Title

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Journal

Current Psychiatry Reports, 15(11)

ISSN

1523-3812

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Publication Date

2013-11-01

DOI

10.1007/s11920-013-0404-1

Peer reviewed

Published in final edited form as:
Curr Psychiatry Rep. 2013 November ; 15(11): . doi:10.1007/s11920-013-0404-1.

Depression and Insomnia in Cancer: Prevalence, Risk Factors, and Effects on Cancer Outcomes

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Abstract

Over two-thirds of the 11.4 million cancer survivors in the United States can expect long-term survival, with many others living with cancer as a chronic disease controlled by ongoing therapy. Behavioral co-morbidities often arise during treatment and persist long-term to complicate survival and reduce quality of life. This review focuses on depression and insomnia with an emphasis on understanding the role of cancer-specific factors and their contribution to the prevalence of these behavioral co-morbidities in cancer patients following cancer diagnosis and treatment. The clinical significance of depression and insomnia for cancer patients is further stressed by epidemiological observations that link depression and insomnia to cancer morbidity and mortality risk.

Keywords

Depression; Insomnia; Cancer; Sleep disturbance; Inflammation; Fatigue; Anxiety; Depressive symptoms; Major depression; Psychiatry

Introduction

Considerable advancements in diagnosis and treatment of cancer have occurred over the last decade. With over 11.4 million cancer survivors, nearly 5% of the US population being diagnosed with cancer in 2006 [1], it is estimated that the number of cancer survivors will grow dramatically due to the aging of the population and the resultant increased cancer incidence. Moreover, over two-thirds of individuals diagnosed with cancer today can expect long-term survival and many others will live with cancer as a chronic disease controlled by ongoing therapy. Despite these gains in early detection of cancer and treatment, long-term behavioral co-morbidities such as depression and sleep disturbance are prominent. In this review, the prevalence of depression and insomnia are reviewed with a focus on the cancer-related factors that contribute to the incidence of these symptoms and syndromes during treatment, as well as during long-term survivorship. Better understanding of the cancer-specific risk profiles associated with these behavioral co-morbidities has the potential to

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Compliance with Ethics Guidelines

Conflict of Interest

Michael R. Irwin declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

inform the development of strategies for the prevention and treatment of depression and insomnia. Finally, increasing evidence is discussed that links depression as well as sleep disturbance to cancer incidence and mortality risk, which together further emphasize the clinical significance of these behavioral co-morbidities in cancer.

Depression

Prevalence

Depression is one of the most common mental health problems worldwide. In the community, the one-month prevalence of depression is about 5%, with an incidence of depression approaching 9% over 12 months. Among patients with cancer, depression is thought to be even more prevalent, with an often-cited median point prevalence (15% to 29%) that is approximately three to five times greater than the general population [2-4]. Furthermore, evidence suggests that the relative risk of depression in patients with cancer exceeds that of patients who had stroke, diabetes, and heart disease [5, 6].

Despite an extensive literature of nearly 900 articles (i.e., PubMed search for title keywords: “depression” “cancer”), the prevalence of depression in clinically meaningful subgroups of people with cancer remains unclear. Indeed, varying prevalence estimates from 1.5% to 50% are reported, possibly depending on the cancer type, as well as the definition of depression and method of assessment [7, 8]. Furthermore, as reviewed by Walker et al. [9], several issues have made it difficult to determine how common depression is among people with cancer. First, many studies have not used diagnostic interviews to assess depression. Second, there is striking variability in methodological quality between studies, and many reviews of observational studies have included results of low-quality studies that are biased by limitations in instrument choice. Third, research on depression in cancer has often neglected to consider that cancer is a biologically and clinically heterogeneous disorder, and have pooled data across various cancer populations to provide one overall estimate of depression. Finally, there has frequently been use of self-report instruments or single items to categorize the presence of depression; the effects of different methods of diagnosing depression on prevalence estimates has not been considered.

To address these concerns, two recent meta-analyses have been performed which imposed a number of strict quality assessment measures for inclusion of studies in an effort to provide a better estimate of depression prevalence in cancer [9, 10]. Walker et al. [9] identified 499 studies that reported on the prevalence of depression in cancer patients. However, among these 499 studies, 433 were deemed as not being relevant due to their study design; many were clinical trials where depression assessment was simply part of the trial. Of the 66 relevant studies, only 15 met four rigorous quality criteria: use of random or consecutive sampling methods to identify the sample; availability of data on at least 70% of the eligible patients; definition of depression case-ness using standard diagnostic criteria (i.e., major depression from the Diagnostic and Statistical Manual of Mental Disorder, DSM or depressive episode from the International Classification of Diseases, ICD); and assessment of depression in at least 100 study participants. Among these 15 studies, prevalence estimates again remained variable, ranging from 5% to 16% in outpatients, 4% to 14% in inpatients, 4% to 11% in mixed outpatient and inpatient samples and 7% to 49% in palliative care. Also, even though all studies used standard diagnostic criteria to define depression caseness, those in which an expert (psychiatrist or clinical psychologist) administered interviews reported a lower estimate of current depression prevalence than studies that employed less expert interviewers. Furthermore, among those studies that used the Structured Clinical Interview for Diagnosis (SCID), depression prevalence tended to be lower (range of 5% to 9%) as compared with those that used other interviews (range 8% to 16%). Finally, it is also important to note that because of the small number of high quality

studies, estimates of the prevalence of depression in clinically relevant subgroups of cancer patients was not possible.

The second meta-analyses of depression prevalence in cancer patients, which was also restricted to studies that used psychiatric interviews, generated somewhat higher prevalence estimates [10]. For palliative care settings, a total of 24 studies with 4007 individuals across seven countries were identified. When depression was defined by the DSM or ICD criteria, the meta-analytical pooled prevalence of depression was 16·5% for DSM-defined major depression, and 9·6% for DSM-defined minor depression. When all types of depression were combined, prevalence was 24·6%. For oncological and haematological settings, a total of 70 studies with 10071 individuals across 14 countries were identified, which yielded similar prevalence estimates. Again, prevalence of depression was 14.9% for DSM-defined major depression and 19.2 % for DSM-defined minor depression. When all types of depression were combined, prevalence was 20·7%. Among this larger number of included studies, there was no effect of age, sex, or clinical setting. However, there was again inadequate data to examine the role of cancer type and illness duration on depression prevalence, although no difference was reported in studies that simply included breast cancer patients alone (14·1%; 95% CI 10·0–18·7; n=19)[10].

Together, these recent meta-analyses that focus on interview-defined depression indicate that major depression is less common in patients with cancer than previously thought. Yet, some combination of mood disorders occurs in about 20% of patients in hospital settings without a significant difference between palliative-care and non-palliative-care settings [10]. In addition, this rate in hospital settings appears to be nearly identical to the 12-month rate of major depression in patients diagnosed with cancer and living in the community[11]. Even though rates appear to be even lower when an expert psychiatrist or psychologist administers the interview, the reported prevalence of depression together with improvements in cancer survival has led to an increase in the actual number of depression cases, which now reaches a level that is estimated to be over 2 million in the USA with major depression and cancer at any time (calculated as prevalence of cancer × prevalence of depression)[10].

Role of Cancer in Precipitating the Occurrence of Depression

Because of the relatively higher prevalence of depression in cancer patients, and the association of depression with mortality as discussed below, it is important to identify what factors contribute to depression in this population; identification of the factors that comprise this risk profile might then be targeted in the development of intervention or preventative approaches to attenuate depression risk. To understand the risk profile, it is important first to evaluate what cancer- specific factors might drive the occurrence of depression. In this regard, it appears that the interval after receiving a diagnosis of cancer, and managing the subsequent psychological and physiological challenges of treatment, appears to be a time when cancer patients are most at risk for the occurrence of depression. Rates of depressive symptoms markedly rise after diagnosis, with increases typically highest in the first 6 months, followed by declines over time with adjustment to the initial shock of diagnosis and acute effects of cancer treatment [12]. Additionally, cancer treatments alone are associated with increased risk of depressive symptoms. Prior to medical treatment, about 10% of patients diagnosed with various cancers show depressed mood or anhedonia, two hallmark symptoms of depression, whereas during treatment, over 20% endorse one of these symptoms [13].

Recent cross-sectional observational studies confirm these findings and suggest that the rate of depression is higher in cancer patients especially during the immediate diagnosis and treatment interval. Honda and colleagues[14] evaluated the presence of depression between 45 patients with cancer and 5826 people without cancer, with depression case-ness defined

by the WHO Composite International Diagnostic Interview (CIDI). Within 12 months of the cancer diagnosis, the rate of major depression in patients with cancer was 3.6 times greater than those without cancer. In a second study, depression was assessed using the CIDI with a survey of over 36,000 people [11]. A total of 118 reported that a diagnosis of cancer, and the 12-month prevalence of major depression was 15·5%, higher than the rate of 5·4% in patients aged 15–54 without cancer. Finally, using the Danish Cancer Registry, Dalton and colleagues[15] examined linked data from 608,591 adults diagnosed with cancer and identified an over 20% higher relative risk of depression in the first year after a cancer diagnosis (RR 1·16–3·08).

Prospective data extend these cross-sectional observations and suggest that cancer diagnosis and treatment actually provokes the occurrence of depression during the first two years after diagnosis as compared those who remain medically healthy. Furthermore, the rate of depression occurrence is higher than found in other chronic diseases. Polsky et al.[6] examined depressive symptoms prior to and after disease diagnosis in 5 biennial waves of the Health and Retirement Study involving more than 8,000 adults aged 51 to 61 without depressive symptoms at study onset. Within 2 years following diagnosis, individuals with cancer had the highest risk of significant depressive symptoms relative to no incident disease (Hazard Ratio 3.55) and other diagnosed diseases (e.g., heart disease, arthritis). Despite the strengths of these prospective and observational data, it is not yet known what factors contribute to depression risk, especially during the period of early diagnosis and treatment. Specifically, information on the role of modifiable risk factors such as sleep disturbance is lacking as discussed below.

Depression and Cancer Disease Burden

Depression in cancer patients substantially affects health functioning and also impacts mortality risk, which could be due to the effects of depression on several clinical factors related to treatment. Indeed, meta-analytic findings demonstrate that depression triples the risk for nonadherence to medications [8], and depressed patients are also less likely to adhere to cancer therapy recommendations. In turn, lower medical adherence, which is associated with poorer understanding of treatment recommendations, heightens anxiety about treatment adverse effects in depressed cancer patients [16]. Together, these factors are thought to contribute to increased use of emergency and medical inpatient services. For example, the use of emergency and medical inpatient services at nearly two-fold the rate for those Medicare beneficiaries diagnosed with cancer with depressive symptoms than those without such symptoms [17]. Likewise when co-morbid depression occurs with other diseases there are increases health care use, functional disability, and work absence [18].

In addition to the consequences of depression on health functioning and clinical treatment adherence in cancer patients, depression also has a substantial impact on morbid outcomes, including mortality risk. The presence of depression either before- or after cancer diagnosis increases the risk of cancer- and all-cause mortality, similar to the effects of depression on risk of morbidity and mortality in several other chronic diseases, including AIDS [19] and cardiovascular disease [20]. Indeed, three recent meta-analyses show that there is a robust association between depression and cancer mortality [21-23]. Chida et al. [21] found that that depression was associated with higher cancer mortality, both in community-based samples of cancer survivors (RR 1.34) and in cancer patients (RR 1.08). Likewise in a meta-analysis of 25 observational studies, Satin el al [22] showed that cancer patients diagnosed with major or minor depression had a 39% higher all cause mortality rate (RR 1.25–1.39) [22]. Finally, Pinquart and Duberstein evaluated 76 prospective studies and found that the relative risk for mortality increases by 19% in the depressed as compared with the non-depressed group, and that this relationship was similar in studies that assessed depression

before cancer diagnosis as well as in studies that assessed depression following cancer diagnosis [23].

These meta-analytic results show a consistent relationship between depression and mortality, because they are founded in part on several large scale epidemiologic studies which warrant a brief description here in view of their robust samples, methodological quality, and effect sizes. For example, in 10,025 participants in the National Health and Nutrition Examination Survey with and without cancer were compared [24], participants with both cancer and depressive symptoms had a 19% increased risk of death compared to participants with cancer only after adjusting for confounders. Likewise, in a prospective study of 61,349 adults in Norway followed for 4.4 years after depression assessment, Mykletun [25] found a 33% increased risk of death from cancer associated with disorder-level depressive symptoms. Finally, Pril et al reported that presence of major depression was associated with worse survival in patients with non-small cell lung carcinoma, although treatment of such depression did not yield survival benefit [26]. However, the lack of effect of depression treatment on survival outcomes diverges from that of Giese-Davis who evaluated mortality in 125 women with metastatic breast cancer who had completed a randomized trial of supportive-expressive group therapy vs. education control. Among women with decreasing symptoms of depression between one and over two years after the trial, median survival time was over twice (53.6 months) that for women with increasing depressive symptoms during the immediate intervention follow-up period (25.1 months), with a significant effect of change in CES-D over the first year on survival out to 14 years.

Sleep disturbance

Understanding of the link between insomnia and depression in cancer patients remains limited, and there is a need for research in this area for several significant reasons. First, as detailed below, sleep disturbance appears to be common in cancer patients. Second, considerable data have shown that insomnia is an independent risk factor for depression in healthy adult- and older adult populations [27], yet there are no prospective data in cancer patients to evaluate this relationship. The absence of such information is especially salient, given that cancer-specific factors are known to heighten the risk of depression and may act together with sleep disturbance to increase depression risk. Third, sleep disturbance activates biologic mechanisms, such as inflammation [28-32], which are increasingly thought to contribute to depression[29, 33]. Moreover, given that certain cancers and their treatment also induce inflammation [34], the combined effects of sleep disturbance and cancer specific factors may work together to catalyze the onset of depression in cancer patients, particularly during the early interval after diagnosis and treatment. Finally, sleep disturbance alone, as well as depression, appear to have the potential to increase the risk of cancer morbidity and related mortality. [35]

Prevalence

In contrast to the substantial literature on depression and cancer, research examining sleep or insomnia in cancer is relatively smaller with only about 300 such titled research articles (i.e., PubMed search for title keywords: “cancer” “sleep” “insomnia). Additionally, few studies have applied insomnia diagnostic criteria in a random sample of cancer patients to estimate insomnia prevalence. Furthermore, most have used small convenience samples; characterized insomnia symptoms in heterogeneous samples of cancer patients, which have not been sufficiently large to compare the prevalence of insomnia across cancer sites; relied on cross-sectional design; examined cancer patients without consideration of the time since treatment completion; and relied on one- or two-item self-reported scales; for review, see [36-38].

To address the limitation of prior research, recent studies have substantially advanced the field by using clinical interviews or validated questionnaires to assess and classify symptoms of insomnia. For example, Savard and colleagues [39] examined the prevalence of insomnia symptoms and insomnia disorder in breast cancer patients, and showed that over 50% of these women who received radiotherapy reported such symptoms and nearly 20% met criteria for clinically significant insomnia. A somewhat higher prevalence of clinically significant insomnia at 39% was identified in women with stages I-IIIA breast cancer who were up to 4 years post-diagnosis [40]. This rate of insomnia was similar to the findings of Davidson who evaluated cancer survivors in an outpatient clinic and found that 31% had insomnia symptoms that reach clinical severity thresholds [41]. Additionally, Davidson et al. [41] suggested that insomnia symptoms were most common in breast (38%), lung (37%), gastrointestinal (32%) and gynaecological (29%) cancer patients. In one of the largest cross-sectional studies, insomnia was examined insomnia in 823 patients receiving chemotherapy for various types of cancer (all stages)[42]. Again, The prevalence of insomnia symptoms, as defined by depression questionnaires, was the highest in patients with breast and gynecologic cancer (39%), whereas rates of insomnia syndrome were greater in patients with lung cancer (>50%). Taken together, it appears that sleep disturbance and clinically significant insomnia are substantial problems in cancer patients. Even in view of various definitions and measures, the prevalence of insomnia is greater by about 3-fold than the 7.0–9.5% rate reported in general population studies.

Role of Cancer in Precipitating Insomnia Symptoms

Several cancer-related and other factors appear to be associated with the occurrence of insomnia in cancer patients. For example, the distress associated with cancer diagnosis and the start of treatment appears to be associated with some of the highest levels of insomnia symptoms. In a recent large population-based longitudinal study involving 991 cancer patients with non-metastatic disease, self-report scales and an insomnia diagnostic interview were completed at the perioperative period and again two months later[43]. Initially, nearly 30% of the patients met diagnostic criteria for an insomnia syndrome, and 31% had insomnia symptoms. Two months later there was evidence that insomnia symptoms had lessened somewhat, with an insomnia remission rate of 32%. Similarly, Palesh et al[42] assessed insomnia symptoms in 823 patients receiving subsequently cycle of chemotherapy for various types of cancer (all stages), and found modest decreases in insomnia symptoms from cycle 1 (79.6%; 43% with insomnia syndrome) to cycle 2 (68.3%; 35.2% with insomnia syndrome). Nevertheless, a substantial number of patients showed an emergence of insomnia symptoms in association with chemotherapy treatment. For example, among good sleepers at cycle 1, 34.6% developed insomnia symptoms by cycle 2 (10% developed an insomnia syndrome). Finally, in a study 962 patients with cancer (mixed sites), insomnia diagnostic interviews were obtained at the perioperative phase, as well as at 2, 6, 10, 14, and 18 months after curative surgery for non-metastatic disease [44]. Again, there were high rates of insomnia at baseline (59%), including 28% with an insomnia syndrome. Whereas the prevalence of insomnia generally declined over time, it remained pervasive even at the end of the 18-month period (36%). Indeed, 15% of patients had a first incidence of insomnia during the study, and 19.5% experienced relapse. Additionally, remission in insomnia was much less likely for patients with an insomnia syndrome (10.8% to 14.9%) than for those with insomnia symptoms (42.0% to 51.3%), and over 37% of patients with an insomnia syndrome at baseline still had insomnia during the 18-month period.

Savard et al. [43] identified several predisposing factors that were associated with insomnia symptoms during this early treatment interval. These included female sex; the presence of an arousability trait; and a diagnosis of head and neck cancer. In addition, other factors were identified as being precipitating factors, which led to the occurrence of insomnia after cancer

diagnosis including the administration of surgery; an increase in anxiety symptoms from entry to two months later; and an increase dysfunctional beliefs about sleep, sleep monitoring, and maladaptive sleep behaviors. To some extent, similar findings were generated in the Australian Ovarian Cancer Study – Quality of Life Study, in which insomnia was assessed using the Insomnia Severity Index (ISI). Predictors of clinically significant insomnia included higher levels of "unmet needs" in the physical/daily living domain (OR = 1.02; CI 1.01–1.03) and elevated anxiety (OR = 1.83; CI 1.04–3.24). Interesting, young (not old) age was associated with insomnia, which contrasts with older age predicting primary insomnia in non-cancer populations. The associations between insomnia and risk factors of younger age and anxiety appear to be similar between men and women cancer patients. For example, men being treated with radiation therapy are likely to have sleep disturbance at rates similar to breast cancer survivors, and again younger (not older) men with co-occurring depression and anxiety appear to be at greatest risk for sleep disturbance during radiation therapy [45].

Cross-sectional data suggest that high rates of insomnia persist beyond the perioperative and early treatment interval, and extend into survivor populations. Desai et al [46] examined the prevalence and risk factors of insomnia among 413 women receiving aromatase inhibitors, a standard treatment to increase disease-free survival among breast cancer patients. Using the insomnia severity index (ISI) as the primary outcome, 31.5 % had sub- threshold insomnia and 18.6% exceeded the threshold for clinically significant insomnia. Adverse effects of aromatase inhibitor treatment were associated with insomnia such as severe joint pain, and mild/moderate hot flashes. Older age, as well as time since breast cancer diagnosis, were also found to be significant risk factors. Alterations of endogenous reproductive hormones appear to have similar effects in men. In prostrate cancer patients, androgen deprivation therapy is associated with an increased risk for insomnia, and side effects of androgen deprivation therapy also appear to play a role in the development of insomnia in this population[47]. Finally, Bardwell and colleagues [40] completed one of the most comprehensive studies of risk factors for insomnia in 2645 early breast cancer survivors, and found that lower education; less physical activity; more pain, vasomotor, genitourinary, gastrointestinal symptoms; less social support more social strain, life events and depressive symptoms were all associated with insomnia. However, in multivariate analysis, only depressive symptoms and vasomotor symptoms (night sweats in particular) were significant predictors of insomnia.

In general, polysomnographic data confirm these self-report observations and show that reduced sleep efficiency, prolonged latency to fall asleep, and increased awake time during the night are prominent in cancer survivors [39], with lung cancer patients showing marked reductions in sleep efficiency as compared to insomniacs or breast cancer survivors [48]. Likewise, in a study of 60 prostate cancer patients taking androgen deprivation therapy, actigraphy was used to assess sleep and found that cancer patients had a sleep-onset latency of 43.0 min, a wake after sleep onset of 49.4 min, a total sleep time of 5.9 h, and a sleep efficiency of 75.0% [49][13]. A sleep efficiency (ratio of the total sleep time on the total time spent in bed 100) of <85%, a sleep-onset latency and wake after sleep onset of <30 min, and a total sleep time of <6 h are generally accepted as indicating insomnia.

Sleep Disturbance and Disease Burden

Cancer-related fatigue is a frequently associated with sleep disturbance, and is thought to be a consequence of sleep disturbance [38]. Prospective data demonstrate that disturbed sleep predicts fatigue, and that there is a reciprocal relationship between fatigue and poor sleep in which less physical activity as a result of fatigue leads to a worsening of sleep disturbance. Yet, this relationship between sleep disturbance and fatigue is not simply due to less night-time sleep as total sleep as objectively assessed by actigraphy was not related to fatigue

among women undergoing chemotherapy for breast cancer. Rather, subjective reports of poor sleep quality appear to be more strongly related to fatigue [50].

Sleep disturbance is a potent predictor of depression occurrence [27] and depression relapse in persons with a history of prior depression [51]. However, there are no prospective data to address the contribution of sleep disturbance to depression occurrence or recurrence in cancer survivors. However, it is known sleep disturbance and depression are inter-related in cancer patients. Clevenger et al. [52] prospectively examined rates of sleep disturbance; contributions of depression, anxiety, and medication use in sleep disturbance; and associations between sleep quality and quality of life (QOL) during the first year after diagnosis among women with ovarian cancer. Medications for sleep and pain were associated with worse sleep at all time points. Greater increases in depression were associated with increased disturbances in sleep quality over time, which in turn led to declines in health functioning.

Epidemiological data also implicate insomnia as a predictor of all-cause disease mortality over and above age, gender, and medical burden [53-57]. Indeed, EEG measures of prolonged sleep latency, sleep efficiency, and percentage of REM sleep predict all-cause mortality taking into the account of other known factors (e.g., age, gender, medical burden) in non-cancer older adult populations (odds ratio 2.1, 95% CI: 1.25–3.66; odds ratio 1.93, 95% CI: 1.14–3.25; odds ratio, 1.7, 95% CI: 1.01–2.91) [57].

An emerging literature has begun to suggest that sleep disturbance may have specific effects on cancer risk [58]. Indeed in 2007, the International Agency for Research on Cancer (IARC) designated shift work involving circadian disruption, which is known to be associated with sleep disturbance, as a probable carcinogen in humans. This ruling was based primarily on data showing that women working night shifts had approximately 50% higher risk of breast cancer as compared with those who had not worked night shifts. Similar findings have been found in men and prostate cancer risk. Two Japanese cohort studies and two Canadian case–control studies have suggested an association between shift work and prostate cancer risk [59-62]; although a Swedish cohort study reported no association [63].

The prospective role of sleep disturbance on cancer risk has also been specifically evaluated. Recently, the prospective AGES-Reykjavik cohort study examined the associations between sleep disruption and prostate cancer risk in 2,102 men enrolled the Icelandic Cancer Registry. Compared with men without sleep disruption, those with problems falling and staying asleep were at significantly increased risk of prostate cancer [HR, 1.7 (95% CI, 1.0–2.9) and 2.1 (95% CI, 1.2–3.7)][35]. Moreover, when analyses were restricted to those with advanced prostate cancer, these associations became even stronger [HR 2.1 (95% CI, 0.7–6.2) and 3.2 (95% CI, 1.1–9.7)]. A similar link between extremes in sleep duration and colorectal cancer has been found [64]. In the Women's Health Initiative Observational Study, 75 828 postmenopausal women reported habitual sleep duration at baseline and were followed on average for 11.3 years. Compared with those with 7 h of sleep, short (<5 h) and long- sleep (>9 h) were associated with increase risk of colorectal cancer (HR 1.36, 95% CI 1.06–1.74; 1.47 95% CI 1.10–1.96) after adjusting for age, ethnicity, fatigue, hormone replacement therapy (HRT), physical activity, and waist to hip ratio. Other data suggest that the impact of sleep disturbance on cancer risk is similar to the risk associated with other chronic diseases [65]. In 23 620 middle-aged participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, participants with sleep duration of <6 h had a significantly increased risk of stroke (Hazard Ratio (HR) = 2.06, 95% confidence interval (CI): 1.18–3.59), cancer (HR = 1.43, 95% CI: 1.09–1.87), and overall chronic diseases (HR = 1.31, 95% CI: 1.10–1.55), as compared to those with 7 hours of sleep.

Inflammatory biology mechanisms linking depression and insomnia in cancer

Discussion of the biological mechanisms that contribute to the associations between sleep disturbance, depression, and cancer risk are beyond the scope of this review. However, there is much current interest in understanding inflammatory biology dynamics in relation to these behavioral co-morbidites and cancer. Sleep disturbance has been found to induce robust increases in inflammation[29-32, 66], and increasing evidence implicates inflammation in the onset of chronic diseases including cancer, as well depression[29]. Indeed, epidemiological studies have shown that chronic inflammation predisposes individuals to various types of cancer including breast cancer, and underlying inflammatory responses are linked to 15–20% of all deaths from cancer worldwide [34]. In addition, chronic inflammation is reported to be associated with recurrence of breast cancer [67]. Moreover, cancer treatments are potential inducers of inflammation. For example, chemotherapy is associated with acute increases in inflammatory markers [68-70], which may persist long into survivorship, with some data suggesting that such increases may be associated with fatigue and sleep disturbance during chemotherapy treatment [71, 72]. Wake–sleep cycles have emerged as homeostatic regulators of inflammatory biology, in which sleep loss induces activation of NF-κB to coordinate the production of inflammatory mediators and systemic inflammation. In turn, proinflammatory cytokines are thought to contribute, in part, to the onset of depressive symptoms and especially fatigue in breast cancer survivors [73].

Conclusions

In non-cancer adults, the risk of depression is due to multiple clinical, behavioral, and biological factors, with evidence that sleep disturbance has a unique prospective role in occurrence, recurrence, and persistence of depression. Despite compelling data that cancer specific factors have a marked impact on depression, as well as insomnia, prospective research on these behavioral co-morbidities in cancer survivors is limited; the selective profile of risk indicators for depression in cancer is not known. If insomnia is found to have a unique and specific role for depression risk in cancer populations, this would represent an important paradigm shift in advancing the design of depression prevention trial that target sleep disturbance in cancer survivors with implications for cancer outcomes.

Acknowledgments

Supported by R01-AG034588; R01-AG026364; R01 CA160245-01; R01-CA119159; R01 HL095799; R01 DA032922-01; P30-AG028748 to MRI; and UCLA CTSI UL1TR000124, and the Cousins Center for Psychoneuroimmunology.

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