Original Article

Sleep Disturbance, Distress, and Quality of Life in Ovarian Cancer Patients During the First Year After Diagnosis

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BACKGROUND: Sleep disturbance is a common clinical complaint of oncology patients and contributes to substantial morbidity. However, because most sleep studies have been cross-sectional, associations between sleep quality and distress in patients with ovarian cancer over time remain unclear. This prospective longitudinal study 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. **METHODS:** Women with a pelvic mass completed measures of sleep quality, depression, anxiety, and QOL before surgery. Those diagnosed with primary epithelial ovarian, fallopian tube, or peritoneal cancer repeated surveys at 6 months and 1 year after diagnosis. Mixed modeling was used to examine trajectories of psychosocial measures over time, as well as associations between changes in distress and sleep quality. Relationships between changes in sleep and QOL were also examined. **RESULTS:** The majority of patients reported disturbed global sleep (Pittsburgh Sleep Quality Index > 5) at all 3 time points. 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 ($P < .04$). Worsening sleep was also associated with declines in QOL over time ($P < .001$). **CONCLUSIONS:** Sleep disturbance is common and persistent in women with ovarian cancer, and is linked to depressive symptoms and QOL. Pharmacologic treatment does not appear to adequately address this problem. Results highlight the need for ongoing screening and intervention for sleep disturbance in this population. ***Cancer*** **2013;119:3234-41.** © *2013 American Cancer Society.*

KEYWORDS: ovarian cancer; insomnia; depression; anxiety; quality of life.

INTRODUCTION

Sleep disturbance is common and contributes to substantial morbidity among patients with cancer.[1-4] Rates of sleep disturbance in patients with cancer are higher than in the general population[1] and have been documented by polysomnography.[2] Among patients with heterogeneous advanced cancers, 72% reported sleep disturbance, with common complaints including difficulties with sleep onset and maintenance, not feeling rested in the morning, and daytime fatigue.[3] Chemotherapy has been associated with significantly poorer sleep quality[4] and daytime sleepiness.[5] Disturbed sleep has functional consequences as it has been associated with poorer quality of life (QOL) in women with breast cancer, including impaired ability to perform work and daily tasks,[6] although not all studies have yielded consistent results.[7] A recent study of patients with ovarian cancer within 5 years of diagnosis reported that sleep disturbance contributes to poorer QOL regardless of disease stage and chemotherapy status.[8]

Sleep disturbance often persists over extensive time periods in patients with cancer. Disturbed sleep and fatigue have been reported in women with breast cancer even before initiation of treatment.[9] Generally, sleep disturbance in patients with breast or prostate cancer declines over the 6 months following treatment.[10] However, at least one study has found

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that 23.3% of women treated for early-stage breast cancer still have symptoms of insomnia for up to 2 to 5 years after treatment completion.[11]

Because of poor prognosis and rigorous treatment protocols,[12] patients with ovarian cancer often suffer high distress at the time of diagnosis and during treatment,[13] potentially placing them at elevated risk for sleep disturbance. However, little is known about the trajectory of sleep disturbance following diagnosis and what factors confer increased risk for poor sleep in ovarian cancer patients over time. To address these issues, the first objective of this study was to characterize prevalence of self-reported sleep disturbance in women with ovarian cancer prior to surgery, and at 6 months and 1 year after diagnosis. The second objective was to examine risk factors for poor sleep trajectories, including depression, anxiety, and menopausal status at the time of surgery, and to examine the extent to which antidepressants, pain, and sleep medications alleviate sleep disturbance over time. Because ovarian cancer surgery initiates menopause in premenopausal patients, we hypothesized that sleep disturbance would be worse in premenopausal patients.[14] To date, no studies have followed patients with ovarian cancer prospectively to assess how depression, anxiety, and quality of life are related to sleep disturbance over time. Depression is common among individuals with cancer[15] and has been associated with decreased sleep duration, daytime sleepiness, and nocturnal awakening among patients with breast cancer.[16] Anxiety is also commonly experienced by patients with ovarian cancer[17,18] and has been cross-sectionally associated with insomnia in this population.[19] Thus, we hypothesized that worsening depression and anxiety over time would contribute to poorer sleep over time, and that poorer sleep trajectories would contribute to poorer QOL.

MATERIALS AND METHODS

Participants

Following institutional review board approval, women older than 18 years with a pelvic mass suspicious for ovarian cancer were recruited presurgically as part of a larger prospective study examining psychosocial factors and cancer progression. Exclusion criteria included corticosteroid use in the previous month, history of previous cancer, current pregnancy, inability to accurately answer questions, comorbid condition with known effects on immune function, and nonovarian primary site. Inclusion was confirmed following surgical diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer. The final sample is described in Figure 1. At the presurgical stage, 173 women had histological confirmation of diagnosis with epithelial ovarian cancer and had complete data on relevant measures; at 6 months after diagnosis, 119 of these patients were available for assessment; at 1 year, 108 were available for assessment. Women completed psychosocial questionnaires prior to surgery and again at follow-up visits.

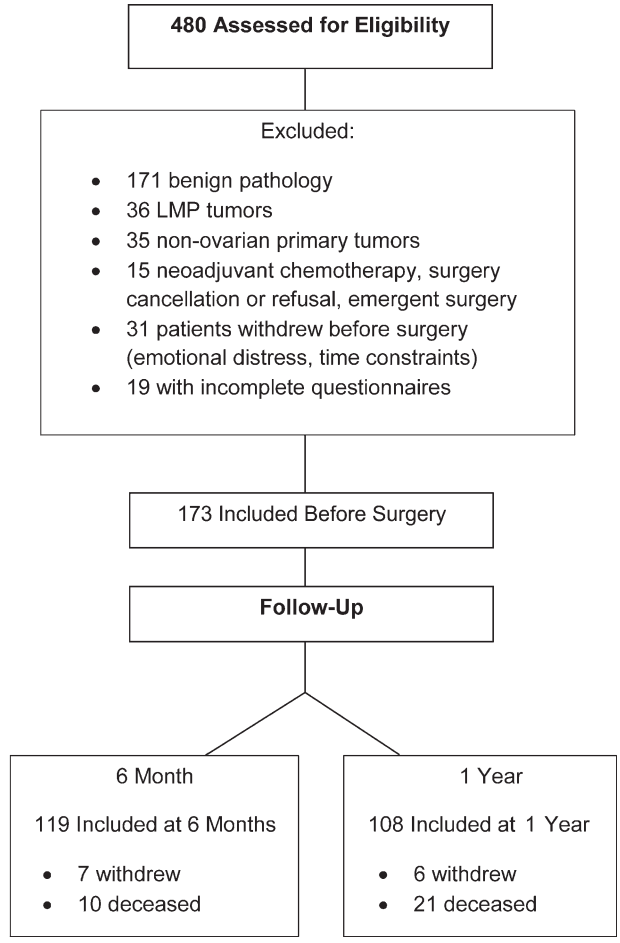

Figure 1. Patient inclusion chart of participants before surgery and at follow-up visits.

Measures

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report measure assessing types and frequency of sleep disturbances experienced over the last month.[20] Seven subscale scores are summed to yield a global score; global scores > 5 indicate poor sleep,[20] and scores > 10 are considered to indicate clinically impaired sleep (M. Hall, written communication, 2011). The scale has a diagnostic sensitivity of 89.6% and specificity of 86.5%.[21] The scale

is psychometrically sound in patients with cancer[22] and correlates with sleep log data in primary insomnia.[23]

Depressive Symptoms

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item self-report measure rating mood during the previous week. Higher scores indicate greater depressive symptomatology, with scores ≥ 16 consistent with clinical depression.[24] The CES-D is considered a valid and reliable assessment for depressive symptoms in cancer patients.[25,26]

Anxiety

The Profile of Mood States short-form (POMS-SF) is a 37-item inventory assessing 6 dimensions of mood[27] often used in research with patients who have cancer.[28,29] This study used the anxiety subscale as the indicator of anxiety.

Quality of Life

The Functional Assessment of Cancer Therapy (for ovarian patients) (FACT-O) assesses QOL in individuals with cancer. The FACT provides a total QOL score as well as subscales for physical, functional, social, spiritual, and emotional well-being from 51 items.[30] Statements are rated on a scale from 0 ("not at all") to 4 ("very much") and cued to well-being during the previous week.

Performance Status

Participants rated physical functioning in the past 7 days from 0 ("fully active") to 3 ("completely disabled") using the Gynecologic Oncology Group Performance Status measure.[31] This was used as a covariate in regression analyses.

Demographic and Clinical Information

Self-reported information on age, education, race, ethnicity, and marital status was collected prior to surgery. Clinical information including tumor stage and grade, menopausal status, and use of medications was extracted from medical records.

Statistical Analysis

Analyses were conducted using SPSS (Statistical Package for the Social Sciences), version 19.0 (SPSS, Chicago, Ill). Data distributions were examined for violations of normality and outliers. Descriptive statistics were used to examine the presence of poor sleep at baseline and 1 year. One-way analyses of variance were used to examine differences in sleep disturbance between users and nonusers of specific medications at each time point as well as between patients receiving versus not receiving chemotherapy at follow-up. Because sleep disturbance, depression, and anxiety were unrelated to chemotherapy status, this variable was not included in subsequent analyses (all P values $> .13$).

Longitudinal analyses used repeated measures mixed models (SPSS MIXED procedure). All models included disease stage, presurgical menopausal status, and the use of pain medications, anxiolytics/antidepressants, and sleep medications prior to surgery as a priori covariates. Moreover, we tested models with additional potential psychosocial, medical, and demographic covariates to determine if they exerted a significant influence on model estimations. Covariates exerting a significant influence on model estimations were retained in final models. Models examining the change in sleep quality as a function of change in depression and anxiety included change in self-reported disability as a covariate. Changes in depression and anxiety were both included in models examining the effects of distress on sleep quality to disaggregate the effects of depression versus anxiety on changes in sleep.

Covariance structure was evaluated with Wald z-tests of rho covariance parameters and comparison of Schwarz's Bayesian criterion (BIC) between models with different covariance structures, as suggested by existing literature.[32,33] First-order autoregressive covariance structures were supported for all models by significance of rho covariance parameters (all P values $< .001$) and lower BIC compared to diagonal and unstructured covariance structures. Pairwise comparisons of estimated marginal means, using a Sidak adjustment, were conducted to examine changes from baseline to 6 months and from 6 months to 1 year.

Covariates

Income; race; ethnicity; relationship status; body mass index; histopathology; presence/absence of residual tumor; use of caffeine, alcohol, and nicotine; presence/absence of chemotherapy at 6 months and 1 year; and presence of comorbid conditions such as chronic obstructive pulmonary disease, diabetes, sleep apnea, heart disease, or hypertension were nonsignificant covariates in all models (all P values $> .112$). Disease stage was not a significant predictor of change in QOL, global sleep score, depression, or anxiety (all P values $> .32$). Significant interactions of covariates with outcomes in longitudinal models will be addressed in the Results section.

RESULTS

Participant Characteristics

Participants were primarily non-Hispanic Caucasians with a mean age of 56 years. The majority of participants

had advanced stage and high-grade disease. The association between sleep disturbance and presence of ascites at the time of surgery was nonsignificant ($r = .13$, $P = .09$) (Table 1).

Medication Use and Sleep Quality

Medication use was largely similar before surgery and at 6 months and 1 year after diagnosis (Table 1). At all time points, patients using prescribed sleep or analgesic medications reported significantly worse sleep quality than those not using these medications (all P values $> .025$). There were generally no differences in global sleep quality for users and nonusers of antidepressant and anxiolytic medications (all P values $> .10$), although at 6 months, patients taking antidepressants had significantly worse sleep quality than nonusers ($P = .03$).

In addition, specific patterns of medication use were associated with psychosocial recovery over time. For example, presurgical use of pain medication was associated with less improvement in sleep quality, depression, anxiety, and QOL over time (all P values $< .038$). In contrast, sleep medication and anxiolytics/antidepressants generally had no associations with changes in these measures over time (all P values $> .15$).

Menopausal Status

At baseline, mean PSQI scores for premenopausal women were slightly worse (PSQI = 8.98, standard deviation = 3.91) than scores for postmenopausal women (PSQI = 7.25, standard deviation = 3.48), but this difference was nonsignificant. Women who were premenopausal at study entry had less improvement in sleep quality, depression, and anxiety over time than their postmenopausal counterparts (all P values $< .025$). In contrast, menopausal status was not associated with changes in QOL over time ($P = .41$).

Sleep, Depression, Anxiety and QOL Over Time

Prior to surgery, 70.7% of patients reported disturbed global sleep (PSQI > 5); of these patients, 24.3% reported global sleep poor enough to be rated "clinically impaired" (PSQI ≥ 10). During the year following surgery, significant improvements were seen in global sleep quality ($P = .035$), depression ($P < .001$), anxiety ($P < .001$), and QOL ($P < .001$). Pairwise comparisons of sleep, depression, anxiety, and QOL scores revealed significant improvement from surgery to 6 months ($P < .033$), but these factors were relatively stable between 6 months and 1 year (all P values $> .88$). Examination of the clinical meaning of these scores revealed that although global sleep quality had improved from surgery to 6 months, more than half of the sample (58%) still reported disturbed sleep and 14.3% remained in the clinically impaired range. By 1 year, almost two-thirds of patients (64.8%) still reported disturbed sleep, and 19.4% reported clinical impairment (Fig. 2). In contrast, a majority of patients

TABLE 1. Characteristics of Patients With Ovarian Cancer

Characteristic	Value
Age, years, mean (standard deviation)	59.39 (12.46)
Ethnicity	
Non-Hispanic	90.9%
Hispanic	9.1%
Race	
American Indian/Alaska Native	1.1%
Asian	0.5%
Pacific Islander	0.0%
Black/African American	2.7%
White	95.7%
Education	
Less than high school graduate	5.2%
High school graduate	29.7%
Trade school/some college	31.8%
College graduate	15.6%
Postgraduate	7.3%
Marital status	
Single	10.4%
Divorced/separated	12.2%
Widowed	11.6%
Married/living with partner	65.9%
Stage	
I	20.7%
II	6.5%
III	62.5%
IV	10.3%
Grade	
1	10.3%
2	12.4%
3	77.3%
Tumor histology	
Serous	75.4%
Endometrioid	11.2%
Mucinous	4.8%
Clear cell	3.7%
Other/unknown	4.8%
Surgical debulking	
Optimal	73.1%
Suboptimal	26.9%
Medication use before surgery	
Hypnotics	11.8%
Antidepressants	22.6%
Anxiolytics	12.4%
Pain medications	23.1%
Medication use at 6 months	
Hypnotics	11.3%
Antidepressants	12.9%
Anxiolytics	8.6%
Pain medications	17.7%
Medication use at 1 year	
Hypnotics	9.3%
Antidepressants	25.8%
Anxiolytics	13.4%
Pain medications	28.9%

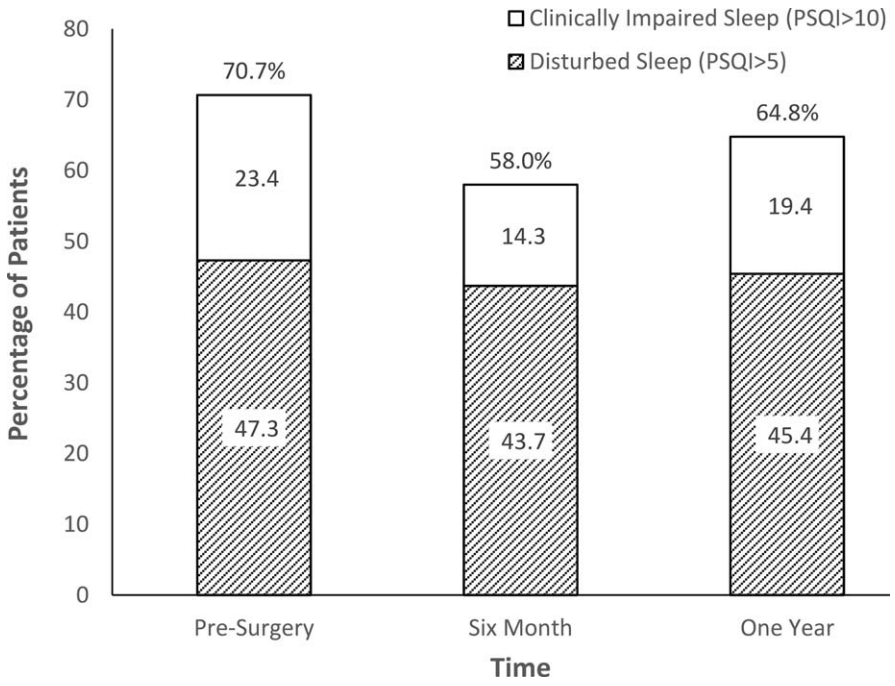

Figure 2. Proportion of patients reporting sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI) is shown before surgery and at 6 months and 1 year after diagnosis.

TABLE 2. Estimated Marginal Means of Psychosocial Measures[a]

Measure	Before Surgery	6 Month	1 Year
Global Sleep	7.26 (1.26)	6.38 (1.29)	6.52 (1.30)
CES-D	22.16 (3.42)	16.10 (3.46)	16.68 (3.49)
POMS Anxiety	11.01 (1.99)	7.42 (2.05)	7.67 (2.05)
FACT-O Total	69.95 (5.03)	78.03 (5.10)	78.93 (5.15)

[a] All values are given as means (standard error).
Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; FACT-O, Functional Assessment of Cancer Therapy (Ovarian); POMS, Profile of Mood States.

reported improvement to nonclinical levels of depression over time. Specifically, at the presurgical stage, 45% of patients reported depression scores above the CES-D clinical depression cutoff ($\geq$ 16); percentages of patients above the cutoff improved to 20.7% at 6 months and 20.9% at 1 year after surgery (Table 2).

Associations Between Changes in Distress and Changes in Sleep Quality

After adjusting for cancer stage, menopause, performance status, and medications, increased depression from surgery to 1 year was associated with less improvement in overall sleep quality ($P < .001$). Changes in anxiety were not significantly associated with changes in sleep quality ($P = .09$). However, those patients using pain ($P = .017$) or sleep medications ($P = .001$) before surgery or who had been premenopausal before surgery ($P = .027$) showed less improvement in sleep quality as their depression improved. Improved self-reported performance status was also significantly associated with improved sleep ($P = .005$).

Change in QOL as a Function of Change in Sleep

Between surgery and 1 year after diagnosis, improvements in global sleep quality were associated with improvements in QOL scores, adjusting for stage, menopausal status, and medication use ($P < .001$). Women with earlier stage disease showed more QOL improvement with improved sleep than did those with advanced stage disease ($P = .03$).

DISCUSSION

The present data demonstrate that a high proportion of women with ovarian cancer reported sleep disturbance before surgery, and these disruptions in sleep tended to persist over the first year after diagnosis, independent of whether patients were receiving chemotherapy. The proportion of patients with ovarian cancer reporting sleep disturbances at each of the measured time points was similar to rates in other oncology populations.[8,9] At all time

points, patients using either sleep or pain medication reported worse global sleep than those not taking these medications; in contrast, antidepressant and anxiolytic medication use was generally unrelated to sleep quality. Longitudinal improvements in depression were associated with improvements in global sleep, although improvements over time in anxiety were not independently associated with better sleep. Despite statistically significant improvement in global sleep between the presurgical stage and 6 months after diagnosis, mean sleep quality remained in the disturbed range over the course of the study. Furthermore, as predicted, sleep disturbance was a risk factor for diminished QOL over time, whereas improvements in sleep improved QOL.

The current study is the first to longitudinally assess sleep disturbance in ovarian cancer survivors and to demonstrate that sleep disturbance is common and persistent during the first year after diagnosis. These data thus extend previous cross-sectional descriptions of sleep problems in ovarian cancer.[18,19] These data highlight risk factors associated with disturbed sleep trajectories and reveal that sustained sleep disruptions have a significant impact on patients' overall QOL. Risk factors for sustained sleep disturbance include depression, performance status, use of pain medication, and premenopausal status. The associations between depressive mood and sleep disturbance are consistent with findings in patients with metastatic breast cancer, where depressive symptoms predict worsening of sleep over time.[16]

Potential Mechanisms

Several mechanisms may underlie disrupted sleep in cancer patients. Dysfunctions in the gamma-aminobutyric acid (GABA) system as well as in serotonin receptors have been associated with sleep disturbance and depression.[34,35] Depression has been related to heterogeneous difficulties including sleep maintenance and early morning awakening.[36] Because difficulties with sleep onset and maintenance both contribute to the global sleep disturbance score, it is possible that multiple mechanisms are operating here. Depression may also contribute to worse sleep; thus, a bidirectional mechanism may underlie the current findings.

Tumor-related processes may also contribute to both depressive symptoms and discomfort, thereby causing impaired sleep. For example, before surgery, abdominal bloating and ascites may contribute to discomfort[37] with concomitant sleep impairment. This may be reflected in the association of poor performance status with impaired sleep; however, presence of ascites per se was not associated with sleep disturbance. In addition, tumor-derived inflammatory cytokines may play a role in both sleep and depression. For example, we and others have previously reported elevations in the proinflammatory cytokine interleukin-6 (IL-6)[38,39] and links between poorer sleep quality and elevated IL-6 in patients with ovarian cancer.[40] High levels of circulating proinflammatory cytokines such as IL-6 have in turn been associated with central vegetative symptoms including fatigue, malaise, and sleep alterations, as well as depressive symptoms.[41] Thus, it is possible that tumor-derived inflammation may contribute to both depressive symptoms and sleep disturbance. Alternatively, sleep and cytokines may have a bidirectional relationship whereby alterations in sleep influence cytokine expression, and cytokines in turn have a regulatory influence on sleep.[42]

Bidirectional relationships may exist between chronic pain and sleep disturbance.[43] Specifically, chronic pain is thought to contribute to poorer sleep, which in turn may increase pain sensitivity. Although untreated pain may contribute to discomfort and inability to initiate and maintain sleep, analgesic medications may produce daytime side effects that also interfere with nighttime sleep.[44] Although there was not a direct measure of pain in the current study, the present findings support an association between pain medications and poorer sleep.

Women who were premenopausal prior to surgery reported worse sleep trajectories over time. Surgical oophorectomy induces an immediate menopause and thus may initiate the onset of classic menopausal symptoms such as nocturnal temperature fluctuations and hot flashes, both of which interfere with sleep.[14] In addition, facing a life-threatening diagnosis at a younger age and/or loss of childbearing status may give rise to sleep disturbances.

Limitations

The absence of data on premorbid sleep patterns limits our ability to determine how the sleep patterns reported here may relate to long-term disturbance. We also do not have data regarding contextual issues, such as insomnia arising from sleeping with a partner who snores. In addition, study data rely on self-report measures, which are subject to reporting biases and retrospective recall. Although polysomnography and actigraphy provide objective assessments of sleep disturbances, these technologies were deemed too intrusive for this patient population, particularly when facing surgery for a life-threatening disease. Because study design was correlational, definitive causal relationships cannot be

determined, and it is possible that sleep disturbance may lead to depression as well.[45] Because of the minimal numbers of women taking hormone replacement therapy in this sample, influences of hormone replacement on sleep could not be examined. In addition, potential third variables such as inflammation, cortisol dysregulation, and stressful life events could also be contributing to poor sleep, affective disorders, and poor QOL.

Clinical Implications

The extent of initial and sustained sleep disturbance in this population, and its impact on QOL, highlights the clinical relevance of this problem in ovarian cancer patients. These findings suggest the importance of screening for possible sleep disturbance, both at time of diagnosis, as well as during treatment and follow-up. The extent of sleep disturbance, combined with findings that hypnotics, antidepressants, anxiolytics, and pain medications do not appear to facilitate improved sleep, suggest that other effective interventions for sleep disturbance may need to be explored. For example, behavioral interventions such as cognitive behavioral therapy and mindfulness-based stress reduction have known effectiveness for insomnia[46,47] and have shown positive benefits in oncology patients.[48,49]

Conclusions

Women with ovarian cancer report sustained sleep quality disturbance up to 1 year after diagnosis, and this disturbance is associated with impaired QOL. Furthermore, depression confers increased risk for poor sleep quality in this population. These findings highlight the importance of ongoing screening for sleep disturbance in clinical cancer care. Furthermore, because pharmacological interventions appear to have limited effectiveness in this population, behavioral interventions to alleviate depression and improve sleep quality may contribute to improved QOL and decreased morbidity in this population.

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The authors made no disclosure.

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