second chemotherapy cycle. Paroxetine 20 mg/day for 8 weeks was found to be more effective than placebo in ameliorating depressive symptoms during chemotherapy. In the Musselman’s double-blind randomized placebo-controlled trial [119], the sample consisted of 40 patients with malignant melanoma receiving high-dose interferon alpha therapy. Paroxetine 20–40 mg/day significantly reduced depressive symptoms and the incidence of MDD.

The SSRI fluoxetine has been found to be effective in reducing depressive symptoms in advanced solid tumors [120], but not in reducing MDD rate in a trial that included patients with various cancer sites [121]. In the Fisch’s double-blind randomized placebo-controlled trial [120], the sample consisted of 163 patients with expected survival between 3 and 24 months. Fluoxetine-treated patients 20 mg/day for 12 weeks showed significantly lower depression severity at the end of the follow-up. In the Razavi’s double-blind randomized placebo-controlled trial [121], the sample consisted of 91 patients with MDD. Fluoxetine 20 mg/day for 5 weeks did not show any advantage over placebo on depression improvement.

A very recent double-blind randomized placebo-controlled study [122] on 189 participants with different cancer sites indicated that, in patients without MDD, sertraline 50 mg/day was not effective in reducing depression, fatigue and anxiety symptoms and in improving survival rate. This study suggests that antidepressant treatment should be limited to patients with proper indication, such as major depressive disorder.

The efficacy of the tetracyclic mianserin has been demonstrated in improving depressive symptoms in various types of cancer [123,124]. In the double-blind randomized placebo-controlled trial by van Heeringen and Zivkov [123] the sample consisted of 55 patients with breast cancer, with a diagnosis of unipolar depression. Mianserin 60 mg/day significantly reduced depressive symptoms at 4 and 6 weeks of follow-up. Similarly, in the Costa’s randomized placebo-controlled trial [124], mianserin significantly improved depressive symptoms in 73 women with various cancer sites and a MDD diagnosis.

Thus, there is evidence that antidepressants may be effective in improving depressive symptoms in adult cancer patients with MDD. However, more data are needed in order to clarify both antidepressant efficacy and their side effects and tolerability in cancer patients [116]. Unfortunately, no strong conclusion can be drawn on the effectiveness of antidepressants for improving depression in elderly cancer patients, given the absence of studies in this subgroup. Additional methodological problems linked to the difficulty in enrollment and to the high rates of dropouts in elderly cancer patients should be considered.

Another aspect to keep in mind, complicating the treatment of depression in cancer patients, is the deleterious effect that certain chemotherapeutic drugs have on mood [125–127]. Thus, the presence of depressed mood in cancer patients may be induced by treatment with chemotherapeutic agents, such as corticosteroids, used as premedication or for treatment of lymphomas, and vinca alkaloids such as vinblastine and vincristine, 1-asparaginase, tamoxifen, alfa-interferon, procarbazine, and cyproterone acetate [17,112,125]. However, effects of chemotherapy, radiotherapy and hormonal therapy on depressive symptoms in cancer patients, especially the elderly, need to be studied further.

Finally, there are several barriers that limit cancer treatment and management in the elderly, that is polypharmacy, difficulties in the doctor–patient relationship such as lack of treatment adherence, patient attitudes (i.e. anxiety) hindering treatment and social stigma. All these aspects influence
the compliance of the patient to the overall medical approach [75,128]. Thus, in order to provide a comprehensive treatment strategy, a multidimensional assessment of elderly cancer patients, that takes into account all the physiological, medical, social, emotional and cognitive changes of aging, has been proposed [129].

Because of the interrelation between depression and cancer, it could be hypothesized that an effective psychotherapeutic treatment of depression could improve the course of the disease. As discussed by Spiegel and Giese-Davis [44], there is evidence of both significant reduction in depressive symptoms and increased survival time in cancer patients after psychotherapy. For instance, a study found that 1 year of supportive–expressive group psychotherapy not only reduced anxiety and depression, but also pain, and increased survival time by an average of 18 months, among breast cancer patients [130]. Nevertheless, other studies found no effect of psychotherapy on survival time of cancer patients [131,132]. However, as pointed out by Spiegel and Giese-Davis [44], variables as intervention timing, type, and duration of psychotherapy are crucial in modifying cancer outcome. Depression may affect the incidence or progression of cancer in several ways. On the one hand, it could be argued that depression may have an effect on compliance to medical treatment [133]; thus psychotherapeutic interventions would affect survival simply by improving treatment adherence. On the other hand, there is evidence that dysregulation in diurnal cortisol patterns, which is associated with more rapid cancer progression, becomes normalized during psychotherapeutic treatment [134]. Thus, as we discussed above, and in line with other authors [13,44,135], we can conceive depression as a chronic and maladaptive stress response, affecting HPA and immune functioning. Psychotherapy may affect aspects of endocrine and immune function that plausibly enhance resistance to tumor progression and survival. Unfortunately, to date, this issue has never been investigated in depressed elderly people with cancer. As discussed by Roth and Modi [18] a useful management of depression in elderly cancer patients is given by a combination of supportive psychotherapy and cognitive-behavioral techniques, with antidepressants if necessary. An antidepressant in elderly cancer patients should be chosen on the basis of several factors: the patient’s overall health, cognitive abilities, social and financial resources, comorbidity with other psychiatric conditions, somatic variables (such as pain, fatigue, insomnia), and previous familiar or personal response to antidepressant treatment [18]. In addition, it is also important to consider antidepressant side effects. In fact, some side effects may be useful, for instance a tricyclic antidepressant such as amitriptyline has found to be effective in neuropathic pain treatment [136]. Finally, electroconvulsive therapy may be indicated for elderly cancer patients that are refractory to antidepressants, that are suicidal and/or psychotic, or when the treatment with antidepressants is contraindicated [18].

8. Conclusions and considerations for upcoming studies

From a review of the literature on the topic of mood disorders in elderly patients with cancer, several considerations and suggestions for future studies may be drawn.

Firstly, the evaluation of depressive symptoms in elderly cancer patients may be confounded by the overlap of symptoms of depressive disorder and symptoms of cancer. Therefore, further studies should focus on the distinction between symptoms which are primarily derived from mood disorders and those that are secondarily caused by cancer or by side effects of the cancer treatment. In particular, it is necessary to refine specific diagnostic criteria for depression in elderly cancer patients, and to develop instruments for the assessment of depression severity, standardized for aging patients, that can help to distinguish the relative contribution of somatic or psychological dimensions. Indeed, it is to be considered that the currently used depression scales may be not valid for this special population of cancer patients.

The second problem to solve is the use of DSM-IV-TR categorical diagnosis of depression versus subsyndromal diagnosis. Since there is strong evidence that subclinical levels of depression are commonly reported in the elderly, a subsyndromal diagnosis, which takes into account not only MDD, but also MIND and subthreshold forms of depression, appears to be more appropriate for elderly patients with cancer. Future studies should focus on the differential effect of clinical and subclinical depression, in order to determine their impact on quality of life, medical use and adherence to medical regimens [68]. Additional research is needed to determine measures that reliably and validly differentiate individuals with subclinical versus clinical depression.

Thirdly, there is a consensus on the fact that the evaluation of depressive symptoms in aging patients with cancer cannot disregard the role of comorbidity with other medical and psychiatric conditions. In fact, depressed aging patients with cancer often suffer from pain, fatigue, and are at an increased risk of medical comorbidity. The impact of depression and its association with other psychological/somatic symptoms on long-term outcomes, need to be clearly documented in elderly cancer patients.

Fourthly, the role of immune dysfunction as common pathophysiological ground of depression, cancer and aging should be considered as an emergent issue in oncological research. The most important implication arising from the current biological findings is that a chronic depressive state may favour the development and exacerbation of a cancer, especially in elderly patients that are at increased risk of immune dysregulation. Therefore, a careful assessment of depression could be useful for cancer management in the elderly. However, more research on this issue is needed, in order to clarify the link between immunological dysfunctions and clinically relevant depression in elderly patients with cancer.
Finally, since depression and cancer share the described biological mechanisms, it is possible to hypothesize that antidepressant drugs have a beneficial role not only on mood disorders but also on cancer. Thus, upcoming research should employ clinical controlled trials in order to understand which antidepressant drugs may be indicated in depressed elderly patients with cancer, and to obtain information on their efficacy, tolerability, and moreover on their effect on cancer outcome and consequently on patient quality of life.

In conclusion, with these clinical and biological challenges in mind, future research should aim to provide data about the real prevalence and severity of mood disorders in elderly patients with cancer, to increase our knowledge of possible effects of depression on immune functioning and cancer progression, and to draw specific guidelines for the treatment of depressive symptoms in this population. For all these reasons, higher commitment and much harder work are necessary, in order to improve the quality of life of patients and their caregivers.

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