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Sleep Disruption Among Cancer Patients Following Autologous Hematopoietic Stem Cell Transplantation

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by

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Abstract

Background: Sleep disruption is one of the most commonly reported quality of life concerns among cancer patients who have undergone hematopoietic stem cell transplantation (HSCT). Despite the high percentage of patients reporting sleep concerns, relatively little research has characterized sleep problems or explored relationships with psychological factors. In addition, no studies have used actigraph technology to characterize sleep issues among transplant recipients.

Method: Autologous HSCT recipients who were 6 to 18 months post-transplant were invited to participate. Patients completed self-report measures of cancer-related distress, fear of cancer recurrence, dysfunctional cognitions about sleep, and maladaptive sleep behaviors upon enrollment, wore an actigraph and completed a sleep log at home for 7 days, and completed a self-report measure of sleep disruption on day 7 of the study.

Results: 84 autologous HSCT recipients (age $M = 60$, 45% female) were enrolled and provided complete data. Forty-one percent of patients met criteria for sub-clinical or clinical insomnia based on patient self-report. Examination of actigraph data indicated that certain aspects of sleep were poorer than others (wake after sleep onset $M = 66$ minutes; total sleep time $M = 6.5$ hours; sleep efficiency $M = 78\%$; sleep onset latency $M = 21$ minutes). Measures of cancer-related distress, fear of cancer recurrence, cognitive distortions, and maladaptive behavioral patterns were related to subjectively reported sleep disruption, p's $< .05$, but were not related to objectively measured sleep disruption. Further examination revealed that the cognitive and behavioral factors accounted for the largest unique variance in subjectively reported sleep disruption.

Conclusion: Results from the present study suggest that many HSCT recipients continue to experience sleep disruption during the survivorship period following transplant. Cancer-specific factors, dysfunctional cognitions about sleep, and maladaptive sleep behaviors were related to self-reported sleep disruption and are ripe targets for a cognitive behavioral intervention.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an intensive therapy used to treat hematologic malignancies including leukemia, lymphoma, and multiple myeloma. Cancer patients undergoing this difficult procedure are at risk for a host of treatment-related complications and mortality (Copelan, 2006). In addition to acute treatment-related side effects, many patients continue to experience decrements in quality of life during the post-treatment period. Some of the most common quality of life concerns reported by patients following HSCT include fatigue, lack of appetite, nausea, pain, and sleep disruption (Cohen et al., 2012; Anderson et al., 2007). Sleep disruption may include problems falling asleep or staying asleep, waking earlier than planned, and/or experiencing non-restorative sleep (American Psychiatric Association, 2000). Although sleep disruption has been linked with greater distress, fatigue, depressive symptoms, and worse quality of life among cancer patients recovering from transplant (Rischer, Scherwath, Zander, Koch, & Schulz-Kindermann, 2009; Bevans, Mitchell, & Marden, 2008; Andrykowski et al., 1997), it has often been overlooked or minimized. With these considerations in mind, the current study aimed to determine the prevalence of sleep disruption following HSCT and sought to identify cancer-specific and cognitive-behavioral factors that contribute to this sleep disruption.

Prevalence of Sleep Disruption Among HSCT Recipients

Sleep disruption is one of the most common quality of life concerns following HSCT (Cohen et al., 2012; Bevans et al., 2008) with as many as 77% of patients reporting sleep difficulties (Rischer et al., 2009). In a report by Faulhaber and colleagues, insomnia was the most

prevalent sleep disorder with 23% of HSCT recipients between 1 and 10 years post-transplant reporting problems with insomnia (Faulhaber et al., 2010). Another report by Boonstra and colleagues indicates that 48% of hospitalized HSCT recipients experience subthreshold insomnia symptoms, 23% experience moderate levels of insomnia, and 3% experience severe levels of insomnia (Boonstra et al., 2011). Moreover, it has been consistently demonstrated that sleep quality is worse among HSCT recipients than healthy individuals (Pallua et al., 2010; Bieri et al., 2008; Bishop et al., 2007; Syrjala, Langer, Abrams, Storer, & Martin, 2005; Andrykowski et al., 2005; Gulbrandsen, Hjermstad, & Wisloff, 2004; Edman, Larsen, Hagglund, & Gardulf, 2001; Prieto et al., 1996). It should be noted, however, that much of what is known about sleep disruption among HSCT recipients has been gathered from studies that focus more broadly on quality of life following transplant. Consistent with this broader emphasis, many of these studies have utilized only single-item measures of perceived sleep quality. Additional methodological limitations that characterize much of this research include small sample sizes and exclusive reliance upon self-report with no use of currently available actigraph technology.

Actigraphy involves the objective measurement of movement by means of an accelerometer that records and averages wrist movements (Ancoli-Israel et al., 2003). It has been successfully used to measure sleep/wake patterns in breast and gynecologic cancer patients (Liu et al., 2013; Ancoli-Israel et al., 2006; Jim et al., 2011) as well as patients with advanced cancer (Ma, Chang, & Lin, 2014). For example, studies of breast cancer patients have shown that chemotherapy administration is likely to result in shortened time asleep at night (approximately 6 hours), longer time awake at night (approximately 2 hours), and frequent and longer napping during the day (approximately 1 hour) (Liu et al., 2012; Ancoli-Israel et al., 2006; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007). Moreover, prior research indicates that objective

measurements of sleep using actigraphy do not always align with self-reports of perceived sleep quality (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008; Miaskowski & Lee, 1999). Surprisingly, a review of the literature did not identify any published studies that have used actigraphy to measure sleep following HSCT. To address this gap in knowledge, the present study used both a self-report measure (the Insomnia Severity Index [ISI]) and actigraphy to measure sleep disruption following HSCT.

Trajectory of Sleep Disruption Following HSCT

The focus of many reports examining sleep among HSCT recipients has been on investigating the trajectory of sleep quality in the immediate recovery period following the transplant as well as during the post-treatment survivorship period. Research on the trajectory of sleep problems indicates that sleep quality declines from the period prior to transplant through hospital discharge and eventually returns to pre-transplant levels between hospital discharge and day 100 post-transplant (Rischer et al., 2009; Anderson et al., 2007; Hacker & Ferrans, 2003). Although sleep quality tends to return to pre-transplant levels relatively quickly, sleep is considerably compromised even prior to transplant with a majority of HSCT recipients endorsing sleep difficulties before transplantation (Bevans et al., 2008). Moreover, sleep quality appears to remain relatively stable and does not further improve following day 100 post-transplant suggesting that sleep difficulties are not only highly prevalent, but also are a persistent problem among HSCT survivors (Frodin, Borjeson, Lyth, & Lotfi, 2011; Worel et al., 2002; Bush, Donaldson, Haberman, Dacanay, & Sullivan, 2000; Andrykowski et al., 1999; Kopp et al., 1998; Andrykowski et al., 1997; Andrykowski, Bruehl, Brady, & Henslee-Downey, 1995). Therefore, an argument could be made that examining sleep disruption between 6 and 18 months post-

transplantation would provide a snapshot of these concerns during a time in which they tend to be relatively stable.

Predictors and Correlates of Sleep Disruption

Prior studies examining risk factors for sleep disruption have generally focused on demographic and clinical predictors, factors that are typically not amenable to intervention. For example, older age (Watson et al., 2004; Sherman et al., 2003) and female sex (Heinonen et al., 2001; Hjermstad et al., 1999; Prieto et al., 1996) have been reported to be associated with worse sleep quality among HSCT recipients. There is also evidence to suggest that sleep disruption may differ for patients undergoing an autologous (receive own cells) or allogeneic (receive donor cells) transplant (Diez-Campelo et al., 2004; Hjermstad et al., 2004), indicating it may be useful to examine aspects of sleep disturbance among these two populations separately. However, less is known about potentially modifiable risk factors for sleep disturbance among HSCT recipients. Intrusive thoughts and worry have been linked to sleep disruption in non-cancer populations (Espie, 2007). This may be particularly relevant among cancer patients who are often subjected to additional cancer-specific concerns such as worry about cancer recurrence and intrusive thoughts about their cancer. There is some evidence linking cancer-specific factors such as cancer-related distress and fear of cancer recurrence to sleep disruption (Dupont, Bower, Stanton, & Ganz, 2014; Taylor et al., 2012). For example, intrusive thoughts were linked to more disturbed sleep among women with breast cancer four weeks post-treatment; however, intrusive thoughts did not predict sleep trajectory up to one year later (Dupont et al., 2014). In another study, cancer-related intrusive thoughts were identified as a risk factor for sleep disturbance among a small sample of African American breast cancer survivors (Taylor et al., 2012). The same study found that fear of cancer recurrence did not significantly contribute to disturbed sleep

above and beyond intrusive thoughts and concluded that automatic thoughts such as cancer-related distress may play a more important role in predicting sleep disturbance than specific concerns about recurrence (Taylor et al., 2012). Given the lack of knowledge about modifiable risk factors among HSCT recipients and the potential importance of cancer-specific variables, the present study investigated the extent to which cancer-related distress and fear of cancer recurrence are related to sleep disruption following HSCT.

Cognitive and Behavioral Factors Related to Sleep Disruption

A strong body of evidence exists regarding the contribution of cognitive and behavioral factors to sleep disruption. This evidence has shown that dysfunctional sleep-related thoughts and behaviors contribute to the perpetuation of insomnia symptoms (Edinger & Means, 2005; Morin, Kowatch, Barry & Walton, 1993). Several recent studies have examined the extent to which cognitive and behavioral factors associated with sleep disruption in other populations apply in the context of cancer. For example, dysfunctional beliefs and attitudes about sleep, sleep monitoring, and maladaptive sleep behaviors have been linked to an increased risk for insomnia incidence in a mixed cancer sample (Savard, Villa, Ivers, Simard, & Morin, 2009). Moreover, self-reported insomnia symptoms were found to be significantly reduced among breast cancer survivors receiving individual cognitive-behavioral therapy for insomnia (which included behavioral components such as sleep restriction and cognitive restructuring of patients' dysfunctional beliefs and attitudes about sleep) compared to women in a delayed treatment control group (Fiorentino et al., 2009). Relationships between cognitive-behavioral factors and sleep disruption have not been investigated among HSCT recipients. Given the known persistence of sleep disruption among HSCT recipients and the extant sleep literature suggesting cognitive-behavioral factors are capable of perpetuating sleep disruption, these relationships

could be especially important to study among this population of patients. Therefore, in addition to cancer-specific factors, this study determined the extent to which cognitive and behavioral factors contribute to sleep disruption following HSCT. Specifically, the study investigated the contribution of dysfunctional beliefs and attitudes about sleep, sleep effort, and inhibitory sleep habits to sleep disruption following HSCT.

Aims & Hypotheses

Aim 1. To characterize the prevalence and severity of sleep disruption measured both subjectively and objectively among cancer patients following autologous HSCT.

Aim 2. To characterize the relationship between self-reported and objective indices of sleep disruption following HSCT. Based on prior literature (Ancoli-Israel et al., 2006; Dhruva et al., 2012; Grutsch et al., 2011), a modest relationship (observed as a medium effect size) between subjectively- and objectively-reported sleep disruption was predicted.

Aim 3. To investigate whether cancer-specific factors (i.e., cancer-related distress and fear of recurrence) are related to sleep disruption following HSCT. Patients with greater cancer-related distress and fear of cancer recurrence were expected to report greater sleep disruption measured either subjectively or objectively following HSCT.

Aim 4. To investigate whether cognitive and behavioral factors are related to sleep disruption following HSCT. Based on prior research on the importance of cognitive-behavioral factors for insomnia (Edinger & Means, 2005), patients who report greater dysfunctional beliefs and attitudes about sleep, sleep effort, and inhibitory sleep habits were expected to report greater sleep disruption measured either subjectively or objectively following HSCT.

Aim 5. To explore the incremental variance accounted for by cancer-specific factors and cognitive and behavioral factors to sleep disruption following HSCT.

Method

Participants

The study sample was comprised of adults who underwent an autologous HSCT at the H. Lee Moffitt Cancer Center for treatment of a hematologic disease. Participants were recruited between May 2015 and February 2016. Eligibility criteria required that participants: 1) be diagnosed with a hematologic malignancy, 2) have undergone an autologous HSCT approximately 6 months to 18 months prior to study enrollment, 3) be ≥18 years of age, 4) have no history of other cancers other than non-melanoma skin cancer, 5) have no evidence of disease progression at the time of study enrollment, 6) be able to speak and read English, and 7) be able to provide informed consent.

Procedures

Study eligibility was determined via consultation with physicians, clinical staff, and medical record review. Eligible patients returning to clinic for a follow-up appointment within the next six months were approached during their clinic visit and had the study protocol explained to them. Those wishing to participate were asked to sign an informed consent form. They were then given an initial and a follow-up questionnaire, an actigraph, a sleep log, and a postage-paid envelope. Participants were asked to complete the initial questionnaire assessing demographics, cognitive and behavioral factors related to sleep disruption, and cancer-specific factors the day of their clinic visit. Eligible patients who expressed interest in the study but who were not able to start the study the day of their clinic visit received study materials via mail. Participants were instructed to wear the actigraph for seven consecutive 24-hour periods and

complete a sleep log daily to document napping periods, sleep medication use, bedtime, and wake time. The sleep log was used as an aid in computing objective sleep disruption parameters. Participants completed a follow-up questionnaire assessing sleep disruption on the seventh and final day of the study so that both outcome variables (subjective and objective sleep disruption) covered the same time frame. Participants were instructed to return all study materials in the postage-paid envelope. Relevant clinical information, including cancer/hematologic diagnosis, conditioning regimen, number of inpatient hospital days, medications, and disease status, was collected via medical record review.

Measures (see Appendix)

Demographic characteristics. Participants completed a standardized self-report form assessing demographics including age, sex, race, ethnicity, education, income, marital status, employment status, as well as height and weight as part of the initial assessment. Participants also completed a self-report version of the ECOG performance status scale and reported on recent use of medications to promote sleep.

Cancer-related distress. Participants completed the intrusion subscale of the Impact of Events Scale (IES) on the first day of the study. The intrusion subscale of the IES is a 7-item self-report measure assessing psychological stress during the past week in response to a particular event. Each item is rated on a 4-point Likert scale where 0 indicates no bother and 3 indicates the patient is often bothered by a particular difficulty. The intrusion subscale of the IES has demonstrated good validity and internal consistency (Horowitz, Wilner, & Alvarez, 1979), with a reliability coefficient of $\alpha = 0.89$ in the current study.

Fear of cancer recurrence. Participants completed the Fear of Cancer Recurrence Inventory (FCRI) on the first day of the study. The FCRI is a 42-item self-report measure

assessing fear or worry that cancer will return or progress. This study focused on severity of fear surrounding the possibility of cancer recurrence as well as functional impairments related to fear of cancer recurrence. The FCRI has demonstrated excellent construct validity, temporal stability, and strong internal consistency (Simard & Savard, 2009), with a reliability coefficient of α = 0.94 for the severity subscale and α = 0.93 for the functional impairment subscale in the present study.

Dysfunctional beliefs and attitudes about sleep. Participants completed the abbreviated version of the Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) questionnaire on the first day of the study. The DBAS-16 is a 16-item, self-report scale assessing faulty beliefs, worries, and attentional biases surrounding sleep-related cognitions (Morin, Vallieres, & Ivers, 2007). Each item is rated on an 11-point Likert scale where 0 indicates the patient strongly disagrees with the statement and 10 indicates the patient strongly agrees. A total score is calculated by averaging the items with a higher score indicating more dysfunctional beliefs and attitudes about sleep. The DBAS-16 has demonstrated adequate internal consistency α = 0.79, temporal stability, and concurrent validity among patients with insomnia (Morin et al., 2007) and has been used with cancer patients (Savard et al., 2009). Internal consistency was very good in the present study with a reliability coefficient of α = 0.92.

Sleep effort. Participants completed the Glasgow Sleep Effort Scale (GSES) on the first day of the study. The GSES is a 7-item scale assessing the extent to which individuals engage in effortful attempts to sleep such as a need for control over sleep and trying too hard to sleep (Broomfield & Espie, 2005). Each item is rated on a 3-point Likert scale ranging from "very much true" to "not at all true." The GSES had demonstrated adequate psychometric properties with good internal consistency, α = 0.77 among non-cancer patients with insomnia (Broomfield

& Espie, 2005). The GSES demonstrated good internal consistency in the present study with a reliability coefficient of $\alpha = 0.81$.

Sleep hygiene. Participants completed the Sleep Hygiene Index (SHI) on the first day of the study. The SHI is a 13-item self-report scale assessing the extent to which individuals practice healthy behaviors that facilitate sleep and avoid behaviors that interfere with sleep (Mastin, Bryson, & Corwyn, 2006). The SHI is assessed on a 0 to 4-point Likert scale with 0 indicating the patient never engages in a particular behavior and 4 indicating the patient always engages in a particular behavior. The SHI has demonstrated improved internal consistency ($\alpha = 0.66$) over prior instruments assessing sleep hygiene and good test-retest reliability (Mastin et al., 2006). Internal consistency of the SHI was adequate in the present study with a reliability coefficient of $\alpha = 0.70$. Participants also completed the Sleep Habits Scale (SHS) on the first day of the study. The SHS is a 22-item measure assessing the extent to which patients engage in habits that facilitate or interfere with sleep during the previous week (M. Rumble, personal communication, March 10, 2014). Items are rated on a 0 to 4-point Likert scale with 0 indicating a sleep habit (e.g., I take time to relax before I go to bed; I watch the clock when I am awake in bed) occurred 0 times per week and 4 indicating a sleep habit occurred 6 or more times per week in the past week. This scale was recently developed by researchers at the University of Wisconsin-Madison, and its psychometric properties have not been previously assessed; the SHS demonstrated very good internal consistency in the present study with a reliability coefficient of $\alpha = 0.90$.

Self-reported sleep disruption. Participants completed the 7-item Insomnia Severity Index (ISI) on the seventh and final day of the study. The ISI is a self-report measure assessing the nature, severity, and impact of insomnia during the past two weeks (Bastien, Vallieres, & Morin,

2001). For the purposes of the present study, the recall period was revised to the past week. Each item is rated on a 0 to 4-point Likert scale where 0 indicates no problems and 4 indicates severe problems. The total ISI score ranges from 0 to 28 and is calculated by summing the seven items. Total ISI scores are interpreted as follows: 0-7 indicates no clinically significant insomnia, 8-14 indicates subthreshold insomnia, 15-21 indicates clinical insomnia (moderate severity), and 22-28 indicates clinical insomnia (severe). The ISI has demonstrated good internal consistency (Bastien et al., 2001), with a reliability coefficient of $\alpha = 0.91$ in the present study.

Objective sleep disruption. The Philips Respironics Actiwatch-Score (Philips Healthcare, Andover, MA) was used to objectively quantify sleep patterns. Participants wore the actigraph on their non-dominant wrist continuously for a seven-day period. The Actiwatch is 43 x 23 x 10 mm in size, weighs 16 g, and contains a highly sensitive piezoelectric accelerometer (sampling rate of 32 Hz) that records and averages wrist movements over every minute. Data from the Actiwatch were downloaded and analyzed using ActiLife v6.10.1 (ActiGraph, LLC, Pensacola, Florida). Sleep indices were calculated in combination with patient sleep logs using Philips Actiware 6 software to determine: sleep efficiency or the percentage of time spent sleeping in relation to time spent in bed, sleep onset latency (SOL) or the amount of time taken to fall asleep, wake after sleep onset (WASO) or minutes awake after an extended period of sleep, and total sleep time (TST) or the time spent asleep at night (Berger et al., 2008). Of these, sleep efficiency served as the primary objective outcome of interest. Sleep efficiency was operationalized as scored total sleep time divided by the rest interval duration minus total invalid time and multiplied by 100. SOL was operationalized as the time elapsed between the start of a given rest interval and the following sleep start time, in minutes. WASO was operationalized as the total number of epochs between the start time and the end time of the given sleep interval scored as

wake by Actiware software multiplied by the epoch length in minutes. Finally, TST was operationalized as the time elapsed between the start time and the end time of the given interval scored as sleep by Actiware software multiplied by the epoch length in minutes.

Statistical Analyses

Data analyses were performed using SAS Version 13.2 (Cary, NC). Data were first examined for normality of distribution and outliers. Mean imputation was used to correct for scales with sporadic missing items. Multiple imputation was used for scales for which all items were missing. The number of imputed data points for any scale for which all items were missing never exceeded three participants per scale. To address Aim 1, participants' scores on the ISI were summarized with descriptive statistics (e.g., means, standard deviations, and frequencies) to characterize the prevalence and severity of sleep disruption. Descriptive statistics were also generated using actigraphy data for the major sleep indices that could be derived. To address Aim 2, Pearson correlation coefficients were calculated to test the hypothesized relationship between subjective sleep disruption, as measured by the ISI total score, and objectively measured sleep disruption, as measured by the sleep efficiency score. The resulting correlation/effect size was evaluated in relation to the anticipated effect size ($r = 0.30$).

Following this, medical and sociodemographic variables were examined for their relation to subjective and objective sleep disruption outcomes. Variables found to be significantly ($p < .10$) related to outcome measures were included as covariates in all subsequent analyses. To address Aim 3, separate hierarchical multiple regression analyses for the subjective and objective outcome measures described above were conducted to test hypotheses regarding whether the following cancer-specific factors are related to sleep disruption after accounting for relevant demographic and clinical variables: (a) cancer-related distress as measured by the IES; and (b)

fear of cancer recurrence as measured by the FCRI. To address Aim 4, hierarchical multiple regression analyses were also conducted to test hypotheses regarding whether each of the following cognitive and behavioral factors was related to sleep disruption after accounting for relevant demographic and clinical variables: (a) dysfunctional beliefs and attitudes about sleep as measured by the DBAS; (b) sleep effort as measured by the GSES; and (c) sleep habits as measured by the SHI. Scales with missing data were corrected by conducting regression analyses within a multiple imputation framework.

Finally, to address Aim 5, hierarchical multiple regression analyses were conducted to explore the incremental variance accounted for by cancer distress factors and cognitive and behavioral factors in predicting sleep disruption following transplantation. Specifically, a series of successive models were built in order to look at the incremental variance accounted for by cancer-specific distress and the incremental variance accounted for by cognitive and behavioral factors over and above clinical demographic factors. In the first model, all significant demographic and clinical factors from univariate analyses were entered in the first step. In the second model, significant demographic and clinical factors were entered in the first step and cancer-specific factors were entered in the second step. This model indicated whether cancer-specific factors accounted for additional variance over and above the influence of relevant covariates. In the third model, significant demographic and clinical factors were entered in the first step followed by cognitive and behavioral factors in the second step. This model indicated whether cognitive and behavioral factors accounted for additional variance over and above the influence of relevant covariates. In the fourth and final model, significant demographic and clinical factors were entered in the first step, cancer-specific factors were entered in the second step, and cognitive and behavioral factors were entered in the third step. This model yielded the

total variance accounted for by cancer-specific factors and cognitive and behavioral factors when all factors were entered in the model.

Based on previous research (Savard et al., 2009; Rumble et al., 2010), effect sizes for relationships of interest in the present study were expected to be medium (i.e., r = 0.30). A power analysis using G*Power 3.1 indicated that a sample of 84 patients would be needed to detect significance of a medium effect (r = 0.30) with a Type I error rate of 0.05 (two-tailed) and power of 0.80. A second power analysis indicated that a sample of 98 would be needed to detect significance of a medium effect ($f^2 = 0.15$) with a Type I error rate of 0.05 and a power of 0.80 in hierarchical multiple regression analyses testing six predictors such as might be included in the exploratory analyses for Aim 5.

Results

Recruitment and Patient Characteristics

Based on *a priori* power analyses, we aimed to recruit 98 HSCT recipients. Figure 1 depicts the flow of patients through the study. Overall, 273 patients were screened for study eligibility, 189 were deemed eligible, and 124 received a phone call asking if they would be interested in hearing more about the study when they returned to clinic for a follow-up appointment. Of these, 8 indicated they were not interested. Therefore, 116 patients were approached in clinic. Of these, 16 refused participation (primarily due to having too much going on or simply not being interested) and 100 agreed to participate and signed the study consent form (overall participation rate = 81%).

Of the 100 patients who agreed to participate, one dropped out before receiving the baseline study materials, four were ineligible after consent due to disease progression, and three completed baseline study materials but were then lost to follow-up. A total of 92 patients completed both the baseline and follow-up assessments. Of those 92 patients, one reported performing shift-work and was not included in the final sample. Seven patients had less than 3 days of actigraph data primarily due to actigraph recording failure or the patient declining to wear the actigraph. Descriptive statistics and a t-test revealed that the ISI total score did not differ between the 7 patients without actigraph data ($M = 5.86$, $SD = 4.38$) and the 84 patients with actigraph data ($M = 7.07$, $SD = 5.58$), $t(8) = 0.69$, $p = .51$. Therefore, the 7 patients without actigraph data were excluded and the final sample consisted of 84 HSCT patients.

See Table 1 for patient demographic and medical characteristics. Patients were an average of 60 years of age. The majority were male (55%), non-Hispanic (94%), white (87%), and were highly educated with 68% of patients reporting at least some college. The majority of patients were diagnosed with multiple myeloma (69%), while 19% were diagnosed with non-Hodgkin lymphoma, 10% with Hodgkin lymphoma, and 2% with amyloidosis. At the time of study participation, patients were an average of 350 days post-transplant and the majority reported they were not currently taking a sleeping medication (61%).

Sleep Disruption among HSCT Recipients

Table 2 depicts descriptive statistics including means and standard deviations for subjective and objective sleep disruption. On average, subjective reports of sleep disturbance based on the ISI were relatively low (M = 7.07, SD = 5.58). Prevalence rates were as follows: 59% of HSCT patients were classified as good sleepers (ISI total scores $\leq$ 7), 30% had subthreshold insomnia symptoms (ISI total scores of 8 to 14), 10% met criteria for moderate clinical insomnia (ISI total scores of 15 to 21), and 1% met criteria for severe clinical insomnia (ISI total scores $\geq$ 22). Analysis of the objective indices of sleep disruption revealed that, on average, patients took 20 minutes to fall asleep at night, spent one hour awake during the night after initially falling asleep, and spent 6.5 hours asleep at night. Overall, patients had a sleep efficiency of 78%.

Table 3 depicts descriptive statistics for cancer-specific factors and cognitive and behavioral factors. On average, patients reported relatively low levels of intrusion (M = 10.53, SD = 8.21) and functional impairment from fear of cancer progression (M = 5.82, SD = 6.28). Patients self-reported their fear of cancer progression as moderate in severity (M = 15.67, SD = 8.04). Patients endorsed some dysfunctional beliefs and attitudes about sleep (M = 3.87, SD =

2.07) as well as sleep effort (M = 3.52, SD = 2.86). Finally, patients reported relatively low levels of unhealthy sleep habits (SHI M = 26.44, SD = 5.39; SHS M = 26.89, SD = 9.15).

Table 4 depicts relationships among subjective and objective measures of sleep disruption. HSCT recipients' subjective reports of sleep disruption were significantly associated with objectively calculated total sleep time, p = .04. However, subjectively reported sleep was not significantly associated with any of the other objective measures of sleep disruption, all p's > .05. Among objective measures of sleep disruption, sleep efficiency was related to sleep onset latency, wake after sleep onset, and total sleep time, p's < .001. Sleep onset latency was related to wake after sleep onset, p = .01, but not total sleep time, p = .12. Finally, wake after sleep onset was related to total sleep time, p = .04.

Univariate Analyses with Sleep Disruption

Examination of relationships between sociodemographic and medical characteristics revealed that age, ethnicity, and time since transplant were the only variables significantly associated with any of the sleep disruption outcomes, p's < .10 (see Table 5). Specifically, age and ethnicity were related to sleep efficiency and sleep onset latency. Given that there were only four Hispanic patients in the sample, we opted not to control for ethnicity. Also, given that time since transplant was only related to total sleep time and was unrelated to any other outcome, we opted not to control for time since transplant. Therefore, age was the only factor controlled for in subsequent analyses. Table 6 depicts relationships between cancer-specific factors, cognitive and behavioral factors, and sleep disruption. Regression analyses controlling for age revealed that IES intrusion, FCRI severity, and FCRI functional impairment were all related with subjective reports of sleep disruption (ISI total score), all p's < .04. None of these cancer-specific factors were significantly related with any of the objective indices of sleep disruption, all p's > .07.

Additional univariate analyses revealed that dysfunctional beliefs and attitudes about sleep as measured by the DBAS, sleep effort as measured by the GSES, and sleep hygiene as measured by both the SHI and the SHS were related to subjective reports of sleep disruption (ISI total score), all *p*'s < .03. None of these cognitive and behavioral factors were significantly related with any of the objective indices of sleep disruption, all p's > .05.

Multivariable Analyses with Sleep Disruption

Factors that were significantly ($p < .10$ for demographic and clinical factors and $p < .05$ for all other factors) related to subjective sleep disruption in univariate analyses were entered in the multivariable models predicting subjective sleep disruption as measured by the ISI. Variance inflation factors were examined and found to be in the appropriate range indicating multicollinearity was not a problem. Therefore, all factors remained in the models. Table 7 depicts results from the four multivariable models. In the first model, age was entered and accounted for 1% of the variance. In the second model, IES intrusion, FCRI severity, and FCRI functional impairment scores were entered after age and accounted for an additional 7% of the variance compared to the first model, $F(4, 78) = 1.48$, $p > .05$. In the third model, DBAS, GSES, SHI, and SHS scores were entered after age and accounted for an additional 27% of the variance compared to the first model, $F(5, 77) = 5.78$, $p < .001$. In the fourth and final model, age was again entered in the first step, IES intrusion, FCRI severity, and FCRI functional impairment were entered in the second step, and DBAS, GSES, SHI, and SHS scores were entered in the third step. All factors entered together in the same model accounted for 34% of the variance in subjective sleep and account for additional variance compared to the first model, $F(8, 74) = 4.63$, $p < .001$. No significant relationships were found between cancer-specific factors, cognitive and

behavioral factors, and objective sleep outcomes in univariate analyses, therefore multivariable analyses were not conducted with any of the indices of objective sleep disturbance.

Discussion

The present study sought to characterize subjective and objective sleep disruption and examine relationships between cancer distress, fear of cancer recurrence, cognitive, and behavioral factors and sleep disruption among autologous HSCT recipients between 6 and 18 months post-transplant. A majority of patients were characterized as good sleepers based on self-report, however, 41% of patients met criteria for subclinical or clinical insomnia. While estimates of the prevalence of sleep disruption in HSCT patients vary widely, results from the present study are generally in line with estimates in the survivorship period following HSCT (Nelson et al., 2014; Faulhaber et al., 2010; Diez-Campelo et al., 2004; Watson et al., 2004). In the only other study to administer the Insomnia Severity Index to transplant patients, Boonstra and colleagues (2011) found that only 26% of transplant patients could be classified as healthy sleepers in the acute period post-transplant. Comparisons to data from the present study suggest that a large percentage of patients' insomnia naturally remits in the time between hospital stay and extended survivorship. Examination of actigraphy data revealed that patients spent an average of 6.5 hours in bed at night, took approximately 20 minutes to fall asleep, and spent over an hour awake during the night after falling asleep. Moreover, average sleep efficiency was only 78%, which is below the recommended 85% often used as a cut point to indicate healthy sleep (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Descriptive reports from the actigraphy data are novel and add to a previous body of literature, which has heretofore focused on subjective reports of sleep. Taken together, these descriptive data indicate that a large minority of HSCT patients could benefit from interventions targeting sleep problems.

It was hypothesized that subjective reports of sleep disruption would be moderately correlated with objective sleep disruption. With the exception of total time patients spent asleep at night, this hypothesis was not supported. At least two possible explanations for this exist. First, it is possible that subjective and objective sleep indices are not related in general and there is mixed support for this (Buysse et al., 2008; Lauderdale et al., 2008). A second possibility is that patients with health conditions may be biased in their reporting of sleep issues. Among patients with chronic or life-threatening illness, response shift, which refers to a patient's change in internal standards, change in values, or reconceptualization of a given construct, is common (Sprangers & Schwartz, 1999). This shift in perspective may at least in part account for the lack of a relationship observed between subjective and objective sleep disturbance among patients with health conditions. If this is the case, this underscores the importance of including objective measures of sleep in clinical assessment with the understanding that patients who report good sleep but demonstrate poor objective sleep quality may also benefit from a sleep intervention. Although self-report has often been shown not to be strongly correlated with actigraphy, actigraphy has been shown to correlate with polysomnography, the gold-standard for measurement of sleep and wake states, at a rate of about 90% agreement (Coke, Kripke, Gruen, Mullaney, & Gillin, 1992). Therefore, actigraphy represents an attractive, more feasible option for obtaining objective descriptions of sleep among HSCT patients given the cancer, treatment, and symptom burden already placed on these patients. While speculating on the lack of a relationship between subjective and objective sleep disruption is interesting, the design of the current study precludes us from providing definitive conclusions on this issue.

The hypothesis that cognitive and behavioral factors would be associated with subjective and objective sleep disturbance was partially supported. Significant relationships were found

between cognitive and behavioral factors and self-reported sleep disruption, but not with objective measures of sleep disruption. These findings regarding self-reported sleep disruption are in line with a large and growing body of evidence examining cognition distortions and maladaptive sleep behaviors as perpetuating factors of insomnia (Savard et al., 2009; Edinger 2005). Findings further suggest that HSCT patients' cognition distortions and maladaptive sleep behaviors could be modified to improve sleep. Similarly, the hypothesis that cancer distress and fear of cancer recurrence would be associated with subjective and objective sleep disturbance was also partially supported with the same pattern of findings; cancer-specific factors were associated with subjective but not objective sleep disruption. These findings regarding subjective sleep disruption are in line with prior literature examining these relationships in other forms of cancer and suggest that cancer-related distress and fear of cancer recurrence represent additional modifiable targets in addressing sleep concerns (Savard et al., 2009).

Finally, cognitive factors, including dysfunctional beliefs and attitudes about sleep and sleep effort, contributed greater incremental variance in predicting subjective sleep compared to cancer-related distress when all factors were entered into an exploratory multivariable model. This pattern of results indicates that it may be patients' distorted cognitions, more than cancer-related distress or unhealthy sleep behaviors, that are the primary drivers of their self-reported sleep disruption. If this is the case, it may be particularly important to change distorted cognitions in addressing HSCT patients' sleep complaints.

The present study was limited by its cross-sectional assessment of sleep, which prevented any examination of how relationships between cancer distress, fear of cancer recurrence, distorted cognitions, maladaptive behaviors, and sleep disruption change over time. The study was also limited by the lack of ethnic and racial diversity of its participants, which limits

generalizability to other groups. In addition, while the study was adequately powered for most of the statistical analyses, it was underpowered for the multivariable analysis, which could have affected study results from that analysis. The final limitation noted has to do with the way sleep efficiency (percentage of time asleep in relation to time in bed) was calculated. While the present study included sleep onset latency, time spent asleep at night, and wake after sleep onset in the denominator of the calculation of sleep efficiency, it has been suggested that the denominator in this calculation should also include time attempting to sleep after final awakening (Reed & Sacco, 2016). Future studies should revise sleep logs to be able to collect this information. Despite these limitations, the present study adds to a strong foundation of prior literature examining perpetuating factors of insomnia. Moreover, this study investigated not only subjective but also objective sleep disruption among a homogenous group of autologous transplant recipients, which to the best of our knowledge has not been done in HSCT recipient survivorship.

Results from this study suggest a number of future directions. First, future studies investigating sleep disruption among HSCT recipients should consider using a longitudinal design in order to gain a clearer picture of how cancer-related distress, fear of cancer recurrence, distorted cognitions, and maladaptive sleep behaviors relate to sleep disruption over time. This is particularly important given the natural waxing and waning pattern of insomnia symptoms over time and given that transplant does not occur in a vacuum and patients may be dealing with a number of other physical and psychosocial issues that often fluctuate over time. Second, further investigation into the relationship between subjectively reported sleep and objectively measured sleep is warranted. It may be particularly important to determine whether clinicians are missing

out on treating patients with objective sleep issues due to response shift and patients underreporting sleep problems.

Third, future research investigating the efficacy of Cognitive Behavioral Therapy for Insomnia (CBT-I) is of central importance. While a majority of autologous HSCT recipients in the present study had no clinically significant sleep issues, a large minority of these patients continued to have insomnia symptoms or insomnia syndrome in the survivorship period. Results from the present study suggest that many of these patients have dysfunctional cognitions about sleep and unhelpful behaviors around bedtime, which are ripe targets for a sleep intervention. Specifically, maladaptive cognitions and behaviors have previously been identified as factors that perpetuate or maintain sleep disruption over time (Spielman & Glovinsky, 1991). CBT-I uses stimulus control, sleep restriction, cognitive restructuring, and sleep hygiene to target factors that perpetuate sleep issues. Moreover, CBT-I is a recommended treatment for clinical sleep issues in cancer patients (Savard & Savard, 2013; Schutte-Rodin et al., 2008; Edinger & Means, 2005). The relationships between sleep and maladaptive cognitions and behaviors among HSCT recipients described in the present study suggest that HSCT recipients may benefit from a CBT-I intervention. A number of barriers to pursuing CBT-I in the context of cancer have been identified including a shortage of trained professionals, time and costs of treatment delivery, and patient transportation burden and costs (Savard & Savard, 2013). These concerns have produced a growing body of research examining different modes of treatment delivery including individual therapy, group therapy, and interactive web-based treatment (Savard, Ivers, Savard, & Morin, 2014; Zhou, Partridge, & Recklitis, 2016). HSCT recipients have a uniquely high treatment and symptom burden; however, with these new modes of delivery comes hope that this potentially efficacious treatment for sleep issues could be more widely disseminated. Given the large body

of evidence demonstrating that sleep concerns are a prevalent and problematic issue often persisting into the survivorship period following HSCT, there is a critical need for research investigating interventions for sleep disturbance among these patients. Therefore, research investigating the efficacy of CBT-I among HSCT recipients should be prioritized.

Table 1. *Demographic and Medical Characteristics*

Characteristic	
Age, years	
M	59.67
SD	11.91
Gender, No. (%)	
Male	46 (54.8)
Female	38 (45.2)
Ethnicity, No. (%)	
Not Hispanic	79 (94.0)
Hispanic	4 (4.8)
Missing	1 (1.2)
Race, No. (%)	
White	73 (86.9)
Nonwhite	11 (13.1)
Marital Status, No. (%)	
Married	64 (76.2)
Not married	20 (23.8)
Education, No. (%)	
High school or less	26 (31.0)
College or more	57 (67.8)
Missing	1 (1.2)
Employment, No. (%)	
Work full-time or part-time	26 (31.0)
Retired	32 (38.1)
Other	25 (29.7)
Missing	1 (1.2)
Income, No. (%)	
< 40K	31 (36.9)
≥ 40K	36 (42.9)
Missing	17 (20.2)
Cancer type, No. (%)	
Multiple Myeloma	58 (69.0)
Hodgkin lymphoma	8 (9.5)
Non-Hodgkin lymphoma	16 (19.1)
Amyloidosis	2 (2.4)

Table 1 (Continued)

Characteristic	
Functional Status, No. (%)	
4	40 (47.6)
3	35 (41.7)
2	6 (7.1)
1	1 (1.2)
Missing	2 (2.4)
Sleeping Medication, No. (%)	
Yes	32 (38.1)
No	51 (60.7)
Missing	1 (1.2)

Note. *SD* = standard deviation.

Table 2. *Subjective and Objective Sleep Disruption Descriptive Statistics*

Outcomes	Score range possible	*M (SD)*	Min	Max
ISI total score	0 – 28	7.07 (5.58)	0	22
SE, %	0 – 100	78.03 (9.44)	42.33	91.64
SOL, min	0 – 1440	21.20 (16.66)	1.29	77.86
WASO, min	0 – 1440	66.03 (34.29)	23.00	196.71
TST, min	0 – 1440	390.49 (72.60)	128.14	543.14

Note. ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time.

Table 3. *Cancer-Specific Factors and Cognitive and Behavioral Factors Descriptive Statistics*

Predictors	Number of items	Score range possible	Reliability Coefficient	*M (SD)*	Min	Max
IES Intrusion	7	0 – 35	0.89	10.53 (8.21)	0.00	31.00
FCRI Severity	9	0 – 36	0.94	15.67 (8.04)	0.00	31.50
FCRI Impairment	6	0 – 24	0.93	5.82 (6.28)	0.00	23.00
DBAS	16	0 – 10	0.92	3.87 (2.07)	0.25	9.25
GSES	7	0 – 14	0.81	3.52 (2.86)	0.00	11.00
SHI	13	13 – 65	0.70	26.44 (5.39)	14.00	41.00
SHS	22	0 – 88	0.90	26.89 (9.15)	6.47	45.29

Note. IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index, SHS = Sleep Habits Scale.

Table 4. *Relationships Among Subjective and Objective Sleep Disruption (N = 84)*

	ISI total score	SE	SOL	WASO	TST
ISI total score	1.0				
SE	-0.19	1.0			
SOL	0.08	-0.55***	1.0		
WASO	0.13	-0.77***	0.27*	1.0	
TST	-0.23*	0.65***	-0.17	-0.23*	1.0

Note. Pearson correlation coefficients depicted in table. ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 5. *Relationship Between Demographic and Medical Factors and Sleep Disruption*

	ISI total score		SE		SOL		WASO		TST	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age	-0.13	.25	**0.19**	**.08**	**-0.25**	**.02**	-0.05	.65	0.14	.20
Gender	0.11	.32	0.07	.55	0.03	.80	-0.11	.30	0.07	.56
Ethnicity	0.16	.17	**0.24**	**.04**	**-0.30**	**.008**	-0.06	.64	0.10	.37
Race	0.00	1.00	0.09	.44	-0.10	.38	0.04	.74	0.16	.16
Marital Status	-0.03	.77	-0.02	.89	0.13	.24	-0.06	.58	0.05	.66
Education	0.01	.90	0.08	.49	-0.01	.89	0.03	.76	0.03	.79
Employment	-0.15	.17	0.01	.96	0.00	.99	-0.02	.84	-0.08	.47
Income	0.05	.68	0.11	.39	0.00	1.00	-0.16	.21	0.10	.41
Cancer Type	0.09	.42	0.16	.15	-0.18	.10	-0.09	.41	0.03	.79
Time Since Transplant	-0.17	.12	0.09	.43	-0.09	.41	0.03	.81	**0.24**	**.03**

Note. Relationships between continuous variables are based on Pearson correlation coefficients while relationships between dichotomous and continuous variables are based on point-biserial correlation coefficients. Significant relationships ($p < .10$) are bolded. ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time.

Table 6. *Relationships Between Cancer-Specific Factors, Cognitive and Behavioral Factors, and Subjective and Objective Sleep Disturbance After Controlling for Age*

	ISI total score			SE			SOL			WASO			TST		
Psychological Factors	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*
IES Intrusion	**0.07**	**0.27**	**.02**	0.08	0.18	.10	0.07	-0.04	.73	0.01	-0.08	.47	0.06	0.18	.11
FCRI Severity	**0.07**	**0.24**	**.03**	0.04	0.11	.32	0.07	.11	.32	0.01	-0.04	.71	0.05	0.18	.10
FCRI Impairment	**0.10**	**0.31**	**.005**	0.05	-0.15	.18	0.10	0.19	.08	0.01	.10	.39	0.02	-0.04	.75
DBAS	**0.29**	**0.54**	**<.001**	0.03	0.01	.91	0.08	0.15	.17	0.00	0.01	.94	0.03	0.10	.36
GSES	**0.46**	**0.68**	**<.001**	0.03	-0.09	.42	0.07	0.15	.15	0.01	0.05	.65	0.02	-0.04	.71
SHI	**0.07**	**0.27**	**.02**	0.03	0.02	.89	0.12	-0.24	.98	0.02	-0.11	.33	0.03	-0.14	.23
SHS	**0.24**	**0.49**	**<.001**	0.04	0.09	.42	0.06	0.08	.48	0.01	-0.04	.71	0.03	0.08	.47

Note. Significant p values are bolded. ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time, IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index, SHS = Sleep Habits Scale.

Table 7. *Multivariable Hierarchical Regression Models with Subjective Sleep Disruption*

Variable	R^2	ΔR^2	β	*p*
Model 1	0.01	-	-	-
Age	-	-	-0.10	.37
Model 2	0.08	0.07	-	> .05
Age	-	-	0.02	.88
IES Intrusion	-	-	0.15	.27
FCRI Severity	-	-	0.03	.82
FCRI Impairment	-	-	0.23	.07
Model 3	0.28	0.27	-	< .001
Age	-	-	0.04	.61
DBAS	-	-	0.15	.18
GSES	-	-	0.49	<.001
SHI	-	-	0.03	.75
SHS	-	-	0.14	.20
Model 4	0.34	0.33	-	< .001
Age	-	-	0.06	.48
IES Intrusion	-	-	0.01	.89
FCRI Severity	-	-	-0.16	.18
FCRI Impairment	-	-	0.14	.16
DBAS	-	-	0.15	.19
GSES	-	-	0.49	<.001
SHI	-	-	0.03	.75
SHS	-	-	0.17	.12

Note: ISI = Insomnia Severity Index, SE = Sleep Efficiency, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, TST = Total Sleep Time, IES = Impact of Events Scale, FCRI = Fear of Cancer Recurrence Inventory, DBAS = Dysfunctional Beliefs and Attitudes about Sleep, GSES = Glasgow Sleep Effort Scale, SHI = Sleep Habits Index, SHS = Sleep Habits Scale.

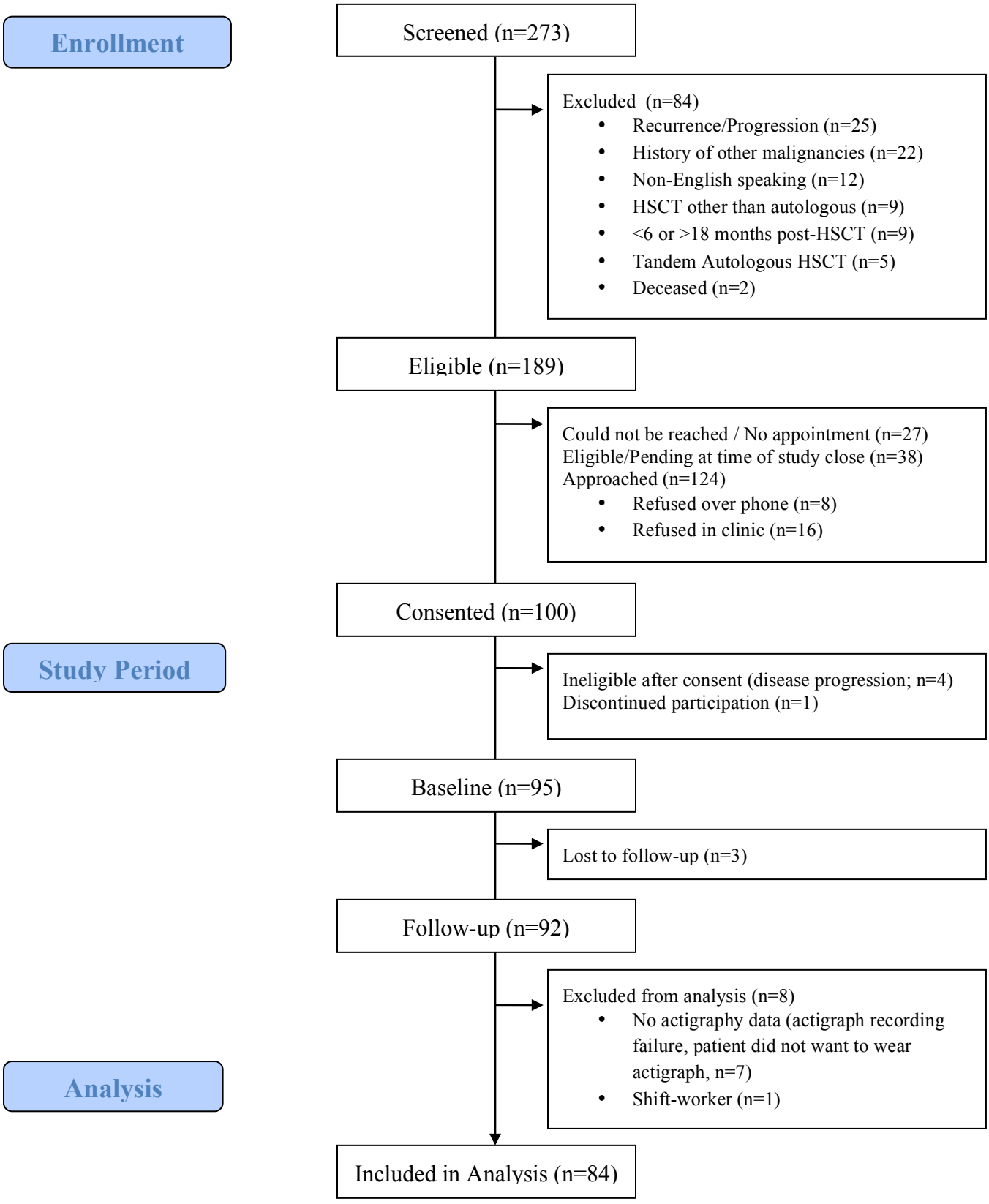

Figure 1. Flow Diagram

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