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Sleep Disruption and Cancer Incidence in a Southeastern Veteran Population

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SLEEP DISRUPTION AND CANCER INCIDENCE IN A
SOUTHEASTERN VETERAN POPULATION

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ABSTRACT

Sleep disruption influences biological processes that can facilitate carcinogenesis. However, studies examining the relationship between sleep disruption and cancer risk have been inconclusive. This retrospective cohort study used de-identified data from the Veterans Administration (VA) electronic medical record to test the hypothesis that sleep disorder diagnoses among Veterans seeking care in the Southeast United States Service Network are associated with increased risk for cancer of the prostate, breast, colorectum, or total cancer (1999-2010, N=663,869). Sleep disorders were defined as patients with an in- or out-patient diagnosis as specified by the International Classification of Sleep Disorders. Cancer cases were defined as patients identified in the VA Tumor Registry during the follow-up period with a histologically confirmed primary tumor (any stage, excluding benign or *in situ* tumors). The relationship between a prior sleep disorder diagnosis and cancer incidence was summarized using extended Cox regression analyses with sleep disorder diagnosis as a time-varying co-variate. Sleep disorders were identified among 56,055 (8%) of eligible patients; sleep apnea (46%) and insomnia (40%) were the most common diagnoses among those with sleep disorders. There were 18,138 cancer diagnoses in the study population (42% prostate, 12% colorectal, 1% female breast, 46% other). Hazard ratios (HRs) for any cancer diagnosis ranged from 1.34 to 1.69 among patients with a diagnosed sleep disorder relative to those without sleep disorders, after adjustment for the effects of age, sex, state of residence, and marital status. There was a tendency for increased cancer risks with increasing sleep disorder duration (1-year HR:

1.04, 95% confidence interval [CI]: 1.03-1.06), (5-year HR: 1.23, 95% CI: 1.16-1.32), or

(10-year HR: 1.52, 95% CI: 1.34-1.73). Results among patients with only sleep apnea,

insomnia, or all other sleep disorder diagnoses were similar to those for all sleep

disorders combined. Results from this study suggest that Veterans with a diagnosed sleep

disorder have an increased cancer risk, and that risk increases with increasing sleep

disorder duration. Optimal sleep and appropriate sleep disorder management represent

modifiable risk factors that may facilitate cancer prevention.

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CHAPTER 1

INTRODUCTION

Sleep has been established as a critical pillar to good health. Short term effects of insufficient sleep or poor quality sleep include fatigue, malaise, and decreased cognitive function [1]. Chronic illnesses such as diabetes, cardiovascular disease, obesity, and hypertension, as well as psychiatric disease, including post-traumatic stress disorder, mood disorders, and depression, have been associated with sleep disorders in epidemiologic studies [2-9]. In addition, both long (more than 9 hours) and short sleep (less than 5 hours) have been linked with higher overall mortality [4]. Impaired immune function and metabolic pathways related to obesity have both been proposed as plausible biological models that may explain how poor sleep can lead to cancer development [10]. The Veteran population, which represents 20 percent of the United States population [11], is a predominantly male, middle-aged population with a high occurrence of chronic and psychiatric disease that increase medical care costs [5, 12]. In this study we sought to characterize the potential relationship between sleep disorder diagnoses and cancer incidence among veterans in the southeastern United States (US).

The relationships between sleep disruption and mortality or chronic disease risk have been evaluated, but studies evaluating potential links between sleep disruption and cancer risk are limited. The role of circadian disruption as a potential breast cancer (BrCA) risk factor has not been carefully evaluated [13-15]. Fatigue and sleep disruption

occur among some cancer patients prior to initiation of chemotherapy [16-19], or among cancer patients without anxiety [17], suggesting that these symptoms may not be associated with the trauma and stress of a cancer diagnosis and may possibly precede tumor development. Sleep disruption is common among shift workers and shift work has been associated in past studies to cancers of the breast, prostate, and colon [20-26], which has led to its designation as a probable human carcinogen [27, 28]. However, it is unclear whether sleep disruption per se, or related biological processes, or a combination of these perturbations actually increases cancer risk among shift workers or in other populations with disrupted sleep. Associations between sleep disruption, immune system dysregulation and inflammation have been described [7]. Chronic inflammation is a risk factor for some cancer types, particularly colon cancer [29, 30]. The demonstrated association of sleep disorders and sleep disruption and several different types of chronic disease as well as increases in mortality [2-9], the high rates of self-reported sleep disruption among Veterans [5, 6], and the fact that cancer is the second leading cause of mortality in the United States [31-33], provides a rationale for studying the relationship between sleep disorder diagnoses and cancer incidence. Recent studies have primarily evaluated breast cancer risk and sleep disruption with varying results, indicating that continued research is relevant and needed to determine the relationship and biologic mechanism that could be present. Many studies have used self-reported sleep disorder status as opposed to clinical sleep disorder diagnosis, which is less reliable for assessment of exposure.

The Veterans Health Administration (VHA) maintains an extensive electronic medical record system that is available for medical and epidemiologic research. This

database allows for cost-effective and timely examination of this study's hypothesis that patients with sleep disorders are at increased risk of cancer (breast, prostate, colorectal, other, or total) compared to those with no sleep disorder history. The study used de-identified data to perform a retrospective cohort study of 663,869 Veterans in the Southeastern United States (VISN-7) who were seen at VHA facilities between January, 1999 and July, 2010. The specific aims are presented below:

AIM 1: Using descriptive epidemiology, determine the frequency and severity of sleep disorder diagnosis among patients in the VISN-7 network from 1999 through 2010.

AIM 2: Conduct a retrospective cohort study to test the hypothesis that individuals with sleep disorder diagnoses are at an increased risk for cancers of the female breast, colon, prostate, other sites combined, and all cancers combined.

AIM 3: Determine whether VHA patients with an increased duration or severity of sleep disorder diagnosis are at greater risk for the development of breast, colorectal, prostate, other, or all cancer combined compared to those with less severe, or shorter sleep disorder duration.

CHAPTER 2

BACKGROUND

Short sleep of less than five to six hours per night or long sleep of more than nine hours per night can increase mortality and chronic disease risk [4, 34-37]. A "U-shaped" relationship has been identified for sleep duration in relation to mortality, which is similar to other risk factors for chronic disease and mortality, such as physical activity, diet, and overall poor health [38]. Cancer is a leading cause of death in the US, and has been linked to many of the same lifestyle risk factors [4, 38]. The relationship between sleep disruption and cancer or overall mortality has been evaluated [4, 34, 36, 38, 39], although few studies have examined the association between diagnosed sleep disorders, or sleep disorder duration or severity, in relation to cancer [40].

EPIDEMIOLOGY OF PROSTATE CANCER

Prostate cancer (PCa) is the most common noncutaneous cancer in the world [41, 42]. It also is the most common cancer type and the second leading cause of cancer related death after lung cancer among men in the US [43]. The 5-year survival rate when PCa is caught in the early stages is 100% [41, 42], yet the US population is still disproportionately affected by this incidence of disease and mortality. The consumption of a western diet high in saturated fats has been noted to increase the risk of cancer and impact the progression of disease [44] though diet alone does not explain PCa cancer rate.

PCa affects African-American (AA) men disproportionally to European-American (EA) men with incidence of disease just over 1.5 times more likely [42] and mortality approximately twice as likely [45]. The elderly are also disproportionally affected by disease with roughly 65% of cases occurring in persons over 65 years of age [42]. A family history of prostate cancer also significantly increases the risk of disease [46]. With developed countries being so highly affected by disease, a better understanding of treatment and co-morbidities of PCa is needed to decrease the global mortality and impacts of this disease.

EPIDEMIOLOGY OF BREAST CANCER

Breast cancer (BrCa) is one of the most disparate cancers among racial groups. EA women are typically diagnosed with lower stage and grade of disease with more favorable outcome than occurs with AA [47-50] and Hispanic women [47]. BrCa survival in the United States (US) has been shown also to be strongly linked to socio-economic status (SES) [51-56] such that women with less education, who are unemployed, are more likely to be diagnosed at a later stage of disease [57-62]. The late stage of diagnosis among those with lower SES is likely due to lower rates of mammography screening and slower follow-up to abnormal screenings due to a lack of health care access or similar barriers to care [50, 63-66]. AA women are also disproportionally affected by disease with higher grade tumors being diagnosed at younger ages, and with shorter survival times, yet even after adjustments for tumor characteristics, a poorer outcome can still be expected [52, 54, 67]. Women with extremely dense breast tissue or who with a close relative with a history of breast cancer have also been found to be at a significantly increased risk of breast cancer [68]. Current

oral contraceptive use, nulliparity, or first birth at 30 years or older have all been associated with an increased risk of breast cancer as well [68]. Breastfeeding, birth of 3 plus children, and first menarche at or after 15 years of age have all been shown to decrease the risk of cancer [68]. Since known risk factors only account for a fraction of breast cancer cases, more research is needed on other possible risk factors such as sleep disorders.

EPIDEMIOLOGY OF COLON CANCER

Colon cancer is the third most commonly diagnosed cancer and the third leading cause of cancer related deaths among men and women in the US [43]. Decreases in colon cancer incidence and mortality have occurred in the United States due to widespread use of colonoscopies as a primary prevention and detection method [69, 70]. There is a known increase in incidence with age and a strong link between healthy lifestyles and disease prevention [71, 72]. Diets high in fat and calories and those low in fiber, vitamin C, and calcium are known to increase cancer risk. In addition, high consumption of alcohol and frequent smoking has also been shown to increase risk. Lifestyles that include limited physical activity are at an increased risk as well [73]. Those affected by colon cancer tend to have more comorbid conditions then those who are not [74]. Differences in incidence and severity have also been noted between racial groups [42, 75-78]. AAs with colon cancer tend to be diagnosed at later stages of disease, which can be at least partially attributed to variations in screening practices, treatments after diagnosis, and follow-up surveillance. Though much is known and understood about colon cancer, approximately 1 in 27 cases occur within 36 months of a colonoscopy, the primary

prevention method [74]. This leads to the question of what other biologic factors, including sleep disorders, may influence the development of disease.

EPIDEMIOLOGY OF SLEEP DISRUPTION

The average human spends about approximately a third of their life sleeping which is essential for the body's physiological balance and the brain's memory consolidation [79]. The optimal amount of sleep that has been associated with decreased morbidity [80-83] and mortality [36, 84-88] is 7 to 8 hours. Sleep is pivotal to regulation of the body's endocrine [81, 83], cardiovascular [81], and metabolic processes [82]. An increase in the risk of accidents in and out of the workplace, absenteeism from school and workplace, and total health care costs has been associated with sleep disturbances [89]. Depression and anxiety disorders are commonly found in sleep disrupted patients, though the order in which these diseases affect a patient is debated as both are commonly linked to other co-morbidities [90-92]. Low SES has been found to be common among people likely to get less than 7 hours of sleep per night, bringing into question whether sleep disruption impacts are associated with chronic diseases that tend to be more common among those with low SES relative to those in higher SES categories [84, 87, 88]. Melatonin produced primarily by the pinal gland and has been found to be related to various aspects of the body's circadian regulation. Altered melatonin production may impact sleep, which can affect both the sleep/wake cycle as well as the quality of sleep achieved [93, 94].

Sleep disruption is present in approximately 75% of patients suffering from Post-Traumatic Stress Disorder (PTSD) which is about 20% higher than those without PTSD [95-98]. Among Vietnam Veterans, approximately 90% self-reported sleep disruption in

varying forms including difficulty falling asleep and staying asleep [99, 100]. Among Veterans without PTSD, only 63% had trouble with sleep disruption though this was still higher than the civilian population (at 53%) [99, 100]. Sleep disturbances may be prolonged by PTSD and may generally predate PTSD, possibly contributing to later development under stressful conditions [101]. Rapid eye movement (REM) sleep in particular is considered to be essential for emotional processing and daily brain functioning and is thought to be most disrupted by PTSD [102, 103]. Due to this, sleep disruption while suffering from PTSD can exacerbate both disorders.

SLEEP DISRUPTION AND CANCER

Few studies have evaluated the potential association between sleep disruption and cancer development, and results among those studies, have been inconsistent. No association between sleep duration and cancer was found in several studies [104, 105]. Results from the Finnish Twin Study indicated that long sleep was protective while short sleep was not found to have any effect on cancer risk [106]. An increased risk of cancer also has been noted among those with short sleep and those with both non-apnea sleep disorders and apnea sleep disorder [40, 107-109]. To compound the complexity and variation of these results, the cancer specific analyses completed to date have equally varying results.

An increased risk of colon cancer has been associated with both long sleep [110, 111] and short sleep duration [111, 112]. Odegaard et al. also noted a protective effect among those with 6-8 hours of sleep duration per night [113], whereas Thompson et al. noted no association between quality of sleep and colon cancer [112].

Breast cancer studies have had the most consistency of any cancer type with the majority of studies finding no association between duration, quality, or sleep disruption and BrCA risk [104, 110, 114-116]. However, a study of Chinese women in Singapore [117] and the Ohaski cohort of Japanese women [118] both found an inverse association between postmenopausal breast cancer risk and long sleep duration. McElroy, et al. also found that long sleep was associated with a moderate increase in BrCA risk while short duration had no association [119]. PCa studies are more limited with finding so far suggesting that sleep disruption and short sleep duration both contribute to increased cancer risk [120, 121].

High estrogen levels are a risk factor for breast cancer and in some cases low estrogen levels have been found in women with elevated melatonin concentrations [122]. This is noteworthy since melatonin has been linked to the quality and duration of sleep achieved [94]. A Singapore study supports previous work that hypothesized that melatonin's possible protective effect on breast cancer risk may be estrogen related [117, 122]. Melatonin has also been hypothesized to have a similar inverse relationship with prostate cancer as well [121, 123-125]. In vitro studies in both breast and prostate cancer cells lines showed that melatonin has an antiproliferative effect [125]. The Ohsaki Cohort of Japanese men found a significant inverse relationship between sleep duration and prostate cancer risk [118]. In addition, men who reported trouble falling asleep or staying asleep have also be found to be at a greater risk of PCa incidence [120]. These and other [10, 126] studies are limited and leave in question the biologic mechanism for an effect of sleep disruption on cancer development, but they suggest that altered melatonin secretion may be involved.

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SHIFT WORK AND CANCER

Shift workers have been shown to have significant sleep loss, fatigue, and circadian disruption, and they have higher rates of injuries and accidents, disrupted lifestyles, and higher risks of gastrointestinal, reproductive, and cardiovascular disease [6, 127-129]. Shift workers also have been shown to have changes in melatonin levels, immune system function, cortisol, and pro-inflammatory cytokine secretion, which are all known to increase cancer risk [6, 129]. The International Agency for Research on Cancer (IARC) has designated shift work as a probable human carcinogen [27] based off recent research showing that shift workers are at an increased risk of colon, breast, prostate, endometrial, and lymphatic system cancers [20-26, 28, 130].

CO-MORBIDITIES AND OTHER RISK FACTORS

Long-term effects of sleep deprivation include obesity, hypertension, reduced parasympathetic tone, increased pro-inflammatory cytokine secretion, increased oxidative stress, and increased evening cortisol and insulin levels [6]. These effects are thought to be a form of allostatic load caused when the body is deprived of sleep over time and contributes to the development of chronic disease [6]. Depression and mood disorders have also been shown to be strongly linked to sleep disruption and sleep quality [92] and quantity have been associated to changes in the immune response and inflammation [131, 132]. Several experimental studies have shown that even as little as half a night of sleep loss can increase blood pressure in patients with hypertension and pre-hypertension and others have linked sleep disruption with cardiovascular disease [133-136]. Long sleep (>8 hours) increases risk of stroke by as much as 50% among those 31 and older compared to those with 6-8 hours of sleep [137]. The body of evidence supporting the chronic health,

immune, and mood disorders that are associated with sleep disruption is convincing to continue to study the effects of poor sleep quality and quantity on other adverse health outcomes including cancer.

VISN-7 AND VETERANS

The Veterans Integrated Service Network-7 (VISN-7) is the medical network that serves approximately 1.3 million veterans. VISN-7 includes medical centers and outpatient clinics covering veterans care in most of Alabama, Georgia, and South Carolina [135]. Recent VA statistics indicate that about 40% of veterans are 65 and older, the median age of all living veterans is 60, and 88% are male, making the population accessing the Veterans Health Administration (VHA) services a predominantly aging-male population [11]. The VISN-7 has seen one of the highest growth increases among all the country's VISN groups. This increase has created a strain on the type and amount of care the medical centers are capable of providing [135].

The VHA uses an electronic medical record system that has been in place for over a decade called VistA (Veterans Health Information Systems and Technology Architecture) [138]. Since 1997, this includes a Computerized Patient Record System (CPRS) which provides a single interface between all medical centers to provide tracking of all medical care given to each patient [137]. The VISN-7 includes 9 tertiary care medical centers, 14 community based outpatient clinics (CBOCs), and 18 primary care clinics [135]. VISN-7 has a large percentage of patients in the chronic care category ranking this center sixth largest among the 21 VISN centers in chronic care patients [135].

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CHAPTER 3

METHODS

This study used data in the VISN-7 Veteran's health database to conduct a retrospective cohort study to determine if veteran's with sleep disorders are at an increased risk of cancer. All statistical analysis was performed using SAS 9.3 (SAS Institute, Inc, Cary, NC). IRB approval from the Dorn Department of Veterans Affairs Medical Center (DVAMC) and the University of South Carolina was obtained. The data was requested from and stored based on VISN-7 data warehouse protocols. The association of sleep disorders and a later cancer diagnosis was evaluated using Cox Extended regression models. Adjustments were made for co-morbidities, gender, age, race, and state of residence. The possibility of a dose-response relationship was evaluated with consideration of length of treatment and severity of sleep disorder in relation to cancer diagnosis.

STUDY POPULATION

A de-identified file of all active medical records between January, 1999 and July, 2010 was obtained from the VISN-7 Corporate Data Warehouse. To be included, patients must have been seen at least once at a VA medical facility or clinic during this time frame. The data extraction from the VISN-7 Corporate Data Warehouse was requested in the format outlined in Table 3.1. Any patient with a cancer diagnosis prior to the beginning of the study period in 1999 was excluded. Cancers of the small intestine

(ICD-9 152), skin (ICD-9 172-173), uterus (ICD-9 179 and 182), cervix (ICD-9 180), thyroid (ICD-9 193), lips, oral cavity, and pharynx (ICD-9 140-149), Hodgkin's lymphoma (ICD-9 201), as well as *in situ* (ICD-9 230-234) and benign (ICD-9 210-229) tumors were excluded. In addition, patients younger than 18 years of age or those without age information were excluded. Original data extraction (N=698,871) was performed by a VISN-7 data manager. After all exclusions were applied, 663,869 eligible patients were included in the analysis. Survival time was defined as the time from entry into the cohort until cancer diagnosis or censoring. Partients who were only seen once at a VISN-7 facility were assigned a total time of 0 months and considered censored at the time of entry.

First occurrence of outpatient sleep disorder diagnosis was identified by ICD-9 codes for sleep disturbance (ICD-9 780.50-59), nonorganic sleep disorders (ICD-9 307.40-49), organic insomnia (ICD-9 327.00-09), organic hypersomnia (ICD-9 327.10-19), organic sleep apnea (ICD-9 327.20-29), and circadian rhythm sleep disorders (ICD-9 327.30-39) based on American Academy of Sleep Medicine International Classification of Sleep disorders (ICSD) categories [139]. Sleep disorder cases were defined as patients with at least two occurrences of the diagnosis 30 or more days apart. Covariate information available for the analysis included: age, gender, marital status, co-morbid diagnoses, medication use, medical procedures combat deployment information, income, and other physician noted factors. Data for combat deployment, smoking status, income, and body mass index were not available. Body mass index is a known deficiency in the VHA data with weight being more consistently recorded in the medical record then height [140]. Co-morbid diagnoses included: diabetes, cardiovascular disease,

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hypertension, and stroke, as well as depression, PTSD, and other mental disorders. The state of residence was assigned to each participant to adjust for spatial variation in social-economic or other risk factors. Veteran Medicare data were merged by the VISN-7 data manager using the social security number to assign race information, when available, for each study participant based on VA Information Resource Center (VIReC) recommendations [141]. VIReC identified this as best practice for race data completeness as it improves data completeness to 75% or higher with use of the VA Medicare data source [142].

Cases of prostate (ICD-9 185), female breast (ICD-9 174), colorectal (ICD-9 153-4), and all combined cancers cases diagnosis were obtained. All combined cancer cases included prostate (ICD-9 185), female breast (ICD-9 174), colorectal (ICD-9 153-4), lung (ICD-9 162), pancreatic (ICD-9 157) kidney (ICD-9 189), brain (ICD-9 191), bladder (ICD-9 188), liver (ICD-9 155), ovarian (ICD-9 183), esophageal (ICD-9 150), and gastric (ICD-9 151) cancers. Cancer diagnosis was validated by the VISN-7 data manager by merging these data with the national VA tumor registry by social security number to confirm the cancer diagnosis and verify that it was a primary cancer.

AIM 1 – DESCRIPTIVE EPIDEMIOLOGY OF SLEEP DISORDERS

The frequency and distribution of all variables was to determine the general characteristics of the population. A chi-squared distribution was used to evaluate whether categorical population characteristics differed among those with and without sleep disorders, and t-tests were used to evaluate continuous data. Sleep disorder frequency and distribution was used to characterize rates of diagnosis, types of disorders, and place of diagnosis for the population. An alpha level of 0.05 was used to determine statistical

significance. Sleep disorder treatment and duration of sleep disorder diagnosis were evaluated to determine if they influenced the relationship between sleep disorder diagnoses and cancer risk. The cumulative sleep disorder treatment variable was developed by combining counts of sleep disorder prescriptions, sleep procedures and surgeries into a single continuous variable. Participants were grouped into a four-level categorical variable based the distribution of tertiles among those with values greater than zero: no treatment (0 prescriptions), mild level of treatment (1 prescription), moderate level of treatment (2-18 prescriptions), and high level of treatment (19-1150 prescriptions). A categorical variable for sleep disorder duration was created in a similar manner by grouping those with sleep disorder duration of 0 months into a single group and then creating tertiles among years of sleep disorder duration (0, 1-26, 27-62, 63-149 months).

Sleep disorders were grouped into the following categories: all sleep disorders, insomnias, sleep apneas, and all others. Race was grouped into European-American (white), African-American (black), and other/unknown due to a low number of individuals in any one race category other than European-American and African-American. Co-morbid conditions (e.g. mental disease, diabetes, hypertension, stroke, cardiovascular disease) were defined using an indicator variable if the condition occurred at least once during the study period. For analysis purposes, the co-morbid conditions of hypertension, stroke, and cardiovascular disease were combined into a single categorical variable if any of them existed in a patient's medical history. Age at entry was grouped into a categorical variable (18-34 years, 35-44 years, 45-54 years, 55-64 years, or ≥65 years).

AIM 2 AND AIM 3 – RETROSPECTIVE COHORT STUDY DATA ANALYSIS

The relationship between sleep disorder diagnosis, treatment, or duration and cancer risk was initially evaluated using the Kaplan Meier (Proc Lifetest) procedure in SAS to develop cumulative survival statistics for each exposure and cancer site at three, five, seven, ten and 12.5 years of follow-up. The data for female breast cancer cases in conjunction with those in the 'other' sleep disorder group were too sparse for evaluation. Kaplan Meir plots were used to graphically display the proportion of those without the cancer endpoint among participants with and without sleep disorders and across levels of duration or treatment. Because of evidence that the proportionality assumption was not met (because of crossing or merging Kaplan Meier curves), subsequent analyses were performed using the Cox extended model with time-dependent variables in SAS. The Phreg procedure was applied with the /rl option to estimate hazard ratios and 95% confidence intervals for each combination of sleep disorder and cancer outcome. Cancer cases were censored at the time of diagnosis.

Possible covariates for inclusion in the Cox proportional hazards models were initially evaluated using individual Kaplan Meier estimates to identify variables associated with each cancer endpoint for subsequent inclusion in the multivariable extended Cox proportional hazards analyses. Hazard ratios and 95% confidence to test the hypotheses stated in Aims 2 and 3 were performed for each combination of the sleep disorder exposure and cancer endpoint using crude, adjusted, and stratified models. Covariates were included in a multivariable (adjusted) Cox proportional hazards models if their inclusion resulted in at least a 10 percent change in the effect estimate for sleep disorder, or if their association with the cancer endpoint was statistically significant.

Interaction terms with the exposure variable were used to evaluate variables for effect modification including race and co-morbid disease (diabetes, mental disorders, cardiovascular disease, hypertension, and stroke). If evidence effect modification was observed, these covariates were excluded from the base models and instead subsequent analyses were stratified by these covariates. This was the case for the co-morbid conditions.

The extended Cox method used for Aim 2 allows for a more accurate evaluation of the relationship between exposure and outcome when the proportional hazards assumption is not met. The method included sleep disorder diagnosis as a time-varying covariate. Using this method, sleep disorder diagnosis was not assessed until the point in time that it was diagnosed (the first of the two occurrences at least 1 month apart). This method was adapted from a previously described study that assessed the exposure at the point of occurrence, but not prior to it [143]. This approach allowed for the assessment of the association between sleep disorders and cancer incidence continuously over time instead of only once.

Aim 3 attempted to evaluate the potential dose-response relationships between of sleep disorder severity and cancer incidence using two derived variables that served as surrogate measures. First, the total time since sleep disorder diagnosis was used to capture the duration of the sleep disorder diagnosis. Second, the total number of sleep disorder prescriptions, procedures and surgeries was used to define a 'cumulative treatment' variable. Time since diagnosis of a sleep disorder and the cumulative number of treatments were included as continuous variables in separate Cox Extended hazard

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analyses. Duration of sleep disorder diagnosis was used in a time-varying model where it was evaluated for its dose-response in relation to cancer incidence.

Sleep disorder duration provided for an assessment of the possible latencies between sleep disorder diagnoses and cancer incidence, and served as a method for avoiding reverse causality. A time-varying model was developed where sleep disorder exposure was assessed after diagnosis of sleep disorder disease at each failure point in the model [47]. This allowed for a more accurate assessment of the latency period between sleep disorder diagnosis and cancer incidence.

The relationship between cumulative sleep disorder treatment and cancer incidence could not be modeled in the same way as the relationship between sleep disorders duration and cancer risk since a sleep disorder diagnosis was not required for the assessment of treatment. Because some of these prescriptions and procedures can also be used to treat other conditions, it was essential that all participants be evaluated to prevent biased results. Therefore, in this analysis, all study participants were evaluated to determine whether the frequency of prescriptions and procedures was associated with a cancer diagnosis, regardless of their sleep disorder status. A Cox extended model was used where the cumulative treatment was multiplied by the total time in the study to account for the lack of proportionality noted previously.

Stratified analysis were conducted on all final models for sleep disorder and cancer incidence, sleep disorder duration and cancer incidence, and sleep disorder treatment and cancer incidence to account for the potential independent association of race or co-morbid conditions on sleep disorder exposure and cancer incidence. The models were stratified by each of the co-morbid condition and race separately and results

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were evaluated. Similar co-morbid conditions were grouped together into mental disorders and mental retardation as one group and hypertension, stroke, and cardiovascular disease in a second group. The co-morbid condition of diabetes was used independently.

Table 3.1: VISN-7 Data Warehouse Variable Request List

Variable Type	Description
Gender	Male Female Unknown
Race/Ethnicity	Race/Ethnicity information from linked Medicare database for complete ethnicity information
Age	Age at entry into dataset
Death Status	Whether the participant was alive or dead at the point of censoring.
State_Residence	State Name at entry into dataset
Provider	Type of Medical Facility: CBOC VAMC Clinic
Sleep Disorder	ICD-9 Code list of diagnosed sleep disorders including: Each disease is coded as own category or column with 1 = Yes / 0 = No. Sleep Disturbance 780.50-59 Nonorganic sleep disturbances 307.40-49 Organic Insomnia 327.00-09 Organic Hypersomnia 327.10-19 Organic Sleep Apnea 327.20-29 Circadian Rhythm Sleep Disorders 327.30-39
Primary Cancer	ICD-9 Code list of diagnosed primary cancer: Each disease is coded as own category or column with 1 = Yes / 0 = No Prostate Cancer 185 Female Breast Cancer 174 Colorectum Cancer 153-154 Non-Hodgkin's Lymphoma 200, 202 Lung Cancer 162 Pancreatic Cancer 157 Leukemia 204-208.9 Kidney Cancer 189 Brain Cancer 191 Bladder Cancer 188 Liver Cancer 155 Ovarian Cancer 183 Esophageal Cancer 150 Gastric Cancer 151
Cancer Stage	SEER cancer stage
Co-Morbid_Cond	ICD-9 Code list of co-morbid conditions to include: Each disease group is coded as own category or column with

	1 = Yes, with disease / 0 = No without disease.
	Diabetes 249-250
	Mental Disorders
	    Mental Disorder/ Organic Psychotic Conditions (290-294):
	   1. Dementias (290)
	   2. Alcoholic & Drug Psychoses (291-292)
	   3. Transient & other Organic psychotic conditions (293-294)
	    Mental Disorders/ Other Psychoses (295-299):
	   1. Schizophrenic disorders (295)
	   2. Episodic Mood Disorders (296)
	   3. Paranoid states (297)
	   4. Other Nonorganic Psychoses and Psychoses with Origin specific to childhood (298-299)
	    Mental Disorders/ Neurotic, Personality and & other non- Psychotic (300-316):
	   1. Neurotic Disorders (300)
	   2. Personality Disorders (301)
	   3. Sexual Deviations and Disorders (302)
	   4. Alcohol and Drug Dependence (303-304)
	   5. Nondependent abuse of drugs (305)
	   6. Physiological malfunction arising from mental factors (306)
	   7. Special symptoms or syndromes not elsewhere classified (includes eating disorder) (307)
	   8. Acute Reaction to Stress (308)
	   9. Adjustment Reaction (309)
	   10. Specific Non-psychotic Mental Disorders following organic brain damage (310)
	   11. Depressive Disorders, not elsewhere classified (311)
	   12. Disturbance of conduct, no elsewhere classified (312)
	   13. Disturbance of emotions specific to childhood adolescence (313)
	   14. Hyperkinetic syndrome of childhood (314)
	   15. Specific Delays in Development (315)
	   16. Psychic factors associated with disease elsewhere classified (316)
	    Mental Retardation (317-319)
	Stroke (434.91)
	Cardiovascular disease (390-459)
	All Hypertension (410-405)
	  Chronic Kidney Disease-related Hypertension (403-404)

Co-Morbid_Proc	Total number of procedures performed for co-morbid

	conditions.
Provider_Sleep	Provider type that diagnosed Sleep Disorder listed as one of the following: CBOC VAMC Clinic
Provider_Ca	Provider type that diagnosed Primary Cancer listed as one of the following: CBOC VAMC Clinic
Rx_Number	Number of prescriptions of any type filled for patient which are not sleep disorder related
Total_SleepRx	Total quantity of sleep medications prescribed to patients
Procedures	Count of sleep disorder related procedures performed on patient
Surgeries	Count of sleep disorder related surgeries performed on patient
Smoking_Status	Taken from patient history information at entry into dataset, list as: Current Past Never
Marital_Status	Taken from patient history information at entry into dataset, list as: Married Single Divorced Widowed
Total_Time	Total time since entry into data in months
Time_SleepCA	Total time in months between initial sleep disorder diagnosis and initial cancer diagnosis or censoring
Time_toSleep	Total time in months from entry to initial sleep disorder or if not sleep disorder to censor
BMI	Body Mass Index or if not available height and weight listed separately at six month intervals from entry into dataset.
Deployment_Combat	Number of times deployed or in combat zones
Rank	Former military rank at entry into dataset
Total_ICD-9	Total number of ICD-9 diagnoses
Age_Sleep	Age at Sleep Disorder Diagnosis
Age_Cancer	Age at Cancer Diagnosis
Co-morbid_PRE	Number of Co-morbid conditions prior to sleep disorder diagnosis
Co-morbid_Post	Number of Co-morbid conditions after sleep disorder diagnosis
BMI_TP#	BMI at each time point that sleep disorders and cancer are

	assessed.
	If not BMI is available at that time point, hole to next time point.
	# should change 1-20 for each time point checked during duration of study.
SD_TP#	Cumulative time in months since sleep disorder diagnosis at assessment point.
	# should change 1-20 for each time point checked during duration of study.
Year Sleep Disorder	Year of sleep disorder diagnosis

CHAPTER 4

RESULTS

The final study population included 663,869 eligible individuals after applying inclusion and exclusion criteria (Figure 4.1). At baseline, 66 percent of the study participants were over the age of 45 years, 52 percent were married, 88 percent were male, and 45 percent were white. Residents of Georgia made up the largest portion of the study participants by state (35%). There was a total of 56,055 total sleep disorders (8.4%) and 18,181 total cancers (2.7%) during the study period. Insomnias comprised 3.4 percent (22,380 cases) of the study population, apneas comprised 3.9 percent (25,602 cases), and other sleep disorders 1.2 percent (8,073 cases) (Figure 4.2). There was an increasing trend of sleep disorder diagnoses across the study period (Figure 4.3).

Baseline characteristics of the study population are presented in Table 4.1. More than 50 percent of the study participants had at least one prescription, procedure, or surgery that could have been ordered for sleep disorder treatment. One-third (33%) of the participants had a diagnosis of cardiovascular disease, stroke, or hypertension, six percent had diabetes, and 16 percent had a mental disorder. Participants with a sleep disorder diagnosis were more likely to be male (92%) and divorced (19%) compared to those without a sleep disorder (Table 4.1). Those without a sleep disorder diagnosis had a median of one treatment that could have been related to a sleep problem relative to a

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median of 26 among those with a sleep disorder diagnosis. The distribution of co-morbid disease was similar between those with and without sleep disorders, but the median number of total co-morbid diagnoses observed among those with a sleep disorder was 157 compared to a median of 39 among those without sleep disorders (Table 4.2). Descriptive statistics for cancer cases are presented in Table 4.3. There were 9,844 (54%) cancer cases diagnosed at a localized SEER stage of disease and 1,271 (7%) had a sleep disorder diagnosis. Cancer cases were predominantly white (53%), from Georgia (40%), male (98%), and married (49.6%). The median age at cancer diagnosis was 64 years with 30 percent of cases 65 or older at entry into the cohort. Among cancer cases, 69 percent received at least 1 sleep disorder related prescription during the study period.

During the evaluation of descriptive statistics, it was found that some of the cancer cases did not have complete stage of disease results from the VA cancer register. Cancer cases with missing stage data were compared to the rest of the study population using an indicator variable ('1' for those without SEER [Surveillance, Epidemiology, and End Results Program] data for cancer and a '0' for all others included in the study). When this variable was included in the Cox extended model there was no impact on the results presented below. Thus, missing cancer stage data was random and infrequent enough that it did not affect the study's results.

The Kaplan Meir curves consistently showed a merging or crossing of the proportion of cancer cases among participants with and without sleep disorder diagnoses or sleep disorder treatments over time usually beginning between 7 and 10 years after follow-up for each cancer type evaluated (Tables 4.4-4.8). In addition to the tables, Kaplan Meir plots (Figures 4.4-4.6) were produced for all cancer and sleep disorder

diagnoses, cumulative treatments, or sleep disorder duration. The Kaplan Meir proportions for cancer incidence suggested that any sleep disorder or an insomnia diagnosis was associated with an increased risk of all cancer and colon cancer after a cross over point. For female breast cancer, there was a tendency towards increased cancer incidence among those with all sleep disorders, insomnias, apneas, or those in the other sleep disorder diagnosis group, but none of the comparisons were statistically significant (Table 4.7). There was an increased risk of all types of cancer incidence with increasing levels of the cumulative sleep disorder treatment (Tables 4.4-4.8). Also noted was a slight increase in cancer incidence with mild exposure to no exposure for sleep disorder duration for all (Table 4.4), colon (Table 4.5), prostate (Table 4.8), and female breast cancer (Table 4.7). The all other cancer group showed a decrease in cancer incidence in all tests for all sleep disorders, insomnias, apneas, the other sleep disorder group, and sleep disorder exposure duration (Table 4.8). The inconsistent nature of these results and the merging or change in direction of the cancer probability trends for the Kaplan Meir results over time suggest that the proportional hazards assumption was not met, and the Cox extended model was applied as an alternative data analysis strategy.

Results from the crude Cox extended time-varying models showed increased HRs among those diagnosed with any type of sleep disorder for each type of cancer evaluated (Table 4.9). The adjusted models indicated an increased risk for all cancer, other cancer group, and prostate cancer among those with any sleep disorder diagnosis, sleep apnea, insomnia, or other types of sleep disorders after adjustment for marital status, state of residence, sex (for non-gender specific models), and age. The adjusted models also indicated an increased risk of colon cancer for sleep apnea and all sleep disorders. No

association of colon cancer and insomnia or the other sleep disorder group was noted in the adjusted models (Table 4.9). The adjusted model results for female breast cancer showed no statistically significant association in relation to any of the sleep disorders evaluated.

When cumulative sleep disorder treatments were evaluated using Cox Extended models, a statistically significant increased risk of cancer was observed among categories with an increasing number of prescriptions or procedures during the study period for each type of cancer that was evaluated (Table 4.10). For all cancer, there was 26 percent higher incidence of cancer among those with at least 25 cumulative treatments, which increased to an HR of 2.5 among those with 100 or more prescriptions. A similar increasing trend in cancer risk was noted for colon cancer, prostate cancer, female breast cancer, and the other cancer group with each level of increasing cumulative treatment that was evaluated (Table 4.10). The all cancer, other cancer, and prostate cancer models indicated the steepest increases in risk associated with increasing levels of sleep disorder treatment, but each cancer type modeled had noteworthy and statistically significant increases in risk with increased sleep disorder treatment.

When the duration of time since the primary sleep disorder diagnosis was considered, there was a statistically significant increased incidence for cancer of the prostate, colon, other, or all cancer with longer latency after initial diagnosis of any sleep disorder (Table 4.11). For all four cancer types, there was approximately a 50 percent increase in the adjusted hazard ratios as the latency of sleep disorder diagnosis increased from 1 year to 10 years. The results for female breast cancer suggested a risk (HR: 1.13

95% CI: 0.96, 1.3 for 1 year) although the association between sleep disorder duration and cancer incidence was not statistically significant.

Each of the models for sleep disorders, duration, and treatment were then stratified by race and the co-morbid conditions of diabetes, mental disorders, and a category that combined cardiovascular disease, stroke, and hypertension (Tables 4.12-4.35). The sleep disorder models stratified by race for time-varying all sleep disorder diagnoses show an increased risk of all and colon cancer and the other cancer group for EA versus AA (Table 4.12). The other/unknown race group had the highest risks for all cancer and the all other cancer group (Table 4.12). The models stratified by diabetes suggest an overall higher risk of colon cancer for each of the sleep disorder models and an overall lower risk of prostate cancer among those with diabetes (Table 4.13-4.15). The models stratified by mental disorders showed a lower overall risk or no association for each of the cancer types and all sleep disorder groups among those with mental disorders (Table 4.20). The sleep disorder models stratified by hypertension, cardiovascular disease, or stroke show a higher risk of colon cancer among those with apnea versus those without (Table 4.26).

The sleep disorder duration models stratified by race indicate a similar risk of all cancer with sleep disorder exposure among both AA and EAs with increasing cancer risk as duration of sleep disorder exposure increases (Table 4.28). For colon cancer and all other cancer, only EAs show a significant risk of cancer with exposure (Table 4.28). The models stratified by diabetes demonstrate a higher risk of all cancer and colon cancer among those with diabetes, a lower risk of prostate cancer, and approximately the same risk of all other cancers (Table 4.30). All models stratified by mental disorders show a

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lower risk or no statistically significant risk of cancer among those with mental disorders compared to those without disorders (Table 4.32). All models stratified by cardiovascular disease, hypertension, and stroke show lower or no risk among those with the co-morbid condition, except for colon cancer (Table 4.34). The stratified model for colon cancer shows higher risk among those with cardiovascular disease, hypertension, and stroke (Table 4.34). Sleep disorder duration did not suggest an association with any cancer group in the stratified models.

The treatment models stratified by race showed notably higher all cancer, prostate, colon, and all other cancer risk among AAs compared to EAs. This risk for each race group is also increased with increasing levels of treatment (Table 4.29). The models stratified by diabetes for all cancer, all other cancers, and prostate cancer show a very similar risk of cancer between those with and without diabetes, though the risk among those with diabetes is slightly higher. The model stratified by diabetes for colon cancer shows a similar, but slightly higher risk of cancer among those with diabetes (Table 4.31). The models stratified by mental disorders show a higher risk of all cancer, colon, prostate, and all other cancers among those with mental disorders particularly at higher levels of treatment (Table 4.33). The models stratified by cardiovascular disease, hypertension, and stroke show similar risk among those with and without the co-morbid condition for all cancer, all other cancers, and colon cancer (Table 4.35). For prostate cancer, the risk of cancer is higher among those with cardiovascular disease, hypertension, and stroke compared to those without, particularly at higher levels of treatment exposure (Table 4.35). For all stratified models, female breast cancer showed

no association at one or both levels of stratification for treatment models (Tables 4.29, 4.31, 4.33, and 4.35).
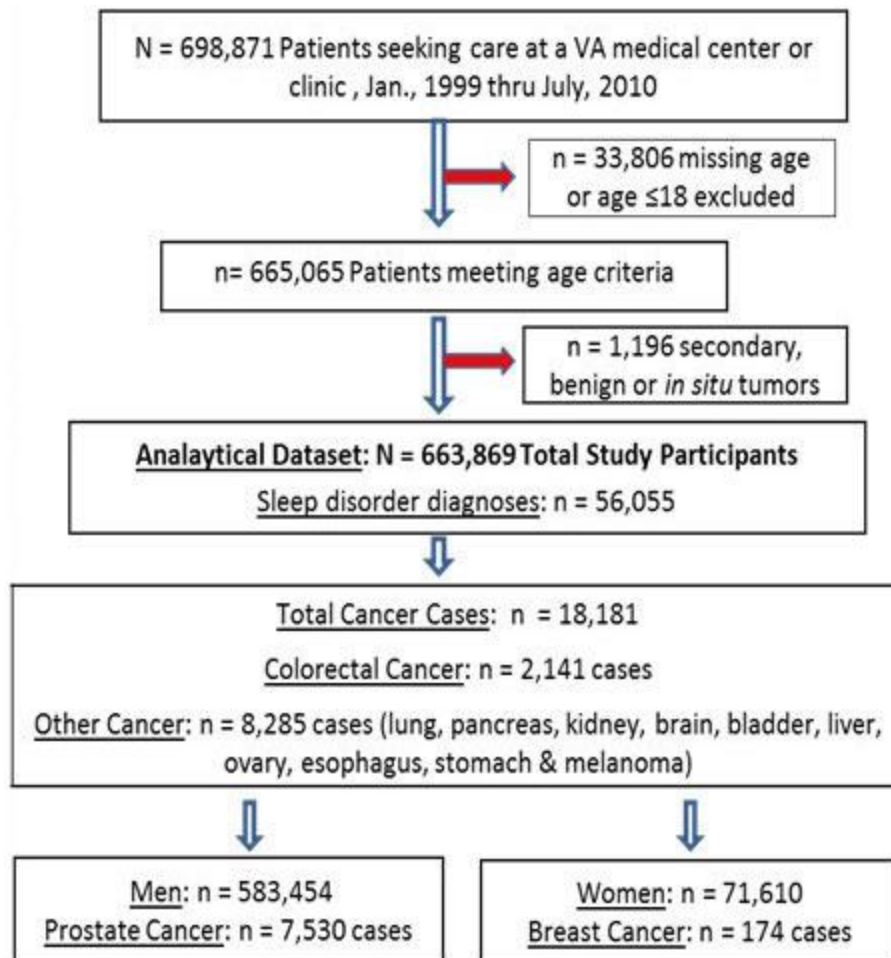
Figure 4.1: Study Population Flow diagram, Veterans in the Southeast United States Service Network, 1999-2010
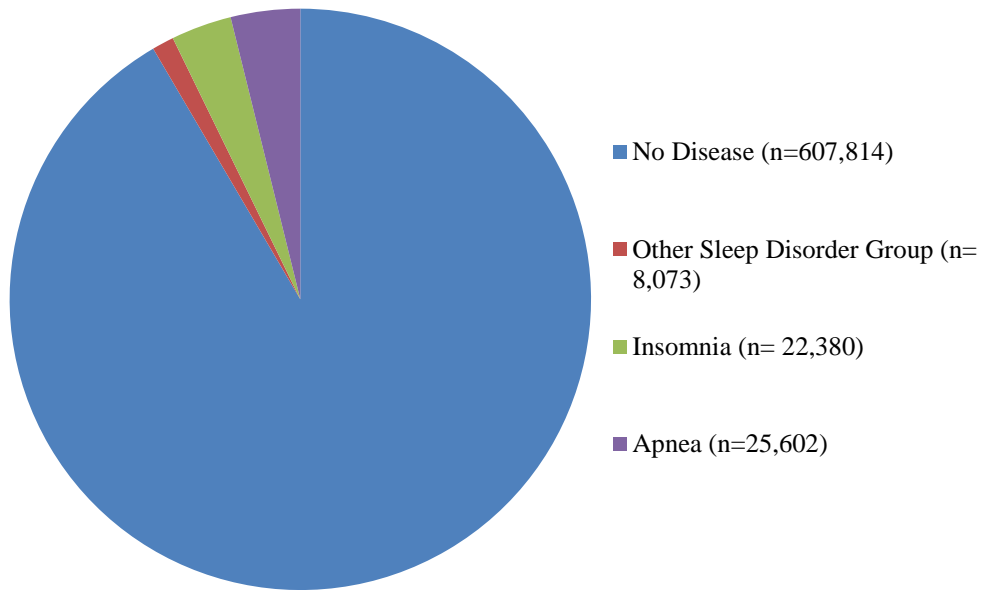
Figure 4.2: Proportion of the population with sleep disorder diagnosis among Veterans in the Southeastern United States, 1999-2010.
Other includes hypersomnia, parasomnia, arousal disorders, and other non-classified sleep disorders.

Legend:
- No Disease (n=607,814)
- Other Sleep Disorder Group (n= 8,073)
- Insomnia (n= 22,380)
- Apnea (n=25,602)
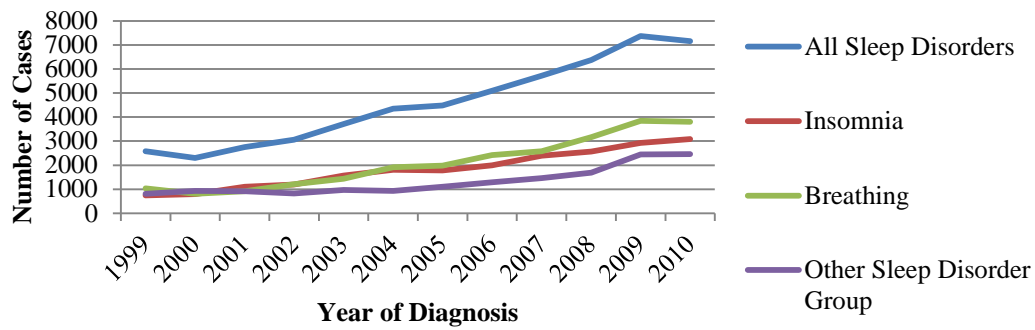
Figure 4.3: Number of Primary Sleep Disorder Cases Diagnosed by Year for Veterans in the Southeastern United States, 1999-2010.
Other includes hypersomnia, parasomnia, arousal disorders, and other non-classified sleep disorders.

Table 4.1: Descriptive Statistics Among Veterans in the SE USA (VISN-7, 1999-2010).

Variable	Total Population %(n) N= 663,869	Sleep Disorder % (n) n= 56,055	No Sleep Disorder % (n) n= 607,814
Age Range at Study Entry (years):			
18-34	15.4 (102,501)	13.4 (7,524)	15.6 (94,977)
35-44	17.9 (118,952)	19.4 (10,893)	17.8 (108,059)
45-54	26.4 (174,996)	33.4 (18,714)	25.7 (156,282)
55-64	15.7 (104,475)	16.4 (9,164)	15.7 (95,311)
65 plus	24.5 (162,945)	17.4 (9,760)	25.2 (153,185)
Race:			
African-American	26.2 (173,942)	30.1 (16,884)	25.8 (157,058)
European American	44.9 (298,339)	53.8 (30,141)	44.1 (268,198)
Other[1]	28.9 (191,588)	16.1 (9,030)	30.0 (182,558)
Sex:			
Male	87.9 (583,454)	92.4 (51,803)	87.5 (531,651)
Female	10.8 (71,610)	6.8 (3,800)	11.2 (67,810)
Unknown	1.3 (8,805)	0.8 (452)	1.4 (8,353)
Marital Status:			
Married	51.5 (342,144)	59.2 (33,159)	50.8 (308,955)
Never Married	7.8 (51,846)	6.2 (3,491)	7.9 (48,355)
Divorce	17.8 (118,148)	19.3 (10,827)	7.7 (107,321)
Widowed	6.9 (45,455)	6.1 (3,394)	6.9 (42,061)
Unknown	16.0 (106,306)	9.3 (5,184)	16.6 (101,122)
State of Residence:			
Alabama	23.5 (156,268)	26.1 (14,655)	23.3 (141,613)

Variable	Total Population %(n) N= 663,869	Sleep Disorder % (n) n= 56,055	No Sleep Disorder % (n) n= 607,814
Georgia	35.7 (237,107)	35.1 (19,677)	35.8 (217,430)
South Carolina	26.4 (175,517)	30.2 (16,939)	26.1 (158,578)
Other[3]	14.3 (94,977)	8.5 (4,784)	14.8 (90,193)
Diabetes: Yes	5.7 (37,760)	5.8 (3,246)	5.7 (34,514)
No	94.3 (626,109)	94.2 (52,809)	94.3 (573,300)
Mental Disorder: Yes	16.3 (108,370)	17.4 (9,734)	16.2 (98,636)
No	83.7 (555,499)	82.6 (46,321)	83.8 (509,178)
Cardiovascular Disease, Stroke, and/or Hypertension: Yes	33.0 (219,247)	29.2 (16,341)	33.4 (202,906)
No	66.9 (444,622)	70.9 (39,714)	66.6 (404,908)
Cancer Type: All Cancer	2.7 (18,181)	2.3 (1,271)	2.8 (16,910)
No Cancer	97.3 (645,688)	97.7 (54,784)	97.2 (590,904)
Prostate	1.1 (7,527)	0.92 (515)	1.2 (7,022)
Colon	0.32 (2,141)	0.39 (216)	0.32 (1,925)
All Other[2]	1.3 (8,285)	0.94 (525)	1.3 (7,760)
Female Breast	0.03 (218)	0.03 (15)	0.03 (203)
Total Time in Cohort (months): Mean (± SD)	129.6 (± 30)	135.9 (± 21)	129.0 (± 31)
Median	143.0	143.0	143.0
Minimum	0	3.0	0
Max	150.0	150.0	150.0

Variable	Total Population %(n) N= 663,869	Sleep Disorder % (n) n= 56,055	No Sleep Disorder % (n) n= 607,814

[1]Other race refers to: Hispanic, Asian, American Indian, Pacific Islanders, and unknown race

[2]All Other Cancer includes: Lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric, and melanoma cancers.

[3]Other state includes a small area of Alabama included in VISN-7 as well as Veterans who cross state lines to receive care inside the VISN-7 area.

Table 4.2: Descriptive statistics of disease exposure Among Veterans in the SE USA (VISN-7, 1999-2010).

Variable	Total Population %(n) N= 663,869	Sleep Disorders % (n) n= 56,055	No Sleep Disorder % (n) n= 607,814
Cumulative Treatment:			
No Treatment (0)	41.2 (273,450)	9.7 (5,456)	44.1 (267,994)
Mild Treatment (1)	7.8 (51,858)	4.6 (2,574)	8.1 (49,284)
Moderate Treatment (2-18)	25.9 (171,793)	29.3 (16,428)	25.6 (155,365)
Frequent Treatment (19-1150)	25.1 (166,768)	56.4 (31,597)	22.2 (135,171)
Count of Sleep Disorder Prescription and Treatments			
Mean (± SD)	25.1 (± 61)	65.7 (± 98)	21.4 (± 56)
Median	2.0	26.0	1.0
Minimum	0	0	0
Maximum	1,150	1,150	1,150
Sleep Disorder Duration: [months (categorical)]			
None (0 months)	91.6 (608,374)	1.0 (560)	99.0 (607,814)
Short (1-26 months)	2.8 (18,755)	33.5 (18,755)	0 (0)
Moderate (27- 62 months)	2.7 (18,158)	32.4 (18,158)	0 (0)
Long (63-149 months)	2.8 (18,582)	33.2 (18,582)	0 (0)
Sleep Disorder Duration: [months (continuous)] Mean (± SD)	86.2 (± 37)	86.2 (± 40)	0 (± 0)
Median	93.0	93.0	0
Minimum	0	0	0
Maximum	143	143	0
Total Co-morbid Diagnoses Mean(± SD)	112.1 (± 195)	242.7 (± 291)	100.1 (± 179)
Median	45.0	157.0	39.0
Minimum	0	1	0
Max	9,368	5,840	9,368

Table 4.3: Descriptive Statistics for Cancer Among Veterans in the SE USA (VISN-7, 1999-2010).

Variable	% (N)
SEER[1] Stage	
Distant Metastasis/Systemic Disease	20.5 (3,724)
Localized	54.2 (9,844)
Regional	18.6 (3379)
Unknown	6.8 (1,234)
Sleep Disorder Type:	
All Sleep Disorders	7.0 (1,271)
Insomnias	2.8 (509)
Apneas	3.1 (568)
Other Sleep Disorder Group[2]	1.1 (194)
No Sleep Disorder	93.0 (16,910)
Age Range (years) At Study Entry	
18-34	0.8 (141)
35-44	7.6 (1,381)
45-54	34.6 (6,286)
55-64	27.2 (4,945)
65 plus	29.8 (5,428)
Age (years) at Cancer Diagnosis	
Mean($\pm$ SD)	64.4 ($\pm$ 10)
Median	64.0
Minimum	23.0
Maximum	100.0
Race	
European American	53.3 (9,686)
African-American	38.6 (7,017)
Other/Unknown	8.1

Variable	% (N)
	(1,478)
State of Residence Alabama	20.5 (3,735)
Georgia	40.1 (7,285)
South Carolina	33.7 (6,120)
Other	5.7 (1,041)
Diabetes Yes	8.3 (1,516)
No	91.7 (16,665)
Mental Disorder/Retardation Yes	25.6 (4,654)
No	74.4 (13,527)
Cardiovascular Disease, Stroke, and/or Hypertension Yes	46.5 (8,460)
No	53.5 (9,721)
Sex: Male	97.8 (17,777)
Female	2.1 (384)
Unknown	0.1 (20)
Marital Status: Married	49.6 (9,024)
Never Married	7.0 (1,272)
Divorce	24.3 (4,414)
Widowed	11.2 (2,039)
Unknown	7.9 (1,432)
Cumulative Sleep Disorder Treatment : No Treatment (0)	30.6 (5,568)

Variable	% (N)
Mild Treatment (1)	9.1 (1,645)
Moderate Treatment (2-18)	33.0 (5,998)
Frequent Treatment (19-1150)	27.3 (4,970)
Count of Sleep Disorder Prescription Treatments: Mean (± SD)	25 (± 56)
Median	3
Minimum	0
Maximum	812
Sleep Disorder Duration: Months (categorical) None (0)	93.1 (16,932)
Mild (1-26)	3.1 (555)
Moderate (27- 62)	2.2 (406)
Severe (63-149)	1.6 (288)
Total Time (months) in Cohort Mean (± SD)	81.6 (± 42)
Median	86.0
Minimum	0
Maximum	150.0

[1]SEER: Surveillance, Epidemiology, and End Results Program. [2]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders.

Table 4.4: Results of Kaplan Meier Survival Analysis: ALL CANCER, for Veterans in the SE USA (VISN-7, 1999-2010).

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
All Sleep Disorders	No	607,814	0.005870	0.01030	0.01480	0.023200	0.049300	<0.0001
	Yes	56,055	0.001090	0.00319	0.00614	0.014400	0.061600	
Apneas	No	638,267	0.005650	0.01000	0.01440	0.022800	0.050600	<0.0001
	Yes	25,602	0.000978	0.00287	0.00552	0.013900	0.046900	
Insomnias	No	641,489	0.005630	0.00997	0.01430	0.022800	0.049100	<0.0001
	Yes	22,380	0.000897	0.00307	0.00618	0.014300	0.079800	
Other Sleep Disorders[1]	No	655,796	0.005510	0.00980	0.01410	0.022600	0.050600	0.0116
	Yes	8,073	0.001990	0.00452	0.00801	0.015800	0.042200	
Cumulative Sleep Disorder Treatment	No Treatment (0)	273,450	0.006370	0.01010	0.01330	0.018500	0.022200	<0.0001
	Mild Treatment (1)	51,858	0.006970	0.01180	0.01630	0.025900	0.044300	
	Moderate Treatment (2-18)	171,793	0.006580	0.01210	0.01740	0.028800	0.068200	
	Frequent Treatment (19-1150)	166,768	0.002380	0.00618	0.01100	0.021800	0.066600	
Sleep Disorder Duration (months)	None(0)	608,374	0.005870	0.01030	0.01480	0.023300	0.049300	<0.0001
	Mild (1-26)	18,755	0.002740	0.006430	0.010800	0.022600	0.139500	
	Moderate (27-62)	18,158	0.000386	0.003000	0.006250	0.014500	0.038100	
	Severe (63-1149)	18,582	0	0	0.001130	0.005930	0.043600	
Age at Study Entry	18-34	102,501	0.000156	0.000225	0.000352	0.000637	0.001390	<0.0001
	35-44	118,952	0.000674	0.001780	0.003090	0.006710	0.045600	
	45-54	174,996	0.003610	0.007550	0.012500	0.025500	0.065800	
	55-64	104,475	0.009450	0.018200	0.026300	0.040300	0.063800	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
	≥ 65	162,945	0.011900	0.019100	0.025600	0.035400	0.061400	
State of Residence	SC	175,517	0.006530	0.012200	0.018000	0.028400	0.060700	<0.0001
	GA	237,107	0.006250	0.010700	0.014700	0.024400	0.064200	
	AL	156,268	0.004950	0.008780	0.013400	0.021100	0.039900	
	Other	94,977	0.002420	0.004260	0.006060	0.009340	0.016000	
Race	European American	298,339	0.006850	0.012100	0.017300	0.027200	0.050400	<0.0001
	African-American	173,942	0.007620	0.013400	0.01940	0.03170	0.106300	
	Other/Unknown	191,588	0.001360	0.002730	0.00400	0.00656	0.012400	
Sex	Male	583,454	0.006110	0.010900	0.01570	0.02530	0.054700	<0.0001
	Female	71,610	0.000868	0.001730	0.00241	0.00380	0.013500	
	Unknown	8,805	0.000455	0.000912	0.00114	0.00183	0.016900	
Diabetes	No	626,109	0.005320	0.009450	0.01360	0.02180	0.049900	<0.0001
	Yes	37,760	0.007860	0.014500	0.02100	0.03380	0.062000	
Mental Disorder/ Mental Retardation	No	555,499	0.004960	0.008800	0.01260	0.02000	0.041000	<0.0001
	Yes	108,370	0.008070	0.014500	0.02140	0.03530	0.097000	
Cardiovascular Disease, Hypertension, and Stroke	No	444,622	0.004340	0.007720	0.01100	0.01770	0.044300	<0.0001
	Yes	219,247	0.007760	0.013900	0.02030	0.03250	0.063900	
Marital Status	Married	342,114	0.005440	0.009630	0.01390	0.02200	0.041000	<0.0001
	Single	51,846	0.004470	0.007750	0.01160	0.01960	0.048700	
	Divorced	118,148	0.006390	0.012100	0.01750	0.02970	0.064800	
	Widowed	45,455	0.011100	0.019400	0.02730	0.04240	0.085700	
	Unknown	106,306	0.002620	0.004470	0.00636	0.00989	0.059900	

[1]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders.

Covariate	N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Kaplan Meir results presented for 3, 5, 7, 10, and 12.5 years as the proportion of all cancer incidence.							

Table 4.5: Results of Kaplan Meier Survival Analysis: COLON CANCER, for Veterans in the SE USA (VISN-7, 1999-2010).

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Sleep Disorders:								
All	No	607,814	0.000200	0.000417	0.000741	0.001340	0.022600	0.1072
	Yes	56,055	0.000036	0.000181	0.000311	0.000774	0.042200	
Apneas	No	638,267	0.000193	0.000406	0.000719	0.001310	0.024200	0.3316
	Yes	25,602	0	0.000159	0.000319	0.000696	0.027900	
Insomnias	No	641,489	0.000191	0.000406	0.000722	0.001310	0.022800	0.3967
	Yes	22,380	0.000045	0.000135	0.000182	0.000765	0.060300	
Other[1]	No	655,796	0.000186	0.000396	0.000704	0.001290	0.024400	0.3288
	Yes	8,073	0.000125	0.000378	0.000639	0.001050	0.021200	
Cumulative Sleep Disorder Treatment	No Treatment (0)	273,450	0.000067	0.000124	0.000183	0.000250	0.001080	<0.0001
	Mild Treatment (1)	51,858	0.000176	0.000257	0.000532	0.001020	0.013400	
	Moderate Treatment (2-18)	171,793	0.000406	0.000797	0.001300	0.002440	0.035900	
	Frequent Treatment (19-1150)	166,768	0.000158	0.000477	0.00101	0.001950	0.039700	
Sleep Disorder Duration (months)	No Exposure (0)	608,374	0.000199	0.000416	0.000740	0.001340	0.022600	0.0891
	Mild Exposure (1-26)	18,755	0.000108	0.000329	0.000557	0.001210	0.113700	
	Moderate Exposure (27-62)	18,158	0	0.000223	0.000395	0.000947	0.018900	
	Severe Exposure (63-149)	18,582	0	0	0	0.000220	0.032100	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Age (years) at Study Entry	18-34	102,501	0	0	0	0	0.000178	<0.0001
	35-44	118,952	0	0.000110	0.000179	0.000361	0.035900	
	45-54	174,996	0.000115	0.000268	0.000537	0.001250	0.033100	
	55-64	104,475	0.000264	0.000567	0.000946	0.001810	0.017900	
	≥ 65	162,945	0.000469	0.000929	0.001700	0.002870	0.026100	
State of Residence	SC	175,517	0.000186	0.000451	0.000911	0.001630	0.027400	<0.0001
	GA	237,107	0.000245	0.000489	0.000744	0.001390	0.035100	
	AL	156,268	0.000176	0.000367	0.000696	0.001250	0.016800	
	Other	94,977	0.000053	0.000117	0.000250	0.000492	0.006190	
Race	European American	298,339	0.000195	0.000468	0.000859	0.001640	0.019100	<0.0001
	African-American	173,942	0.000345	0.000628	0.001090	0.001810	0.070700	
	Other/Unknown	191,588	0.000027	0.000075	0.000115	0.000273	0.004670	
Sex	Male	583,454	0.000210	0.000442	0.000793	0.001460	0.025400	<0.0001
	Female	71,610	0.000014	0.000085	0.000099	0.001860	0.008730	
	Unknown	8,805	0	0	0	0.000115	0.015100	
Diabetes	No	626,109	0.000182	0.000385	0.000680	0.001230	0.024600	<0.0001
	Yes	37,760	0.000243	0.000583	0.001100	0.002250	0.023000	
Mental Disorder/ Mental Retardation	No	555,499	0.000192	0.000383	0.000654	0.001170	0.017700	<0.0001
	Yes	108,370	0.000150	0.000462	0.000958	0.001870	0.057500	
Cardiovascular Disease, Hypertension, and Stroke	No	444,622	0.000146	0.000313	0.000536	0.000962	0.023700	<0.0001
	Yes	219,247	0.000266	0.000568	0.001050	0.001980	0.026200	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Marital Status	Married	342,114	0.000152	0.000349	0.000675	0.001240	0.015500	<0.0001
	Single	51,846	0.000176	0.000336	0.000706	0.001130	0.026500	
	Divorced	118,148	0.000258	0.000543	0.000856	0.001640	0.029300	
	Widowed	45,455	0.000455	0.000825	0.001490	0.002870	0.039100	
	Unknown	106,306	0.000104	0.000240	0.000319	0.000573	0.048100	

[1]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders.
Kaplan Meir results presented for 3, 5, 7, 10, and 12.5 years as the proportion of colon cancer incidence.

Table 4.6: Results of Kaplan Meier Survival Analysis: PROSTATE CANCER, for Veterans in the SE USA (VISN-7, 1999-2010).

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Sleep Disorders								
All	No	531,651	0.002930	0.005280	0.007640	0.011900	0.014900	<0.0001
	Yes	51,803	0.000426	0.001510	0.002910	0.007360	0.010800	
Apneas	No	559,410	0.002810	0.005100	0.007420	0.011700	0.014700	<0.0001
	Yes	24,044	0.000334	0.001350	0.002550	0.007340	0.010700	
Insomnias	No	563,042	0.002780	0.005060	0.007370	0.011600	0.014700	<0.0001
	Yes	20,412	0.000492	0.001540	0.002970	0.007390	0.010600	
Other[1]	No	576,107	0.002730	0.004980	0.007250	0.011500	0.014600	0.0331
	Yes	7,347	0.000549	0.001940	0.003940	0.007350	0.011800	
Cumulative Sleep Disorder Treatment	No Treatment (0)	226,648	0.003920	0.006350	0.008590	0.011600	0.013600	<0.0001
	Mild Treatment (1)	46,377	0.003030	0.005530	0.008210	0.013400	0.017700	
	Moderate Treatment (2-18)	156,432	0.002750	0.005370	0.007800	0.013400	0.017400	
	Frequent Treatment (19-1150)	153,997	0.000782	0.002260	0.004300	0.008870	0.012500	
Sleep Disorder Duration (months)	None (0)	532,165	0.002920	0.005270	0.007640	0.011900	0.014900	<0.0001
	Mild (1-26)	17,120	0.001120	0.002880	0.005190	0.012000	0.015800	
	Moderate (27-62)	16,746	0.000179	0.001750	0.003120	0.007180	0.010800	
	Severe (63-149)	17,423	0	0	0.000576	0.003230	0.006170	
Age (years) at Study Entry	18-34	72,147	0	0	0.000014	0.000056	0.000267	<0.0001
	35-44	95,513	0.000189	0.000559	0.001160	0.003080	0.005220	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
	45-54	160,173	0.001400	0.003290	0.006010	0.012900	0.018400	
	55-64	98,684	0.004450	0.009280	0.013700	0.021000	0.025200	
	≥ 65	156,937	0.005800	0.009100	0.011900	0.014900	0.016200	
State of Residence	SC	159,255	0.003270	0.006510	0.009810	0.015300	0.019700	<0.0001
	GA	207,473	0.002970	0.005230	0.007390	0.012300	0.016300	
	AL	139,979	0.002290	0.00395	0.00593	0.00925	0.01090	
	Other	76,747	0.001560	0.00271	0.00375	0.00551	0.00608	
Race	European American	279,199	0.002590	0.00467	0.00669	0.01020	0.01260	<0.0001
	African-American	150,732	0.004740	0.00857	0.01260	0.02060	0.02660	
	Other/Unknown	153,523	0.000909	0.00185	0.00282	0.00452	0.00572	
Diabetes	No	547,476	0.002610	0.00475	0.00696	0.01110	0.01410	<0.0001
	Yes	35,978	0.004090	0.00784	0.01100	0.01690	0.02150	
Mental Disorder/ Mental Retardation	No	485,414	0.002510	0.00462	0.00667	0.01050	0.01340	<0.0001
	Yes	98,040	0.003670	0.00650	0.00987	0.01620	0.02050	
Cardiovascular Disease, Hypertension, and Stroke	No	376,738	0.002130	0.00391	0.00570	0.00931	0.01190	<0.0001
	Yes	206,716	0.003760	0.00683	0.01000	0.01560	0.01970	
Marital Status	Married	323,299	0.002680	0.00483	0.00698	0.01110	0.01380	<0.0001
	Single	43,186	0.001910	0.00358	0.00552	0.00969	0.01210	
	Divorced	105,018	0.002710	0.00548	0.00829	0.01400	0.01860	
	Widowed	42,575	0.005640	0.00976	0.01380	0.01990	0.02370	
	Unknown	69,376	0.001500	0.00259	0.00389	0.00605	0.00861	

Covariate	N	3-year	5-year	7-year	10-year	12.5 year	p-Value
[1]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. Kaplan Meir results presented for 3, 5, 7, 10, and 12.5 years as the proportion of prostate cancer incidence.							

Table 4.7: Results of Kaplan Meier Survival Analysis: FEMALE BREAST CANCER, for Veterans in the SE USA (VISN-7, 1999-2010).

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Sleep Disorders								
All	No	67,810	0.000517	0.000935	0.001330	0.001950	0.002480	0.8232
	Yes	3,800	0.000263	0.000263	0.001060	0.001870	0.002690	
Apneas	No	70,288	0.000499	0.000902	0.001290	0.001930	0.002480	0.6766
	Yes	1,322	0.000756	0.000756	0.002280	0.003050	0.003050	
Insomnias	No	69,809	0.000517	0.000922	0.001330	0.001970	0.002480	0.7813
	Yes	1,801	0	0	0.000559	0.001130	0.002870	
Cumulative Sleep Disorder Treatment	No Treatment (0)	40,459	0.000470	0.000720	0.000896	0.001150	0.001390	<0.0001
	Mild Treatment (1)	4,954	0.000808	0.001010	0.001010	0.001840		
	Moderate Treatment (2-18)	13,896	0.000795	0.001520	0.002260	0.003380	0.004130	
	Frequent Treatment (19-1150)	12,301	0.000163	0.000740	0.001740	0.003010	0.004500	
Sleep Disorder Duration	None (0)	67,851	0.000517	0.000934	0.001330	0.001950	0.002480	0.2884
	Mild (1)	1,296	0.000772	0.000772	0.002340	0.003140		
	Moderate (2-18)	1,310	0	0	0.000771	0.002330	0.002330	
	Severe (19-1150)	1,153	0	0	0	0	0.000906	
Age (years) at Study Entry	18-34	27,340	0.000037	0.000073	0.000220	0.000514	0.000846	<0.0001
	35-44	21,329	0.000469	0.000987	0.001510	0.002510	0.003420	
	45-54	12,828	0.001020	0.001800	0.002680	0.003650	0.004310	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
	55-64	4,898	0.001230	0.001440	0.001870	0.002090	0.002310	
	≥ 65	5,215	0.001170	0.002210	0.002440	0.002960	0.002960	
State of Residence	SC	16,179	0.000743	0.001240	0.001620	0.002460	0.003180	0.0106
	GA	29,445	0.000613	0.000956	0.001370	0.001970	0.002720	
	AL	16,112	0.000311	0.000813	0.001320	0.001900	0.002230	
	Other	9,874	0.000101	0.000305	0.000613	0.001130	0.001130	
Race	European American	15,610	0.001220	0.002330	0.002860	0.004090	0.004930	<0.0001
	African-American	20,994	0.000811	0.001290	0.002110	0.003080	0.004210	
	Other/Unknown	35,006	0	0.000029	0.000145	0.000323	0.000383	
Diabetes	No	70,065	0.000486	0.000876	0.001240	0.001800	0.002360	<0.0001
	Yes	1,545	0.001310	0.001970	0.004670	0.008860		
Mental Disorder/ Mental Retardation	No	62,206	0.000419	0.000727	0.001140	0.001700	0.002190	<0.0001
	Yes	9,409	0.001070	0.002030	0.002470	0.003570	0.004470	
Cardiovascular Disease, Hypertension, and Stroke	No	60,567	0.000364	0.000564	0.000816	0.001210	0.001520	<0.0001
	Yes	10,769	0.001270	0.002750	0.004070	0.006090	0.007970	
Marital Status	Married	18,799	0.000479	0.001020	0.001400	0.002000	0.002510	<0.0001
	Single	8,659	0.000579	0.001040	0.001280	0.002230	0.002950	
	Divorced	13,129	0.000840	0.001450	0.002380	0.003790	0.005070	
	Widowed	2,878	0.002460	0.004290	0.005060	0.006320	0.006320	
	Unknown	28,145	0.000142	0.000178	0.000395	0.000540	0.000763	

[1]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders.

Kaplan Meir results presented for 3, 5, 7, 10, and 12.5 years as the proportion of breast cancer incidence.

Table 4.8: Results of Kaplan Meier Survival Analysis: ALL OTHER CANCER, for Veterans in the SE USA (VISN-7, 1999-2010).

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
Sleep Disorders:								
All	No	607,814	0.003050	0.005220	0.007730	0.011500	0.014200	<0.0001
	Yes	56,055	0.000644	0.001570	0.003050	0.006670	0.010100	
Apneas	No	638,267	0.002930	0.005050	0.007040	0.011200	0.014100	<0.0001
	Yes	25,602	0.000626	0.001380	0.002660	0.006160	0.009220	
Insomnias	No	641,489	0.002930	0.005020	0.007000	0.022300	0.014000	<0.0001
	Yes	22,380	0.000405	0.001490	0.003210	0.006770	0.011000	
Other[1]	No	655,796	0.002860	0.004930	0.006910	0.011100	0.013900	0.0163
	Yes	8,073	0.001370	0.002390	0.003820	0.008000	0.010800	
Cumulative Sleep Disorder Treatment	No Treatment (0)	273,450	0.002980	0.004580	0.005940	0.008530	0.009900	<0.0001
	Mild Treatment (1)	51,858	0.004010	0.006490	0.008380	0.012900	0.015600	
	Moderate Treatment (2-18)	171,793	0.003610	0.006290	0.008880	0.014100	0.017700	
	Frequent Treatment (19-1150)	166,768	0.001480	0.003540	0.005900	0.011500	0.016300	
Sleep Disorder Duration	None (0)	608,374	0.003050	0.005220	0.007240	0.011500	0.014200	<0.0001
	Mild (1-26)	18,755	0.001560	0.003330	0.005320	0.010300	0.014500	
	Moderate (27-62)	18,158	0.000220	0.001770	0.002940	0.006760	0.009500	
	Severe (63-149)	18,582	0	0	0.000594	0.002710	0.006010	
Age (years) at Study Entry	18-34	102,501	0.000146	0.000205	0.000283	0.000460	0.000796	<0.0001
	35-44	118,952	0.000430	0.001300	0.001710	0.003420	0.005250	
	45-54	174,996	0.002120	0.004120	0.006280	0.012300	0.017000	

Covariate		N	3-year	5-year	7-year	10-year	12.5 year	p-Value
	55-64	104,475	0.004940	0.008810	0.012500	0.019000	0.023200	
	≥ 65	162,945	0.005830	0.009340	0.012500	0.018400	0.020800	
State of Residence	SC	175,517	0.003290	0.005760	0.008110	0.012900	0.016500	<0.0001
	GA	237,107	0.003320	0.005550	0.007380	0.012200	0.015900	
	AL	156,268	0.002700	0.004800	0.007300	0.011500	0.013700	
	Other	94,977	0.001090	0.001920	0.002720	0.004300	0.004880	
Race	European American	298,339	0.004160	0.007150	0.010000	0.015900	0.020000	<0.0001
	African-American	173,942	0.003060	0.005200	0.007280	0.012000	0.015300	
	Other/Unknown	191,588	0.000606	0.001160	0.001610	0.002650	0.003240	
Sex	Male	583,454	0.003190	0.005490	0.007720	0.012400	0.015700	<0.0001
	Female	71,610	0.000350	0.000745	0.001000	0.001670	0.002290	
	Unknown	8,805	0.000228	0.000456	0.000685	0.000916	0.000916	
Diabetes	No	626,109	0.002800	0.004820	0.006730	0.010800	0.013600	<0.0001
	Yes	37,760	0.003600	0.006280	0.009190	0.015200	0.019200	
Mental Disorder/ Mental Retardation	No	555,499	0.002520	0.004300	0.005990	0.009520	0.012000	<0.0001
	Yes	108,370	0.004500	0.007980	0.011400	0.018800	0.023300	
Cardiovascular Disease, Hypertension, and Stroke	No	444,622	0.002340	0.004010	0.005540	0.008810	0.011000	<0.0001
	Yes	219,247	0.003870	0.006740	0.009640	0.015800	0.020100	
Marital Status	Married	342,114	0.002720	0.004650	0.006570	0.010300	0.012900	<0.0001
	Single	51,846	0.002610	0.004260	0.006090	0.010100	0.012300	
	Divorced	118,148	0.003630	0.006520	0.009100	0.015500	0.019900	
	Widowed	45,455	0.005240	0.009210	0.012800	0.021000	0.026400	
	Unknown	106.306	0.001480	0.002460	0.003380	0.005220	0.006710	

Covariate	N	3-year	5-year	7-year	10-year	12.5 year	p-Value
[1]Other sleep disorders includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. Kaplan Meir results presented for 3, 5, 7, 10, and 12.5 years as the proportion of all other cancer incidence.							

Cumulative Incidence for All Cancer
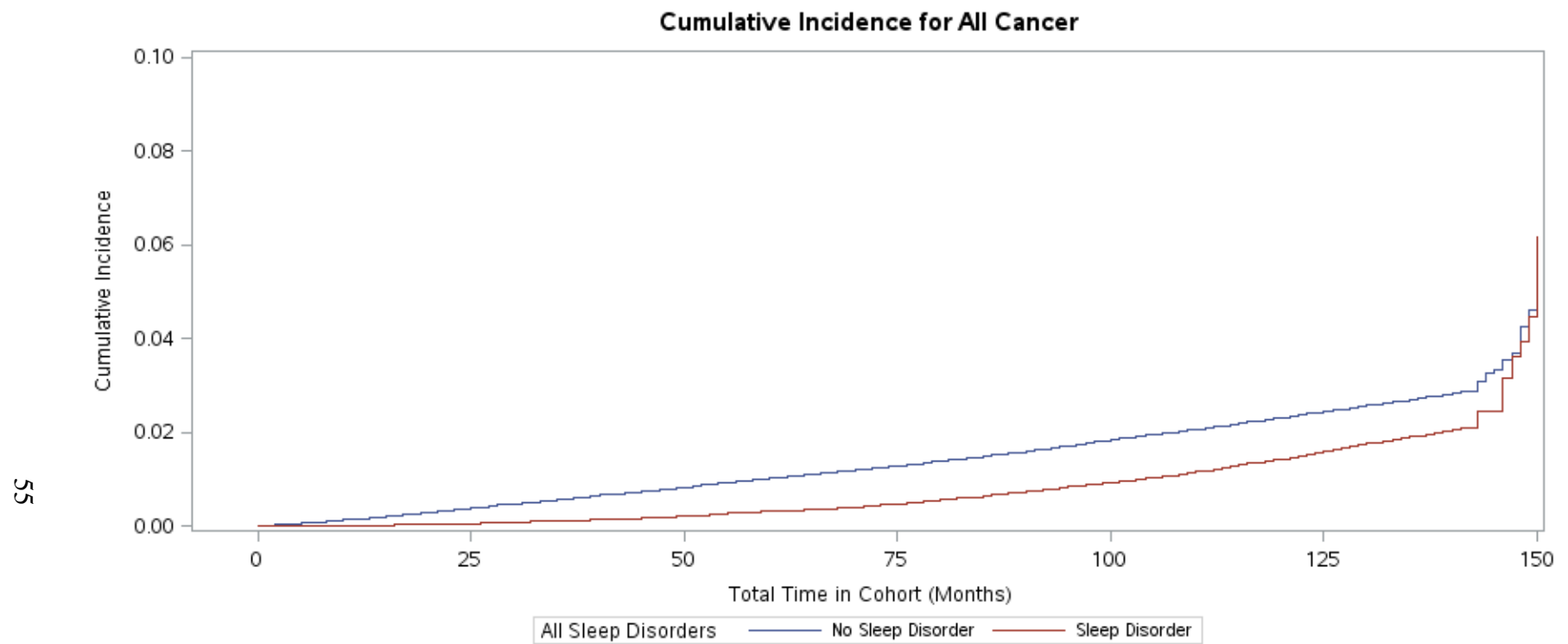
Figures 4.4: Kaplan Meir survival plots for all cancer by all sleep disorder.
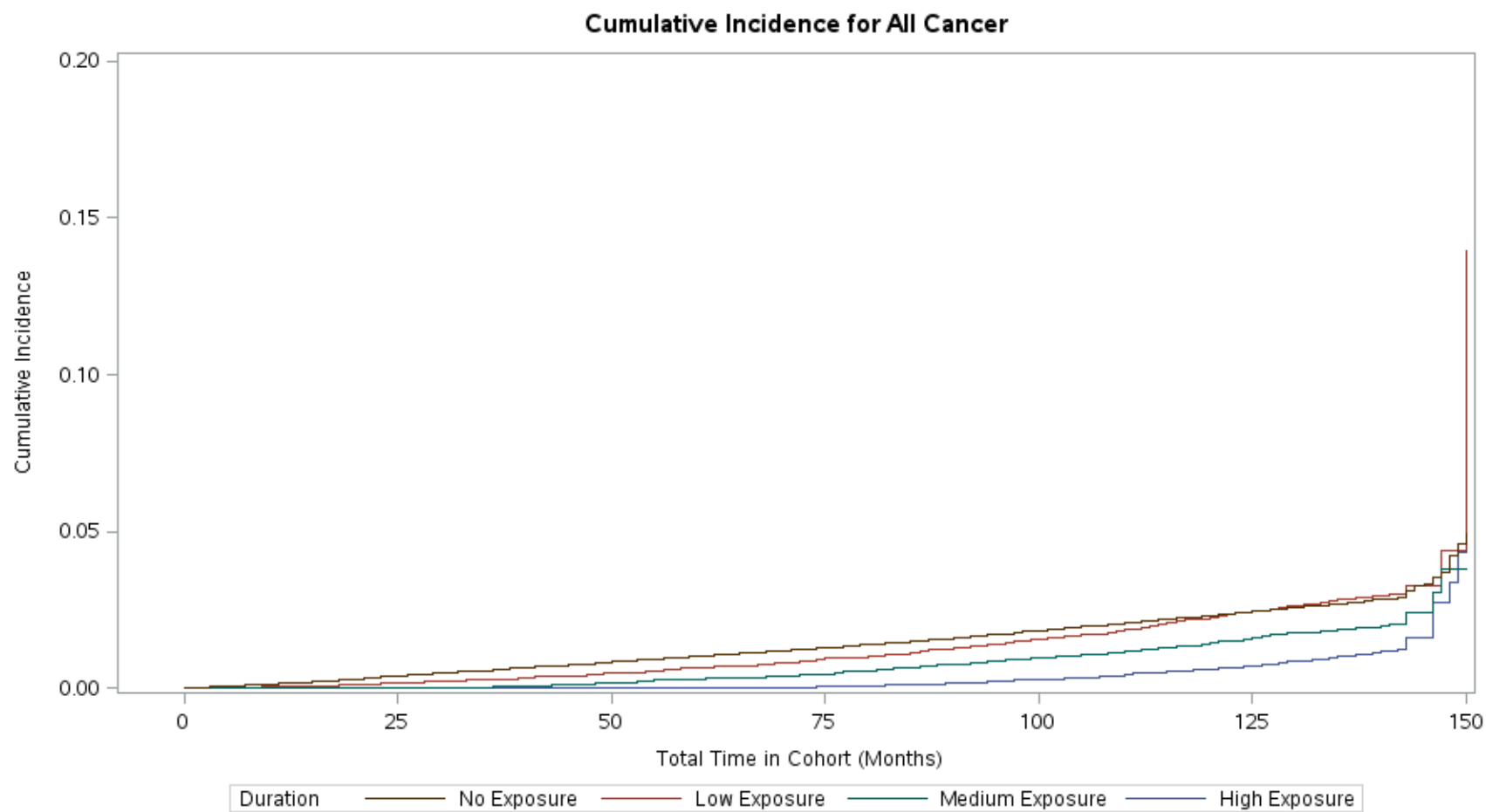
Figure 4.5: Kaplan Meir survival plots for all cancer by sleep disorder duration.
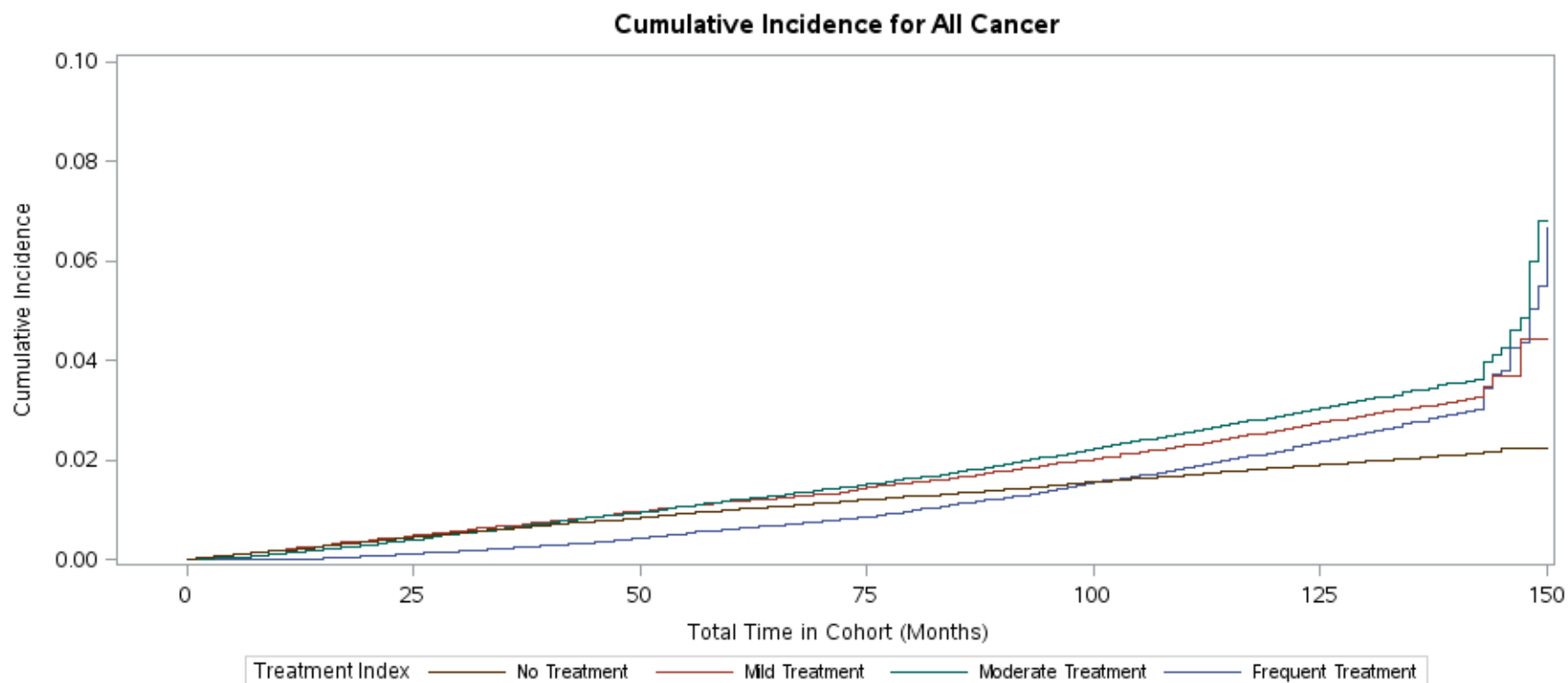
Figure 4.6: Kaplan Meir survival plots for all cancer by sleep disorder treatment.

Table 4.9: Sleep Disorder Diagnoses and Cancer Incidence Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Crude		Adjusted[3]	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI
All	All	1.75	(1.66, 1.86)	1.45	(1.37, 1.54)
Prostate	All	1.73	(1.58, 1.90)	1.50	(1.37, 1.64)
Colon	All	1.52	(1.32, 1.75)	1.34	(1.16, 1.54)
Female Breast	All	2.87	(1.50, 5.49)	1.69	(0.88, 3.24)
Other[1]	All	1.75	(1.60, 1.91)	1.45	(1.33, 1.59)
All	Insomnias	1.73	(1.58, 1.89)	1.39	(1.27, 1.52)
Prostate	Insomnias	1.64	(1.43, 1.90)	1.39	(1.20, 1.60)
Colon	Insomnias	1.46	(1.17, 1.82)	1.22	(0.98, 1.51)
Female Breast	Insomnias	2.98	(1.21, 7.30)	1.78	(0.73, 4.38)
Other[1]	Insomnias	1.84	(1.61, 2.10)	1.46	(1.28, 1.67)
All	Apneas	1.70	(1.55, 1.84)	1.44	(1.32, 1.57)
Prostate	Apneas	1.72	(1.51, 1.96)	1.52	(1.38, 1.73)
Colon	Apneas	1.48	(1.21, 1.81)	1.38	(1.12, 1.69)
Female Breast	Apneas	3.31	(1.22, 8.99)	1.90	(0.69, 5.17)
Other[1]	Apneas	1.59	(1.39, 1.82)	1.37	(1.20, 1.57)
All	Other[2]	1.68	(1.46, 1.94)	1.47	(1.28, 1.70)
Prostate	Other[2]	1.69	(1.35, 2.11)	1.54	(1.23, 1.92)
Colon	Other[2]	1.53	(1.08, 2.16)	1.41	(0.99, 1.99)
Other[1]	Other[2]	1.68	(1.35, 2.09)	1.47	(1.18, 1.83)

[1]Other Cancer includes: Lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric, and melanoma cancers. [2]Other sleep disorders include: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. [3]Adjusted for marital status, state or residence, sex (except for gender specific cancers), and age. CI: Confidence Interval.

Table 4.10: Cumulative Sleep Disorder Treatments and Cancer Incidence Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Variable	Cumulative Treatments[2]	Crude		Adjusted[3]	
			Hazard Ratio	95% CI	Hazard Ratio	95% CI
All	Treatment	--	0.96	(0.96, 0.97)	0.96	(0.95, 0.96)
	Treatment*Time	1	1.01	(1.01, 1.01)	1.01	(1.01, 1.01)
		25	1.22	(1.20, 1.24)	1.26	(1.24, 1.28)
		50	1.49	(1.45, 1.53)	1.60	(1.54, 1.65)
		100	2.22	(2.09, 2.35)	2.55	(2.38, 2.72)
Prostate	Treatment	--	0.95	(0.95, 0.96)	0.94	(0.94, 0.95)
		1	1.01	(1.01, 1.01)	1.01	(1.01, 1.01)
	Treatment*Time	25	1.31	(1.27, 1.35)	1.35	(1.30, 1.39)
		50	1.71	(1.61, 1.81)	1.81	(1.70, 1.93)
		100	2.91	(2.58, 3.29)	3.28	(2.88, 3.74)
Colon	Treatment	--	0.99	(0.98, 0.99)	0.98	(0.97, 0.99)
		1	1.004	(1.002, 1.005)	1.004	(1.002, 1.006)
	Treatment*Time	25	1.10	(1.06, 1.14)	1.10	(1.06, 1.15)
		50	1.21	(1.11, 1.30)	1.22	(1.12, 1.33)
		100	1.45	(1.24, 1.70)	1.49	(1.25, 1.77)
Female Breast	Treatment	--	0.99	(0.97, 1.00)	0.97	(0.95, 0.99)
		1	1.00	(1.00, 1.01)	1.006	(1.001, 1.01)
	Treatment*Time	25	1.10	(0.99, 1.23)	1.17	(1.02, 1.34)
		50	1.22	(0.98, 1.51)	1.36	(1.04, 1.78)
		100	1.49	(0.97, 2.29)	1.85	(1.08, 2.18)
Other[1]	Treatment	--	0.97	(0.96, 0.97)	0.96	(0.96, 0.97)
		1	1.007	(1.007, 1.008)	1.01	(1.01, 1.01)
	Treatment*Time	25	1.20	(1.18, 1.23)	1.24	(1.22, 1.27)
		50	1.45	(1.39, 1.51)	1.54	(1.48, 1.61)
		100	2.09	(1.93, 2.27)	2.38	(2.18, 2.60)

Treatment includes a sum of sleep disorder prescriptions, procedures, and surgeries. [1]Includes: lung, pancreatic, kidney, brain, bladder,

liver, ovarian, esophageal, gastric cancers, and melanoma. Cumulative sum of sleep disorder prescriptions, procedures, and surgeries. [3]Adjusted for: marital status, state or residence, gender (except for gender specific cancers), and age. CI: Confidence Interval.

Table 4.11: Sleep Disorder Duration and Cancer Incidence Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Crude		Adjusted[1]	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI
All	1	1.08	(1.07, 1.10)	1.04	(1.03, 1.06)
	5	1.48	(1.39, 1.58)	1.23	(1.16, 1.32)
	10	2.20	(1.94, 2.50)	1.52	(1.34, 1.73)
Prostate	1	1.07	(1.05, 1.10)	1.04	(1.02, 1.07)
	5	1.43	(1.28, 1.59)	1.24	(1.11, 1.38)
	10	2.04	(1.65, 2.53)	1.53	(1.24, 1.90)
Colon	1	1.08	(1.06, 1.11)	1.05	(1.03, 1.08)
	5	1.48	(1.31, 1.67)	1.29	(1.14, 1.46)
	10	2.18	(1.70, 2.79)	1.65	(1.29, 2.12)
Female Breast	1	1.13	(0.96, 1.33)	1.03	(0.87, 1.23)
	5	1.86	(0.82, 4.23)	1.17	(0.49, 2.80)
	10	3.46	(0.67, 17.85)	1.38	(0.24, 7.83)
Other[2]	1	1.08	(1.05, 1.10)	1.04	(1.01, 1.06)
	5	1.45	(1.30, 1.61)	1.20	(1.07, 1.33)
	10	2.10	(1.70, 2.59)	1.43	(1.15, 1.77)

[1]Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.

Table 4.12: All Sleep Disorder Diagnosis and Cancer Incidence Stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Race Stratification	N	Hazard Ratio	95% CI
All	All	African-American	173,942	1.28	(1.16, 1.41)
		European American	298,339	1.37	(1.27, 1.48)
		Unknown/Other	191,588	1.76	(1.41, 2.20)
Prostate	All	African-American	150,732	1.46	(1.29, 1.67)
		European American	279,199	1.33	(1.15, 1.53)
		Unknown/Other	153,523	2.03	(1.52, 2.73)
Colon	All	African-American	173,942	1.04	(0.81, 1.33)
		European American	298,339	1.35	(1.23, 1.61)
		Unknown/Other	191,588	1.21	(0.59, 2.48)
Female Breast	All	African-American	20,994	1.03	(0.37, 2.86)
		European American	15,610	1.31	(0.47, 3.67)
		Unknown/Other	35,006	7.75	(1.64, 36.56)
Other[1]	All	African-American	173,942	1.15	(0.96, 1.37)
		European American	298,339	1.39	(1.25, 1.54)
		Unknown/Other	191,588	1.52	(1.01, 2.28)
Adjusted for: marital status, state or residence, gender (except for gender specific cancers), and age. [1] Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancer, and melanoma. CI: Confidence Interval.					

Table 4.13: Insomnia Sleep Disorder Diagnosis and Cancer Incidence Stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Race Stratification	N	Hazard Ratio	95% CI
All	Insomnias	African-American	173,942	1.33	(1.15, 1.53)
		European American	298,339	1.27	(1.13, 1.43)
		Unknown/Other	191,588	1.65	(1. 18, 2.30)
Prostate	Insomnias	African-American	150,732	1.44	(1.18, 1.76)
		European American	279,199	1.12	(0.88, 1.42)
		Unknown/Other	153,523	2.06	(1.36, 3.14)
Colon	Insomnias	African-American	173,942	1.21	(0.85, 1.72)
		European American	298,339	1.14	(0.86, 1.51)
		Unknown/Other	191,588	0.34	(0.05, 2.41)
Female Breast	Insomnias	African-American	20,994	0.57	(0.08, 4.13)
		European American	15,610	2.01	(0.62, 6.48)
		Unknown/Other	35,006	6.95	(0.87, 55.39)
Other[1]	Insomnias	African-American	173,942	1.24	(0.95, 1.62)
		European American	298,339	1.40	(1.19, 1.64)
		Unknown/Other	191,588	1.47	(0.81, 2.68)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancer, and melanoma. CI: Confidence Interval.

Table 4.14: Apnea Sleep Disorder Diagnosis and Cancer Incidence stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Race Stratification	N	Hazard Ratio	95% CI
All	Apneas	African-American	173,942	1.16	(1.00, 1.35)
		European American	298,339	1.41	(1.27, 1.57)
		Unknown/Other	191,588	1.80	(1.29, 2.51)
Prostate	Apneas	African-American	150,732	1.40	(1.16, 1.69)
		European American	279,199	1.45	(1.19, 1.77)
		Unknown/Other	153,523	1.97	(1.26, 3.08)
Colon	Apneas	African-American	173,942	0.85	(0.57, 1.26)
		European American	298,339	1.50	(1.17, 1.91)
		Unknown/Other	191,588	1.41	(0.52, 3.84)
Female Breast	Apneas	African-American	20,994	1.41	(0.34, 5.78)
		European American	15,610	0.98	(0.14, 7.14)
		Unknown/Other	35,006	10.42	(1.29, 84.09)
Other[1]	Apneas	African-American	173,942	0.96	(0.72, 1.29)
		European American	298,339	1.34	(1.14, 1.57)
		Unknown/Other	191,588	1.62	(0.89, 2.95)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancer, and melanoma. CI: Confidence Interval.

Table 4.15: Other Sleep Disorder Diagnosis and Cancer Incidence stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Race Stratification	N	Hazard Ratio	95% CI
All	Other[2]	African-American	173,942	1.39	(1.11, 1.74)
		European American	298,339	1.33	(1.09, 1.61)
		Unknown/Other	191,588	1.73	(0.98, 3.05)
Prostate	Other[2]	African-American	150,732	1.51	(1.11, 2.06)
		European American	279,199	1.34	(0.97, 1.95)
		Unknown/Other	153,523	1.70	(0.76, 3.80)
Colon	Other[2]	African-American	173,942	1.11	(0.61, 2.02)
		European American	298,339	1.27	(0.81, 2.01)
		Unknown/Other	191,588	3.28	(1.04, 10.34)
Other[1]	Other[2]	African-American	173,942	1.36	(0.90, 2.06)
		European American	298,339	1.34	(1.03, 1.75)
		Unknown/Other	191,588	1.26	(0.41, 3.93)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. CI: Confidence Interval.

Table 4.16: All Sleep Disorder Diagnosis and Cancer Incidence Stratified by the Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	All	No Diabetes	626,109	1.46	(1.37, 1.55)
		Diabetes	37,760	1.44	(1.18, 1.77)
Prostate	All	No Diabetes	547,476	1.54	(1.40, 1.69)
		Diabetes	35,978	1.21	(0.78, 1.61)
Colon	All	No Diabetes	626,109	1.28	(1.10, 1.49)
		Diabetes	37,760	1.94	(1.29, 2.90)
Female Breast	All	No Diabetes	70,065	1.80	(0.94, 3.47)
		Diabetes	1,545	0	(0, 0)
Other[1]	All	No Diabetes	626,109	1.44	(1.31, 1.58)
		Diabetes	37,760	1.55	(1.12, 2.14)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1] Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval

Table 4.17: Insomnia Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Insomnias	No Diabetes	626,109	1.41	(1.29, 1.55)
		Diabetes	37,760	1.16	(0.80, 1.67)
Prostate	Insomnias	No Diabetes	547,476	1.41	(1.22, 1.63)
		Diabetes	35,978	1.12	(0.62, 2.04)
Colon	Insomnias	No Diabetes	626,109	1.20	(0.96, 1.52)
		Diabetes	37,760	1.44	(0.71, 2.92)
Female Breast	Insomnias	No Diabetes	70,065	1.86	(0.76, 4.59)
		Diabetes	1,545	0	(0, 0)
Other[1]	Insomnias	No Diabetes	626,109	1.49	(1.30, 1.71)
		Diabetes	37,760	1.06	(0.56, 1.98)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: Lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.

Table 4.18: Apnea Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Apneas	No Diabetes	626,109	1.42	(1.30, 1.55)
		Diabetes	37,760	1.66	(1.27, 2.16)
Prostate	Apneas	No Diabetes	547,476	1.54	(1.35, 1.77)
		Diabetes	35,978	1.31	(0.83, 2.08)
Colon	Apneas	No Diabetes	626,109	1.28	(1.03, 1.60)
		Diabetes	37,760	2.14	(1.28, 3.58)
Female Breast	Apneas	No Diabetes	70,065	2.07	(0.76, 5.63)
		Diabetes	1,545	0	(0, 0)
Other[1]	Apneas	No Diabetes	626,109	1.34	(1.16, 1.54)
		Diabetes	37,760	1.75	(1.15, 2.67)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1] Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.					

Table 4.19: Other Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type[2]	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Other	No Diabetes	626,109	1.50	(1.29, 1.73)
		Diabetes	37,760	1.24	(0.72, 2.15)
Prostate	Other	No Diabetes	547,476	1.64	(1.31, 2.05)
		Diabetes	35,978	0.46	(0.12, 1.85)
Colon	Other	No Diabetes	626,109	1.36	(0.94, 1.96)
		Diabetes	37,760	1.88	(0.70, 5.07)
Other[1]	Other	No Diabetes	626,109	1.45	(1.15, 1.82)
		Diabetes	37,760	1.83	(0.87, 3.86)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. CI: Confidence Interval.					

Table 4.20: All Sleep Disorder Diagnosis and Cancer Incidence Stratified by the Co-morbid Mental Disorders and Mental Retardation Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	All	No Mental Disorders or Mental Retardation	555,499	1.56	(1.46, 1.67)
		Mental Disorders or Mental Retardation	108,370	1.16	(1.02, 1.31)
Prostate	All	No Mental Disorders or Mental Retardation	485,414	1.54	(1.39, 1.71)
		Mental Disorders or Mental Retardation	98,040	1.38	(1.13, 1.68)
Colon	All	No Mental Disorders or Mental Retardation	555,499	1.53	(1.31, 1.79)
		Mental Disorders or Mental Retardation	108,370	0.84	(0.60, 1.17)
Female Breast	All	No Mental Disorders or Mental Retardation	62,206	1.82	(0.88, 3.78)
		Mental Disorders or Mental Retardation	9,404	1.21	(0.28, 5.16)
Other [1]	All	No Mental Disorders or Mental Retardation	555,499	1.59	(1.44, 1.76)
		Mental Disorders or Mental Retardation	108,370	1.11	(0.91, 1.35)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.					

Table 4.21: Insomnia Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Mental Disorders and Mental Retardation Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	Confidence Interval
All	Insomnias	No Mental Disorders or Mental Retardation	555,499	1.47	(1.33, 1.62)
		Mental Disorders or Mental Retardation	108,370	1.14	(0.95, 1.37)
Prostate	Insomnias	No Mental Disorders or Mental Retardation	485,414	1.39	(1.18, 1.64)
		Mental Disorders or Mental Retardation	98,040	1.31	(0.98, 1.76)
Colon	Insomnias	No Mental Disorders or Mental Retardation	555,499	1.32	(1.03, 1.69)
		Mental Disorders or Mental Retardation	108,370	0.92	(0.57, 1.47)
Female Breast	Insomnias	No Mental Disorders or Mental Retardation	62,206	1.92	(0.70, 5.24)
		Mental Disorders or Mental Retardation	9,404	1.23	(0.17, 9.07)
Other[1]	Insomnias	No Mental Disorders or Mental Retardation	555,499	1.59	(1.37, 1.85)
		Mental Disorders or Mental Retardation	108,370	1.10	(0.83, 1.46)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.					

Table 4.22: Apnea Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Mental Disorders and Mental Retardation Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Apneas	No Mental Disorders or Mental Retardation	555,499	1.55	(1.417, 1.71)
		Mental Disorders or Mental Retardation	108,370	1.15	(0.94, 1.40)
Prostate	Apneas	No Mental Disorders or Mental Retardation	485,414	1.57	(1.36, 1.82)
		Mental Disorders or Mental Retardation	98,040	1.40	(1.04, 1.88)
Colon	Apneas	No Mental Disorders or Mental Retardation	555,499	1.64	(1.32, 2.04)
		Mental Disorders or Mental Retardation	108,370	0.63	(0.35, 1.14)
Female Breast	Apneas	No Mental Disorders or Mental Retardation	62,206	2.57	(0.94, 7.04)
		Mental Disorders or Mental Retardation	9,404	0	(0,0)
Other[1]	Apneas	No Mental Disorders or Mental Retardation	555,499	1.47	(1.27, 1.71)
		Mental Disorders or Mental Retardation	108,370	1.17	(0.87, 1.57)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age.[1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma.. CI: Confidence Interval.					

Table 4.23: Other Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Mental Disorders and Mental Retardation Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type[2]	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Other	No Mental Disorders or Mental Retardation	555,499	1.58	(1.35, 1.85)
		Mental Disorders or Mental Retardation	108,370	1.18	(0.86, 1.61)
Prostate	Other	No Mental Disorders or Mental Retardation	485,414	1.59	(1.24, 2.04)
		Mental Disorders or Mental Retardation	98,040	1.37	(0.84, 2.25)
Colon	Other	No Mental Disorders or Mental Retardation	555,499	1.47	(0.99, 2.18)
		Mental Disorders or Mental Retardation	108,370	1.22	(0.61, 2.45)
Other[1]	Other	No Mental Disorders or Mental Retardation	555,499	1.67	(1.31, 2.12)
		Mental Disorders or Mental Retardation	108,370	0.96	(0.56, 1.63)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2]Includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. CI: Confidence Interval.

Table 4.24: All Sleep Disorder Diagnosis and Cancer Incidence Stratified by the Co-morbid Conditions of Hypertension, Stroke, and/or Cardiovascular Disease Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	Confidence Interval
All	All	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.58	(1.47, 1.70)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.32	(1.20, 1.45)
Prostate	All	No Hypertension, Cardiovascular Disease, and Stroke	376,738	1.61	(1.44, 1.81)
		Hypertension, Cardiovascular Disease, and Stroke	206,716	1.39	(1.19, 1.62)
Colon	All	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.37	(1.14, 1.66)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.36	(1.10, 1.70)
Female Breast	All	No Hypertension, Cardiovascular Disease, and Stroke	60,567	3.03	(1.48, 6.18)
		Hypertension, Cardiovascular Disease, and Stroke	11,043	0.35	(0.05,2.51)
Other[1]	All	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.60	(1.43, 1.79)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.27	(1.09, 1.48)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: Lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric, and melanoma cancers. CI: Confidence Interval.

Table 4.25: Insomnia Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Conditions of Hypertension, Stroke, and/or Cardiovascular Disease Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Insomnias	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.54	(1.39, 1.72)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.21	(1.03, 1.41)
Prostate	Insomnias	No Hypertension, Cardiovascular Disease, and Stroke	376,738	1.56	(1.31, 1.85)
		Hypertension, Cardiovascular Disease, and Stroke	206,716	1.15	(0.88, 1.50)
Colon	Insomnias	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.25	(0.94, 1.66)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.25	(0.88, 1.77)
Female Breast	Insomnias	No Hypertension, Cardiovascular Disease, and Stroke	60,567	3.40	(1.35, 8.55)
		Hypertension, Cardiovascular Disease, and Stroke	11,043	0	(0, 0)
Other[1]	Insomnias	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.62	(1.38, 1.91)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.27	(1.00, 1.61)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.					

Table 4.26: Apnea Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Conditions of Hypertension, Stroke, and/or Cardiovascular Disease Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Apneas	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.49	(1.34, 1.66)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.40	(1.22, 1.60)
Prostate	Apneas	No Hypertension, Cardiovascular Disease, and Stroke	376,738	1.51	(1.28, 1.78)
		Hypertension, Cardiovascular Disease, and Stroke	206,716	1.59	(1.29, 1.95)
Colon	Apneas	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.33	(1.01, 1.75)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.50	(1.11, 2.02)
Female Breast	Apneas	No Hypertension, Cardiovascular Disease, and Stroke	60,567	2.77	(0.86, 9.92)
		Hypertension, Cardiovascular Disease, and Stroke	11,043	0.93	(0.13, 6.70)
Other[1]	Apneas	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.51	(1.28, 1.78)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.20	(0.95, 1.51)
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.					

Table 4.27: Other Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Conditions of Hypertension, Stroke, and/or Cardiovascular Disease Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Type[2]	Co-Morbid Condition	N	Hazard Ratio	95% CI
All	Other	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.64	(1.38, 1.95)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.28	(0.99, 1.63)
Prostate	Other	No Hypertension, Cardiovascular Disease, and Stroke	376,738	1.75	(1.34, 2.29)
		Hypertension, Cardiovascular Disease, and Stroke	206,716	1.29	(0.82, 1.86)
Colon	Other	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.66	(1.09, 2.53)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.13	(0.62, 2.04)
Other[1]	Other	No Hypertension, Cardiovascular Disease, and Stroke	444,622	1.54	(1.17, 2.03)
		Hypertension, Cardiovascular Disease, and Stroke	219,247	1.41	(0.99, 2.03)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Includes: hypersomnia, parasomnia, circadian rhythm, movement disorders, and arousal disorders. CI: Confidence Interval.

Table 4.28: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Race Stratification	N[1]	Hazard Ratio	95% CI
All	1	European American	298,339	1.00	(1.00, 1.01)
		African-American	173,942	1.00	(1.00, 1.01)
		Other/Unknown	191,588	1.00	(1.00, 1.01)
	5	European American		1.17	(1.08, 1.28)
		African-American		1.12	(1.01, 1.25)
		Other/Unknown		1.30	(0.99, 1.71)
	10	European American		1.38	(1.16, 1.64)
		African-American		1.26	(1.02, 1.56)
		Other/Unknown		1.69	(0.98, 2.93)
Prostate	1	European American	279,199	1.00	(0.99, 1.01)
		African-American	150,732	1.00	(1.00, 1.01)
		Other/Unknown	153,523	1.01	(1.00, 1.01)
	5	European American		1.11	(0.93, 1.32)
		African-American		1.19	(1.02, 1.38)
		Other/Unknown		1.66	(1.18, 2.33)
	10	European American		1.23	(0.87, 1.75)
		African-American		1.41	(1.05, 1.90)
		Other/Unknown		2.76	(1.40, 5.45)
Colon	1	European American	298,339	1.00	(1.00, 1.01)
		African-American	173,942	1.00	(0.99, 1.01)
		Other/Unknown	191,588	0.99	(0.99, 1.01)
	5	European American		1.27	(1.09, 1.49)
		African-American		1.14	(0.91, 1.41)
		Other/Unknown		0.92	(0.42, 2.02)
	10	European American		1.62	(1.18, 2.21)
		African-American		1.29	(0.83, 1.99)

Table 4.28: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Race Stratification	N[1]	Hazard Ratio	95% CI
		Other/Unknown		0.85	(0.18, 4.10)
Female Breast	1	European American	15,610	0.99	(0.96, 1.02)
		African-American	20,994	1.00	(0.98, 1.02)
		Other/Unknown	35,006	1.02	(0.98, 1.06)
	5	European American		0.52	(0.07, 3.85)
		African-American		1.18	(0.39, 3.59)
		Other/Unknown		3.25	(0.38, 27.76)
	10	European American		0.27	(0.01, 14.82)
		African-American		1.40	(0.15, 12.87)
		Other/Unknown		10.58	(0.15, 770.74)
Other[2]	1	European American	298,339	1.00	(1.00, 1.01)
		African-American	173,942	1.00	(0.99, 1.00)
		Other/Unknown	191,588	0.99	(0.99, 1.01)
	5	European American		1.15	(1.02, 1.46)
		African-American		1.01	(0.82, 1.25)
		Other/Unknown		0.93	(0.51, 1.70)
	10	European American		1.33	(1.03, 1.72)
		African-American		1.02	(0.67, 1.57)
		Other/Unknown		0.87	(0.26, 2.89)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented are for the main effect. [2] Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.

Table 4.29: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Race Stratification	N[1]	Hazard Ratio	95% CI
All	Treatment		European American	298,339	0.96	(0.95, 0.96)
			African-American	173,942	0.93	(0.92, 0.94)
			Other/Unknown	191,588	0.94	(0.92, 0.96)
	Treatment* Time	1	European American		1.01	(1.01, 1.01)
			African-American		1.02	(1.01, 1.02)
			Other/Unknown		1.01	(1.01, 1.02)
		25	European American		1.25	(1.22, 1.27)
			African-American		1.44	(1.39, 1.50)
			Other/Unknown		1.41	(1.28, 1.55)
		50	European American		1.56	(1.50, 1.62)
			African-American		2.08	(1.92, 2.25)
			Other/Unknown		1.98	(1.64, 2.39)
		100	European American		2.42	(2.24, 2.62)
			African-American		4.32	(3.68, 5.07)
			Other/Unknown		3.92	(2.70, 5.70)
Prostate	Treatment		European American	279,199	0.95	(0.94, 0.96)
			African-American	150,732	0.92	(0.91, 0.93)
			Other/Unknown	153,523	0.93	(0.91, 0.96)
	Treatment*Time	1	European American		1.01	(1.01, 1.01)
			African-American		1.02	(1.02, 1.02)
			Other/Unknown		1.02	(1.01, 1.02)
		25	European American		1.31	(1.26, 1.37)
			African-American		1.54	(1.44, 1.64)
			Other/Unknown		1.46	(1.27, 1.68)
		50	European American		1.72	(1.58, 1.87)
			African-American		2.36	(2.07, 2.69)

Table 4.29: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Race Stratification	N[1]	Hazard Ratio	95% CI
			Other/Unknown		2.13	(1.61, 2.82)
		100	European American		2.96	(2.51, 3.49)
			African-American		5.56	(4.28, 7.22)
			Other/Unknown		4.54	(2.61, 7.93)
Colon	Treatment		European American	298,339	0.99	(0.98, 0.99)
			African-American	173,942	0.97	(0.95, 0.99)
			Other/Unknown	191,588	0.98	(0.93, 1.03)
	Treatment*Time	1	European American		1.00	(1.00, 1.01)
			African-American		1.01	(1.00, 1.01)
			Other/Unknown		1.01	(0.99, 1.02)
		25	European American		1.09	(1.04, 1.15)
			African-American		1.20	(1.08, 1.34)
			Other/Unknown		1.13	(0.86, 1.49)
		50	European American		1.19	(1.07, 1.32)
			African-American		1.44	(1.16, 1.78)
			Other/Unknown		1.28	(0.74, 2.22)
		100	European American		1.41	(1.15, 1.73)
			African-American		2.07	(1.34, 3.18)
			Other/Unknown		1.65	(0.55, 4.92)
Female Breast	Treatment		European American	15,610	0.96	(0.93, 1.00)
			African-American	20,994	0.96	(0.92, 1.00)
			Other/Unknown	35,006	0.92	(0.65, 1.29)
	Treatment*Time	1	European American		1.01	(0.99, 1.02)
			African-American		1.01	(1.00, 1.02)
			Other/Unknown		1.02	(0.95, 1.10)
		25	European American		1.21	(0.98, 1.48)

Table 4.29: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by race Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Race Stratification	N[1]	Hazard Ratio	95% CI
			African-American		1.24	(0.99, 1.56)
			Other/Unknown		1.58	(0.26, 9.67)
		50	European American		1.46	(0.97, 2.20)
			African-American		1.55	(0.99, 2.42)
			Other/Unknown		2.50	(0.07, 93.49)
		100	European American		2.13	(0.94, 4.83)
			African-American		2.40	(0.98, 5.85)
			Other/Unknown		6.23	(0.01, 8,739.77)
Other[2]	Treatment		European American	298,339	0.96	(0.95, 0.97)
			African-American	173,942	0.94	(0.93, 0.95)
			Other/Unknown	191,588	0.94	(0.91, 0.96)
	Treatment*Time	1	European American		1.01	(1.00, 1.01)
			African-American		1.01	(1.01, 1.02)
			Other/Unknown		1.01	(1.01, 1.02)
		25	European American		1.24	(1.21, 1.28)
			African-American		1.41	(1.33, 1.50)
			Other/Unknown		1.43	(1.22, 1.67)
		50	European American		1.54	(1.47, 1.63)
			African-American		1.99	(1.76, 2.26)
			Other/Unknown		2.03	(1.49, 2.77)
		100	European American		2.39	(2.15, 2.64)
			African-American		3.96	(3.09, 5.09)
			Other/Unknown		4.14	(2.22, 7.69)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented for the main effect. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Cumulative sum of sleep disorder prescriptions, procedures, and surgeries. CI: Confidence Interval.

Table 4.30: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Co-Morbid Stratification	N[1]	Hazard Ratio	Confidence Interval
All	1	Diabetes	37,760	1.01	(1.00, 1.01)
		No Diabetes	626,109	1.00	(1.00, 1.01)
	5	Diabetes		1.33	(1.06, 1.66)
		No Diabetes		1.23	(1.15, 1.31)
	10	Diabetes		1.76	(1.12, 2.77)
		No Diabetes		1.51	(1.32, 1.73)
Prostate	1	Diabetes	35,978	1.00	(0.99, 1.01)
		No Diabetes	547,476	1.00	(1.00, 1.01)
	5	Diabetes		1.17	(0.78, 1.77)
		No Diabetes		1.25	(1.11, 1.39)
	10	Diabetes		1.38	(0.60, 3.14)
		No Diabetes		1.55	(1.24, 1.94)
Colon	1	Diabetes	37,760	1.01	(1.00, 1.01)
		No Diabetes	626,109	1.00	(1.00, 1.01)
	5	Diabetes		1.65	(1.56, 2.35)
		No Diabetes		1.25	(1.10, 1.43)
	10	Diabetes		2.72	(1.34, 5.53)
		No Diabetes		1.57	(1.20, 2.04)
Female Breast	1	Diabetes	1,545	0	(0, 0)
		No Diabetes	70,065	1.00	(0.99, 1.02)
	5	Diabetes		0	(0, 0)
		No Diabetes		1.23	(0.52, 2.91)
	10	Diabetes		0	(0, 0)
		No Diabetes		1.51	(0.27, 8.45)
Other[2]	1	Diabetes	37,760	1.00	(0.99, 1.01)
		No Diabetes	626,109	1.00	(1.00, 1.01)

	5	Diabetes		1.21	(0.80, 1.82)
		No Diabetes		1.20	(1.07, 1.34)
	10	Diabetes		1.46	(0.65, 3.29)
		No Diabetes		1.43	(1.15, 1.79)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented are for the main effect. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.

Table 4.31: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by the Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
All	Treatment		Diabetes	37,760	0.96	(0.95, 0.97)
			No Diabetes	626,109	0.96	(0.95, 0.96)
	Treatment*Time	1	Diabetes		1.01	(1.01, 1.01)
			No Diabetes		1.01	(1.01, 1.01)
		25	Diabetes		1.27	(1.21, 1.34)
			No Diabetes		1.26	(1.24, 1.29)
		50	Diabetes		1.62	(1.46, 1.80)
			No Diabetes		1.60	(1.54, 1.65)
		100	Diabetes		2.62	(2.12, 3.25)
			No Diabetes		2.55	(2.37, 2.73)
Prostate	Treatment		Diabetes	35,978	0.95	(0.93, 0.96)
			No Diabetes	547,476	0.94	(0.94, 0.95)
	Treatment*Time	1	Diabetes		1.01	(1.01, 1.02)
			No Diabetes		1.01	(1.01, 1.01)
		25	Diabetes		1.33	(1.20, 1.47)
			No Diabetes		1.35	(1.30, 1.40)
		50	Diabetes		1.77	(1.44, 2.16)
			No Diabetes		1.82	(1.70, 1.96)
		100	Diabetes		3.12	(2.08, 4.68)
			No Diabetes		3.33	(2.90, 3.82)
Colon	Treatment		Diabetes	37,760	0.97	(0.94, 1.00)
			No Diabetes	626,109	0.98	(0.98, 0.99)
	Treatment*Time	1	Diabetes		1.01	(0.99, 1.01)
			No Diabetes		1.00	(1.00, 1.01)
		25	Diabetes		1.17	(0.99, 1.38)

Table 4.31: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by the Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
			No Diabetes		1.10	(1.05, 1.15)
		50	Diabetes		1.36	(0.97, 1.89)
			No Diabetes		1.21	(1.01, 1.32)
		100	Diabetes		1.85	(0.95, 3.59)
			No Diabetes		1.45	(1.21, 1.74)
Female Breast	Treatment		Diabetes	1,545	1.09	(0.84, 1.40)
			No Diabetes	70,085	0.97	(0.95, 0.99)
	Treatment*Time	1	Diabetes		0.97	(0.91, 1.04)
			No Diabetes		1.01	(1.00, 1.01)
		25	Diabetes		0.49	(0.10, 1.58)
			No Diabetes		1.16	(1.02, 1.32)
		50	Diabetes		0.25	(0.01, 6.67)
			No Diabetes		1.34	(1.04, 1.75)
		100	Diabetes		0.06	(0, 44.45)
			No Diabetes		1.81	(1.07, 3.05)
Other[2]	Treatment		Diabetes	37,760	0.96	(0.95, 0.98)
			No Diabetes	626,109	0.96	(0.95, 0.97)
	Treatment*Time	1	Diabetes		1.01	(1.01, 1.01)
			No Diabetes		1.01	(1.01, 1.01)
		25	Diabetes		1.23	(1.44, 1.32)
			No Diabetes		1.24	(1.22, 1.27)
		50	Diabetes		1.51	(1.31, 1.75)
			No Diabetes		1.55	(1.48, 1.62)
		100	Diabetes		2.29	(1.71, 3.05)
			No Diabetes		2.40	(2.18, 2.63)

Table 4.31: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by the Co-morbid Diabetes Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented for the main effect. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancer, and melanoma. CI: Confidence Interval.						

Table 4.32: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Mental Disorders Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
All	1	Mental Disorders or Mental Retardation	108,370	1.00	(0.99, 1.00)
		No Mental Disorders or Mental Retardation	555,499	1.00	(1.00, 1.01)
	5	Mental Disorders or Mental Retardation		1.03	(0.88, 1.19)
		No Mental Disorders or Mental Retardation		1.31	(1.22, 1.40)
	10	Mental Disorders or Mental Retardation		1.06	(0.78, 1.43)
		No Mental Disorders or Mental Retardation		1.70	(1.48, 1.97)
Prostate	1	Mental Disorders or Mental Retardation	98,040	1.00	(0.99, 1.01)
		No Mental Disorders or Mental Retardation	485,414	1.00	(1.00, 1.01)
	5	Mental Disorders or Mental Retardation		1.12	(0.87, 1.44)
		No Mental Disorders or Mental Retardation		1.28	(1.13, 1.44)
	10	Mental Disorders or Mental Retardation		1.25	(0.76, 2.06)
		No Mental Disorders or Mental Retardation		1.63	(1.28, 2.07)
Colon	1	Mental Disorders or Mental Retardation	108,370	0.99	(0.99, 1.00)
		No Mental Disorders or Mental Retardation	555,499	1.01	(1.00, 1.01)
	5	Mental Disorders or Mental Retardation		0.89	(0.64, 1.23
		No Mental Disorders or Mental Retardation		1.41	(1.24, 1.62)
	10	Mental Disorders or Mental Retardation		0.78	(0.41, 1.52)
		No Mental Disorders or Mental Retardation		1.99	(1.53, 2.61)
Female Breast	1	Mental Disorders or Mental Retardation	9,404	1.00	(0.98, 1.03)
		No Mental Disorders or Mental Retardation	62,206	1.00	(0.98, 1.02)
	5	Mental Disorders or Mental Retardation		1.30	(0.27, 6.23)
		No Mental Disorders or Mental Retardation		1.10	(0.39, 3.13)
	10	Mental Disorders or Mental Retardation		1.68	(0.07, 38.79)
		No Mental Disorders or Mental Retardation		1.21	(0.15, 9.82)
Other[2]	1	Mental Disorders or Mental Retardation	108,370	1.00	(0.99, 1.01)
		No Mental Disorders or Mental Retardation	555,499	1.00	(1.00, 1.01)

Table 4.32: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Mental Disorders Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
	5	Mental Disorders or Mental Retardation		1.04	(0.82, 1.32)
		No Mental Disorders or Mental Retardation		1.26	(1.12, 1.42)
	10	Mental Disorders or Mental Retardation		1.08	(0.67, 1.74)
		No Mental Disorders or Mental Retardation		1.59	(1.26, 2.03)
[1]N presented for the main effect. [2]Other Cancer includes: Lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric, and melanoma cancers. Models adjusted for marital status, state or residence, sex (except for gender specific cancers), and age. CI: Confidence Interval.					

Table 4.33: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by the Co-morbid Mental Disorders Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment[2]	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
All	Treatment		Mental Disorders or Mental Retardation	108,370	0.93	(0.92, 0.94)
			No Mental Disorders or Mental Retardation	555,499	0.96	(0.96, 0.96)
	Treatment*Time	1	Mental Disorders or Mental Retardation		1.02	(1.01, 1.02)
			No Mental Disorders or Mental Retardation		1.01	(1.01, 1.01)
		25	Mental Disorders or Mental Retardation		1.45	(1.39, 1.51)
			No Mental Disorders or Mental Retardation		1.24	(1.22, 1.26)
		50	Mental Disorders or Mental Retardation		2.10	(1.93, 2.27)
			No Mental Disorders or Mental Retardation		1.53	(1.48, 1.59)
		100	Mental Disorders or Mental Retardation		4.39	(3.73, 5.17)
			No Mental Disorders or Mental Retardation		2.35	(2.19, 2.53)
Prostate	Treatment		Mental Disorders or Mental Retardation	98,040	0.91	(0.89, 0.92)
			No Mental Disorders or Mental Retardation	485,414	0.95	(0.94, 0.96)
	Treatment*Time	1	Mental Disorders or Mental		1.02	(1.02, 1.02)

			Retardation			
			No Mental Disorders or Mental Retardation		1.01	(1.01, 1.01)
		25	Mental Disorders or Mental Retardation		1.64	(1.51, 1.78)
			No Mental Disorders or Mental Retardation		1.31	(1.26, 1.36)
		50	Mental Disorders or Mental Retardation		2.68	(2.28, 3.16)
			No Mental Disorders or Mental Retardation		1.71	(1.59, 1.84)
		100	Mental Disorders or Mental Retardation		7.18	(5.18, 9.97)
			No Mental Disorders or Mental Retardation		2.92	(2.52, 3.37)
Colon	Treatment		Mental Disorders or Mental Retardation	108,370	0.98	(0.96, 0.99)
			No Mental Disorders or Mental Retardation	555,499	0.98	(0.97, 0.99)
	Treatment*Time	1	Mental Disorders or Mental Retardation		1.01	(1.00, 1.01)
			No Mental Disorders or Mental Retardation		1.00	(1.00, 1.01)
		25	Mental Disorders or Mental Retardation		1.13	(1.02, 1.25)
			No Mental Disorders or Mental Retardation		1.10	(1.05, 1.16)
		50	Mental Disorders or Mental Retardation		1.27	(1.03, 1.56)
			No Mental Disorders or		1.22	(1.10, 1.34)

			Mental Retardation			
		100	Mental Disorders or Mental Retardation		1.61	(1.07, 2.43)
			No Mental Disorders or Mental Retardation		1.48	(1.21, 1.80)
Female Breast	Treatment		Mental Disorders or Mental Retardation	9,404	0.95	(0.89, 1.01)
			No Mental Disorders or Mental Retardation	62,206	0.98	(0.95, 1.00)
	Treatment*Time	1	Mental Disorders or Mental Retardation		1.01	(0.99, 1.03)
			No Mental Disorders or Mental Retardation		1.01	(1.00, 1.01)
		25	Mental Disorders or Mental Retardation		1.33	(0.95, 1.87)
			No Mental Disorders or Mental Retardation		1.15	(0.99, 1.33)
		50	Mental Disorders or Mental Retardation		1.77	(0.90, 3.51)
			No Mental Disorders or Mental Retardation		1.32	(0.98, 1.78)
		100	Mental Disorders or Mental Retardation		3.15	(0.80, 12.32)
			No Mental Disorders or Mental Retardation		1.74	(0.95, 3.16)
Other[2]	Treatment		Mental Disorders or Mental Retardation	108,270	0.94	(0.93, 0.95)
			No Mental Disorders or Mental Retardation	555,499	0.96	(0.96, 0.97)
	Treatment*Time	1	Mental Disorders or Mental		1.01	(1.01, 1.02)

			Retardation			
			No Mental Disorders or Mental Retardation		1.01	(1.01, 1.01)
		25	Mental Disorders or Mental Retardation		1.40	(1.33, 1.48)
			No Mental Disorders or Mental Retardation		1.22	(1.19, 1.25)
		50	Mental Disorders or Mental Retardation		1.96	(1.76, 2.19)
			No Mental Disorders or Mental Retardation		1.49	(1.42, 1.56)
		100	Mental Disorders or Mental Retardation		3.86	(3.08, 4.83)
			No Mental Disorders or Mental Retardation		2.22	(2.01, 2.45)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented are for the main effect. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Cumulative sum of sleep disorder prescriptions, procedures, and surgeries. CI: Confidence Interval.

Table 4.34: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Cardiovascular Disease, Hypertension, or Stroke Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
All	1	Cardiovascular disease, hypertension, and stroke	219,247	1.00	(1.00, 1.01)
		No Cardiovascular disease, hypertension, or stroke	444,622	1.00	(1.00, 1.01)
	5	Cardiovascular disease, hypertension, and stroke		1.18	(1.06, 1.33)
		No Cardiovascular disease, hypertension, or stroke		1.29	(1.20, 1.40)
	10	Cardiovascular disease, hypertension, and stroke		1.39	(1.11, 1.76)
		No Cardiovascular disease, hypertension, or stroke		1.68	(1.44, 1.97)
Prostate	1	Cardiovascular disease, hypertension, and stroke	206,716	1.00	(1.00, 1.01)
		No Cardiovascular disease, hypertension, or stroke	376,738	1.00	(1.00, 1.01)
	5	Cardiovascular disease, hypertension, and stroke		1.19	(0.98, 1.45)
		No Cardiovascular disease, hypertension, or stroke		1.29	(1.14, 1.47)
	10	Cardiovascular disease, hypertension, and stroke		1.41	(0.96, 2.09)
		No Cardiovascular disease, hypertension, or stroke		1.67	(1.29, 2.17)
Colon	1	Cardiovascular disease, hypertension, and stroke	219,247	1.01	(1.00, 1.01)
		No Cardiovascular disease, hypertension, or stroke	444,622	1.00	(1.00, 1.01)
	5	Cardiovascular disease, hypertension, and stroke		1.36	(1.12, 1.66)
		No Cardiovascular disease, hypertension, or stroke		1.29	(1.10, 1.51)
	10	Cardiovascular disease, hypertension, and stroke		1.85	(1.25, 2.75)
		No Cardiovascular disease, hypertension, or stroke		1.66	(1.20, 2.28)
Female Breast	1	Cardiovascular disease, hypertension, and stroke	11,043	0.93	(0.79, 1.09)
		No Cardiovascular disease, hypertension, or stroke	60,567	1.01	(0.99, 1.03)
	5	Cardiovascular disease, hypertension, and stroke		0.01	(0, 179.94)
		No Cardiovascular disease, hypertension, or stroke		1.92	(0.83, 4.44)
	10	Cardiovascular disease, hypertension, and stroke		0	(0, 32379.63)
		No Cardiovascular disease, hypertension, or stroke		3.69	(0.69, 19.68)

Table 4.34: Duration of Sleep Disorder Diagnosis and Cancer Incidence Stratified by Co-morbid Cardiovascular Disease, Hypertension, or Stroke Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Duration (years)	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
Other[2]	1	Cardiovascular disease, hypertension, and stroke	219,247	1.00	(0.99, 1.00)
		No Cardiovascular disease, hypertension, or stroke	444,622	1.00	(1.00, 1.01)
	5	Cardiovascular disease, hypertension, and stroke		1.07	(0.88, 1.31)
		No Cardiovascular disease, hypertension, or stroke		1.30	(1.14, 1.47)
	10	Cardiovascular disease, hypertension, and stroke		1.15	(0.78, 1.70)
		No Cardiovascular disease, hypertension, or stroke		1.68	(1.30, 2.17)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1]N presented are for the main effect. [2]Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. CI: Confidence Interval.

Table 4.35: Cumulative Sleep Disorder Treatment and Cancer Incidence Stratified by the Co-morbid Cardiovascular Disease, Hypertension, and Stroke Among Veterans in the SE USA (VISN-7, 1999-2010).

Cancer Site	Sleep Disorder Treatment Variable	Cumulative Treatment[2]	Co-morbid Stratification	N[1]	Hazard Ratio	95% CI
All	Treatment		Cardiovascular disease, hypertension, and stroke	219,247	0.95	(0.95, 0.96)
			No Cardiovascular disease, hypertension, or stroke	444,622	0.96	(0.95, 0.96)
	Treatment*Time	1	Cardiovascular disease, hypertension, and stroke		1.01	(1.01, 1.01)
			No Cardiovascular disease, hypertension, or stroke		1.01	(1.01, 1.01)
		25	Cardiovascular disease, hypertension, and stroke		1.28	(1.25, 1.31)
			No Cardiovascular disease, hypertension, or stroke		1.26	(1.23, 1.29)
		50	Cardiovascular disease, hypertension, and stroke		1.64	(1.56, 1.72)
			No Cardiovascular disease, hypertension, or stroke		1.58	(1.51, 1.66)
		100	Cardiovascular disease, hypertension, and stroke		2.69	(2.44, 2.97)
			No Cardiovascular disease, hypertension, or stroke		2.51	(2.29, 2.75)
Prostate	Treatment		Cardiovascular disease, hypertension, and stroke	206,716	0.94	(0.93, 0.95)
			No Cardiovascular disease, hypertension, or stroke	376,738	0.95	(0.94, 0.96
	Treatment*Time	1	Cardiovascular disease, hypertension,		1.01	(1.01, 1.02)

			and stroke			
			No Cardiovascular disease, hypertension, or stroke		1.01	(1.01, 1.01)
		25	Cardiovascular disease, hypertension, and stroke		1.39	(1.32, 1.46)
			No Cardiovascular disease, hypertension, or stroke		1.32	(1.27, 1.38)
		50	Cardiovascular disease, hypertension, and stroke		1.93	(1.74, 2.13)
			No Cardiovascular disease, hypertension, or stroke		1.75	(1.60, 1.91)
		100	Cardiovascular disease, hypertension, and stroke		3.71	(3.04, 4.53)
			No Cardiovascular disease, hypertension, or stroke		3.07	(2.57, 3.66)
Colon	Treatment		Cardiovascular disease, hypertension, and stroke	219,247	0.98	(0.97, 0.99)
			No Cardiovascular disease, hypertension, or stroke	444,622	0.98	(0.97, 0.99)
	Treatment*Time	1	Cardiovascular disease, hypertension, and stroke		1.00	(1.00, 1.01)
			No Cardiovascular disease, hypertension, or stroke		1.00	(1.00, 1.01)
		25	Cardiovascular disease, hypertension, and stroke		1.10	(1.03, 1.18)
			No Cardiovascular disease, hypertension, or stroke		1.11	(1.04, 1.17)
		50	Cardiovascular disease, hypertension, and stroke		1.22	(1.06, 1.39)
			No Cardiovascular disease,		1.22	(1.09, 1.39)

			hypertension, or stroke			
		100	Cardiovascular disease, hypertension, and stroke		1.48	(1.13, 1.93)
			No Cardiovascular disease, hypertension, or stroke		1.49	(1.18, 1.89)
Female Breast	Treatment		Cardiovascular disease, hypertension, and stroke	11,043	0.96	(0.92, 0.99)
			No Cardiovascular disease, hypertension, or stroke	60,567	0.98	(0.94, 1.01)
	Treatment*Time	1	Cardiovascular disease, hypertension, and stroke		1.01	(1.00, 1.02)
			No Cardiovascular disease, hypertension, or stroke		1.01	(0.99, 1.01)
		25	Cardiovascular disease, hypertension, and stroke		1.25	(0.99, 1.57)
			No Cardiovascular disease, hypertension, or stroke		1.15	(0.95, 1.39)
		50	Cardiovascular disease, hypertension, and stroke		1.57	(0.99, 2.46)
			No Cardiovascular disease, hypertension, or stroke		1.32	(0.90, 1.94)
		100	Cardiovascular disease, hypertension, and stroke		2.45	(0.99, 6.03)
			No Cardiovascular disease, hypertension, or stroke		1.75	(0.82, 3.75)
Other[2]	Treatment		Cardiovascular disease, hypertension, and stroke	219,247	0.96	(0.95, 0.96)
			No Cardiovascular disease, hypertension, or stroke	444,622	0.96	(0.95, 0.97)
	Treatment*Time	1	Cardiovascular disease, hypertension,		1.01	(1.01, 1.01)

			and stroke		
			No Cardiovascular disease, hypertension, or stroke	1.01	(1.00, 1.01)
		25	Cardiovascular disease, hypertension, and stroke	1.26	(1.22, 1.29)
			No Cardiovascular disease, hypertension, or stroke	1.24	(1.20, 1.28)
		50	Cardiovascular disease, hypertension, and stroke	1.58	(1.48, 1.68)
			No Cardiovascular disease, hypertension, or stroke	1.53	(1.44, 1.63)
		100	Cardiovascular disease, hypertension, and stroke	2.48	(2.18, 2.83)
			No Cardiovascular disease, hypertension, or stroke	2.34	(2.07, 2.66)

Adjusted for: marital status, state or residence, sex (except for gender specific cancers), and age. [1] N presented for the main effect. [2] Includes: lung, pancreatic, kidney, brain, bladder, liver, ovarian, esophageal, gastric cancers, and melanoma. [2] Cumulative sum of sleep disorder prescriptions, procedures, and surgeries. CI: Confidence Interval.

CHAPTER 5

DISCUSSION AND CONCLUSIONS

The major findings of this study were increased cancer risk with sleep disorder diagnosis with evidence of increasing risk with longer durations of sleep disorder exposure, or more sleep disorder-related cumulative treatments, which was used as a possible surrogate measure of sleep disorder severity. Extended Cox adjusted models for cancer incidence with time-varying sleep disorder exposure reflect an increase risk of all, prostate, colon, and other cancers among those with sleep disorders. Our results are similar to those of other studies that have found an increased risk of cancer which used extremes in the length of sleep instead of a clinical sleep disorder diagnosis, including short sleep durations for colon [111, 112], general [108], breast [118], and prostate [121] cancer, and long sleep durations for colon [110, 111] and breast [119] cancer compared to those with normal sleep durations ranging from six to eight hours. Other studies had study populations that were predominantly women in contrast to our predominantly male population. This study's results also were similar to studies that identified a higher incidence of cancer in populations with sleep disorders [40, 120, 144]. Hu, et al. noted a hazard ratio of 1.19 (95% CI: 1.14, 1.24) for non-apnea sleep disorder cancer risk among their study population, which was primarily women with a median age of 44 [40]. For PCa risk, Sigurdardottir, et al. reported a hazard ratio of 1.7 (95% CI: 1.0, 2.9) among those who indicated they had problems falling asleep on questionnaires and an even higher hazard ratio of 2.1 (95% CI: 1.2, 3.7) among those with responses indicating an

increased severity of sleep disruption, which compares to the hazard ratio found in this study of 1.5 (95% CI:1.37, 1.64) for any sleep disorder [120]. Hazard ratios for any sleep disorder in were between 1.34 and 1.69 for the cancer risk group among veterans in the present study, which are similar to the other noted studies. In addition, the increase in cancer risk among veterans in this study with a sleep apnea diagnosis was similar to other studies among those with moderate to severe sleep apnea [107, 109].

Results from this study also indicate that cancer risk increased with increasing sleep disorder duration. There were incremental increases in the hazard ratios for each type of cancer evaluated as sleep disorder duration increased from 1 to 10 years, which suggests a possible dose-response relationship between sleep disorder duration and cancer incidence. We evaluated the risk of cancer incidence at 1, 5, and 10 years of duration, noting increases in cancer hazard ratios ranging from 1.04 to 1.05 after 1 year of diagnosis and increased to 1.52 to 1.65 after 10 years of sleep disorder duration. An increasing risk of each cancer outcome also was observed among those with an increasing number of sleep disorder prescriptions and/or procedures, which may be interpreted as an increase in cancer risk with increasing sleep disorder severity. This also may suggest a dose-response relationship between sleep disorders and cancer incidence. Unfortunately, the number of sleep disorder prescriptions and procedures is only a surrogate for sleep disorder severity, and other interpretations are possible. For example, more treatment may correspond to better managed sleep disorders, or it may suggest an iatrogenic effect or reverse causality of prescription sleep disorder medications on cancer risk, which has been suggested previously [145, 146]. Further research is necessary to determine if the increased risk of cancer is actually due to increased disease severity, or if

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the higher cumulative treatments (primarily prescriptions for sleep medications) are carcinogenic, which has been suggested in some studies [145]. Few studies have focused on sleep disorder duration or severity in conjunction with cancer risk, thus additional research is needed to confirm and extend these observations.

A strength of this study was the use of clinically diagnosed sleep disorders as opposed to self-reported sleep disruption, which was commonly used in previous studies. In addition, the analysis of sleep disorder duration is one of the first to assess the long term impacts of sleep disorders. Other studies have evaluated the duration of sleep during the night in relation to disease [104, 106, 108, 110-112, 114-118, 121], but not the amount of time individuals have suffered from the condition.

This study was limited to information only among veterans seeking care through the Department of Veteran Affairs health care system in the southeastern US. Thus, the generalizability of the results to other populations or geographic areas was limited. Also, veterans who did not visit a VA healthcare center were not included in the analysis. Exclusion of those who transition out of the VA healthcare system could have caused a selection bias in this study. The VA population, though quite large with electronic medical records available for use, has unique demographic characteristics relative to non-veteran populations, making it difficult to generalize the results to the US population. In addition, our analysis was limited by the lack of information related to several known cancer risk factors, including body mass index [140], smoking status, and social economic status. In addition, the presence of undiagnosed sleep disorders may have biased our results towards the null. Finally, it is possible that a pre-diagnostic or occult cancer would have been linked with the onset of a sleep disorder, which may have

resulted in a reverse causality scenario. However, the results obtained from analyses of sleep disorder duration make this an unlikely issue as there was a noted increased cancer risk with longer sleep disorder durations.

Despite these limitations, this study had a robust sample size and is one of the few [40] to evaluate the cancer risk using clinically diagnosed sleep disorders and clinical treatments, as opposed to self-reported or short-term characterization of sleep disruption. Also, no other studies have assessed the effect of the duration of exposure to a sleep disorder over time. Though there are other studies that examined the relationship between of sleep medication use disorder treatment [146, 147], none were found that evaluated the cumulative effect of all such treatments on cancer incidence. No other studies evaluating sleep disorder exposure and cancer incidence in a Veteran population were identified that specifically evaluated the effects of post-traumatic stress disorder with sleep disruption as a symptom.

There was a noticeable increasing trend of sleep disorders diagnosed during the study period. The incidence of sleep disorders diagnosed in 2010 was more than double the number diagnosed in 1999. In particular, the number of apnea sleep disorders diagnosed in 2010 was triple that of 1999 at the beginning of the study. It is unclear if this increase in clinically diagnosed sleep disorders was due to a true increase in incidence of disease or just an increase in physician awareness leading to more clinically diagnosed cases. Sleep disorders were identified in 7% of the study population with sleep apnea (45%) and insomnia (40%) occurring most frequently among those with sleep disorders.

Stratified analysis by diabetes, mental disorders, hypertension, cardiovascular disease, or stroke status did not indicate higher rates of cancer incidence among those suffering from these co-morbid conditions compared to those without co-morbid disease. We observed only modest differences in cancer incidence in the race stratified models for all sleep disorders with AA and EA having similar hazard ratios for all cancer and prostate cancer, but the other/unknown race group having higher risks. For colon cancer, only the EA strata had a statistically significant hazard ratio for cancer among those with any sleep disorders. When the effects of sleep disorder duration were stratified by race, similar increases in hazard ratios for all cancer were observed for both EA and AA participants, although no increases were observed among those in the other/unknown race group. When cumulative treatments were evaluated by race, AAs and the other/unknown race group had higher hazard ratios compared to EAs. Further research is needed to determine whether the impact of sleep disorders on cancer incidence does in fact vary between race groups.

The results of this study suggest a link between sleep disorder diagnoses and cancer incidence. In particular, those who are exposed longer or receive more treatments for a sleep disorder may be at the greatest risk of cancer development. The results may have clinical implications for examining the type and quantity of treatment offered as it might be related to subsequent cancer risk.

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