Energy Balance and Cancer 8

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Impact of Sleep and Sleep Disturbances on Obesity and Cancer

Springer

Energy Balance and Cancer

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ISBN 978-1-4614-9526-0 ISBN 978-1-4614-9527-7 (eBook)
DOI 10.1007/978-1-4614-9527-7
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013955913

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Sleep has recently been recognized as a critical determinant of energy balance, regulating restoration and repair of many of the physiological and psychological processes involved in modulating energy intake and utilization. Emerging data indicate that sleep can now be added to caloric intake and physical activity as major determinants of energy balance with quantitative and qualitative imbalances leading to under- or overnutrition and associated comorbidities. Considerable research is now focused on disorders of sleep and circadian rhythm and their contribution to the worldwide obesity pandemic and the associated comorbidities of diabetes, cardiovascular disease, and cancer. In addition to having an impact on obesity, sleep and circadian rhythm abnormalities have been shown to have significant effects on obesity-associated comorbidities, including metabolic syndrome, premalignant lesions, and cancer. In addition to the observation that sleep disturbances are associated with increased risk for developing cancer, it has now become apparent that sleep disturbances may be associated with worse cancer prognosis and increased mortality. Sleep problems and fatigue also constitute a significant challenge for the ever-expanding group of cancer survivors and their caregivers as well. Moreover, circadian misalignment, such as that experienced by "shift workers," has been shown to be associated with an increased incidence of several malignancies, including breast, colorectal, and prostate cancer, consistent with the increasing recognition of the role of clock genes in metabolic processes. Of increasing concern are the high prevalence of sleep disorders in childhood, their association with childhood obesity, and associated abnormalities of circulating cytokines, adipokines, and metabolic factors, many of which are implicated as etiologic mediators of the connection between obesity and cancer. In fact, sleep disturbances in childhood, through their contribution to obesity and associated adult malignancies, may pose a significant public health problem, possibly parallel to tobacco use in childhood and its association with the later development of multiple tobacco-related adult malignancies. Extensive studies have now been initiated to investigate the mechanisms by which disturbances in sleep duration, sleep continuity, sleep-related breathing, and circadian rhythm affect central and peripheral tissue oxygenation and metabolism,

quality and quantity of dietary intake, and circulating inflammatory cytokines and regulatory hormones. This volume of Energy Balance and Cancer will review current state-of-the-art studies on sleep, obesity, and cancer, with chapters focusing on molecular and physiologic mechanisms by which sleep disruption contributes to normal and abnormal physiology, related clinical consequences, and future research needs for laboratory, clinical, and translational investigation.

This volume, number 8 in the series on Energy Balance and Cancer, *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, was developed to alert cancer researchers and clinicians of the significant increase in scientific research focused on this relation and to provide new insights into the underlying mechanisms as well as the need to consider sleep disturbances in clinical cases. While the sleep research community has been highly interactive with neuro- and cardiovascular physiologists, they only recently have been interacting with basic and clinical cancer researchers. We anticipate that this volume will increase the interaction among these communities, leading to new and productive transdisciplinary approaches to research.

As with previous volumes in the series, we have been fortunate to engage the pioneers and world leaders studying the interface of sleep disturbance and cancer to provide chapters for this volume. In Chap. 1, Carolyn D'Ambrosio (Tufts University School of Medicine, Boston, MA) and Susan Redline (Harvard Medical School, Boston, MA) outline changes in sleep and sleep disorders across the life span. Chapter 2, written by Orfeu Buxton (Harvard Medical School, Boston, MA), Josiane Broussard (Cedars-Sinai Medical Center, Los Angeles, CA), Alexa Zahl (Harvard Medical School, Boston, MA), and Martica Hall (University of Pittsburgh School of Medicine, Pittsburgh, PA), examines the effects of insufficient sleep on metabolic processes and regulatory pathways. In Chap. 3, Katherine Dudley and Sanjay Patel (Harvard Medical School) discuss melatonin metabolism, its normal role in regulating sleep, how it may be altered by disturbances in sleep patterns, and some of its attendant consequences. In Chap. 4, Keith C. Summer and Fred W. Turek (Northwestern University, Chicago, IL) identify many of the molecular components of the circadian clock and how their disruption affects cancer and other disease states. Chapter 5, written by Jayashri Nanduri and Nanduri Prabhakar (University of Chicago, Chicago, IL), provides an expert examination of the molecular and physiologic consequences of intermittent hypoxia and their possible role in cancer. In Chap. 6, F. Javier Nieto (University of Wisconsin, Madison, WI) and Ramon Farré (University of Barcelona, Barcelona, Spain) have teamed up to report the effects of sleep apnea and hypoxia on cancer epidemiology and the important development of an animal model to study these effects. Returning to clinical epidemiology, in Chap. 7, Elizabeth Devore and Eva S. Schernhammer (Harvard Medical School) discuss the important pioneering and continuously evolving insights on the relation of shift work to obesity and cancer. In Chap. 8, Cheryl Thompson and Li Li (Case Western Reserve University, Cleveland, OH) discuss recent studies linking sleep disorders to cancer risk and prognosis. Chapter 9, coauthored by Christine Miaskowski and Bradley Aouizerat (University of California San Francisco, School of Nursing, San Francisco, CA), reviews the important clinical problems associated with sleep disturbances and fatigue in cancer patients, possible interventions, and

corrective interventions, and in Chap. 10, Lavinia Fiorentino and Sonia Ancoli-Israel (University of California San Diego, San Diego, CA) discuss sleep disturbances in cancer survivors, an ever-increasing challenge because of the increase in this population. Chapter 11 completes this volume with a discussion of interventions for sleep disorders by Marie-Pierre St-Onge and Ari Shechter (Columbia University College of Physicians and Surgeons, New York, NY).

The great diversity and transdisciplinary nature of these chapters clearly illustrate the depth and breadth of this relatively recent surge on sleep and cancer. This volume, *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, summarizes recent developments in this rapidly evolving field and provides important directions for much needed research. As with other aspects of the evolving energy balance and cancer story, this volume shows how progress is made when investigators link epidemiology, molecular biology, neurophysiology, biobehavioral, and clinical studies in a transdisciplinary fashion to enhance understanding and promote progress in these complex challenges.

This book should be of interest to students, researchers, and clinicians across a broad range of disciplines, especially those involved in energy balance and cancer research, as well as to clinicians who deal with sleep disturbances in patients undergoing therapy as well as those who are cancer survivors.

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Chapter 1
Sleep Across the Lifespan

Carolyn D'Ambrosio and Susan Redline

Abstract Sleep represents a complex neurophysiological process which varies significantly across the lifespan. Sleep-wake activity is governed by a complex array of neural processes, influenced by the environment, and tightly integrated with other key biological processes such as thermoregulation, hormone release, and feeding behaviors. Changes in sleep quality and duration across the lifespan occur in part as a result of the influences of age-dependent physiological processes (e.g., menopause) or diseases (e.g., heart failure) on sleep. Conversely, changes in sleep over the lifespan impact a wide variety of physiological systems, including those important in modulating weight, metabolism, immune function, and inflammation. Thus, changes in sleep across the lifespan may influence the propensity for age-dependent diseases as well as susceptibility to chronic diseases, including diabetes, vascular disease, and cancer. This chapter reviews key changes in circadian rhythm, sleep architecture, sleep patterns, and sleep disorders across the lifespan, providing an overview of sleep neurophysiology and age-specific sleep characteristics which, as described more fully in other chapters, influence propensity for obesity and chronic diseases. A discussion of sleep in key periods in the lifespan – infants, children, adolescence, middle age, and older adulthood – is provided. A better appreciation of sleep changes across the lifespan may improve our understanding of disease mechanisms and may highlight novel approaches for improving health at critical developmental periods.

Keywords Age • Development • Sleep • Circadian rhythm • Pediatrics • Elderly

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_1,

Introduction

Sleep: Neurophysiological Overview

Sleep is a complex neurophysiological process governed by two intrinsic biological systems, which together determine the timing of sleep and wakefulness [1]. First is the homeostatic process that describes both the increasing pressure to sleep as the duration of prior wakefulness increases (process "S," shaping sleep onset times) and the dissipation of this drive in response to sleep (process "S," influencing wakening times from sleep). Age-related changes in sleep homeostatic processes contribute to the tendency for earlier bedtimes in the elderly and later bedtimes in adolescents. Second is the influence of circadian rhythms (process "C"), determined by the output from the suprachiasmatic nuclei (SCN), the body's pacemaker or biological clock, which causes well-defined diurnal fluctuations in sleep propensity and alertness (e.g., with maximal sleep propensity occurring between 2 am and 4 am). The SCN is located above the optic nerve at the base of the third ventricle, receives light input from the eye, and is close to regulatory centers in the hypothalamus. Circadian rhythms influence 24-h patterns in core body temperature and the secretion of melatonin and cortisol – key markers and modulators of the sleep-wake cycles. External influences (called zeitgebers) help align the circadian clock output with the 24-h day. The major zeitgeber is light, but factors such as feeding, temperature, and other environmental cues can influence circadian alignment.

As the brain develops and ages, the output from neural centers important in circadian and sleep-wake control varies. At 1 month of age, core body temperature has a circadian rhythm, and at 3 months of age, melatonin and cortisol are secreted in a circadian manner. The amplitude and timing of circadian rhythms change with puberty and decline with advanced age. Additionally, over the individual's lifespan, the social environment changes (work, school, and social demands), which also influence bed and wake times. Together, these intrinsic and extrinsic influences cause age-specific differences in diurnal sleep-wake activity, sleep duration, sleep architecture, and sleep propensity. Some factors also vary by gender, and many sleep traits demonstrate age differences that differ in women and men.

Sleep is characterized not only by its presence or absence (and timing) but by its quality. Sleep is composed of distinct neurophysiological stages, each described by specific patterns of brain cortical electroencephalographic activity, and associated with differences in arousal threshold, autonomic and metabolic activity, chemosensitivity, and hormone secretion [2]. Sleep is objectively measured using polysomnography (PSG), which includes scalp electroencephalography (EEG). Each sleep stage is characterized by specific patterns of EEG activity, described by EEG amplitude (partly reflecting the synchronization of electrical activity across the brain) and EEG frequency. Lighter sleep (stages N1, N2) displays relatively low-amplitude and high-frequency EEG activity, while deeper sleep (slow-wave sleep, N3) is of higher amplitude and lower frequency. Stages N1, N2, and N3 comprise non-rapid eye movement (REM) sleep (NREM). In contrast, rapid eye movement (REM)

sleep is a variable frequency, low-amplitude stage, in which rapid eye movements occur and muscle tone is low. Sympathetic tone is highest in stage REM sleep, while parasympathetic tone is highest in stage N3. In adults, over the course of the night, NREM and REM sleep cycles recur approximately every 90 min, although their composition differs across the night: early cycles typically have large amounts of N3, while later cycles have large amounts of REM. The absolute and percentage times in given sleep stages, as well as the pattern and timing of progression from one stage to another, provide information on overall sleep architecture and are used to quantify the degree of sleep fragmentation. Sleep characterized by frequent awakenings, arousals, and little N3 is considered to be lighter or non-restorative and contributes to daytime sleepiness and impaired daytime function. Higher levels of N3 are thought to be "restorative." N3, which usually predominates early in the night, reflects dissipation of homeostatic pressure; its levels may increase in response to levels of mental or physical activity over the prior day, and it is considered to be important in memory consolidation [3]. N3 sleep is also linked to somatotropin axis function (including growth hormone and IGF-1 release), and perturbations in N3 (fragmentation, restriction) have been linked to insulin resistance, diabetes, and hypertension incidence [4, 5]. REM sleep appears important for mood and in memory and is considered to be important to the developing brain, possibly because it provides neural stimulation to form mature neural connections in the newborn. Both stages N3 and REM are reduced when sleep is fragmented due to environmental disturbances, arousals related to primary sleep disorders (sleep apnea, periodic limb movements), certain medication, and substance use factors which may contribute to sleep-related adverse health outcomes.

Age is also a particularly strong determinant of sleep consolidation, state distribution, and micro-architecture [6]. Sleep-activity cycles can be identified electroencephalographically in early fetal life. As the fetus progresses towards infancy and subsequently through adulthood, there are distinctive EEG sleep architecture changes with age. As described later, sleep is characterized by marked reductions in stage N3 in adolescents, with further decreases in aging adults, with greater age-specific decreases in men than in women. Sleep also becomes less consolidated or more fragmented with advancing age. Sleep timing shows shifts from relatively "delayed" phases in adolescents to "advanced" phases in older adults; shifts in circadian phase may influence sleep architecture.

Sleep Disorders

The common sleep disorders sleep-disordered breathing (SDB), insomnia, and restless legs syndrome (associated with periodic limb movement disorder) vary across the lifespan when each may influence age-related diseases such as cardiovascular disease and diabetes.

SDB, particularly obstructive sleep apnea (OSA), is characterized by recurrent collapse of the pharynx during sleep, resulting in sleep disruption, intermittent

hypoxemia, surges of sympathetic activity, and marked swings in intrathoracic pressure. Profound physiological responses to these disturbances may result in surges in nocturnal blood pressure as well as in sustained daytime hypertension, endothelial dysfunction, dyslipidemia, an augmented inflammatory state, and insulin resistance. Patients with SDB are at increased risk for stroke, heart failure, diabetes, cancer, and mortality [7–9]. SDB occurs at all ages, although it is most common in middle-aged and older individuals. Susceptibility relates to the propensity for repetitive upper airway collapse. In any individual, propensity for airway collapse is determined by anatomic and neuromuscular factors that influence upper airway size and/or function. Chemoresponsiveness (particularly to changes in CO_2 and oxygen tensions) and responsivity to arousal also influence propensity for OSA [10]. These factors may vary across the lifespan and may vary by gender. Effects depend on the prevalence of that risk factor at given ages and are influenced by age-related changes in airway size and collapsibility, hormonal changes, and maturation of breathing control systems.

The influence of race/ethnicity on SDB varies by age, with strongest associations between SDB and race observed in children [11]. In particular, SDB is sixfold more common in African-American than white children [12]. African-American children also have a less positive response to adenotonsillectomy than do white children [13]. Other risk factors for SDB that appear particularly salient for children are low socioeconomic status and living in a distressed neighborhood [14]. Thus, minority children and those from low SES status may have a longer lifetime burden of SDB, which may contribute to an increased risk of chronic diseases.

Insomnia, identified by complaints of problems initiating and/or maintaining sleep, is common, especially among women. Insomnia is often associated with a state of hyperarousal and has been linked to increased risk of depression, myocardial infarction, and cardiovascular mortality [15]. Relative risks for cardiovascular disease for insomnia have been estimated to vary from 1.5 to 3.9; a dose-dependent association between frequency of insomnia symptoms and acute myocardial infarction has been demonstrated [16]. Insomnia may be particularly problematic at certain times in the lifespan, especially in the perimenopause period and in association with acute life stresses, such as loss of a loved one. The occurrence of insomnia during critical periods, such as menopause, may contribute to increased cardiometabolic risk factors at those times.

Short sleep duration may occur secondary to a primary sleep disorder or secondary to behavioral/social issues. Regardless of etiology, short sleep duration has been associated with increased risk of obesity, weight gain, diabetes, cardiovascular disease, and premature mortality [17, 18]. Effects are thought to be mediated by sympathetic nervous system activation, alterations of the hypothalamic pituitary adrenal axis influencing secretion of cortisol and the renin-angiotensin system, and augmented systemic levels of inflammation such as elevations in C reactive protein (CRP) levels. These physiological perturbations contribute to renal dysfunction, endothelial dysfunction, and atherosclerosis. Associations with obesity are seen across the lifespan, with evidence that associations are strongest among young children. This suggests the importance of improving sleep in individuals of all ages,

particularly infants and children. Abnormal sleep duration also is associated with low socioeconomic class, obesity, minority race, poorer mental health, tobacco use, alcohol, and poorer overall general health. Thus, there are potential additive or multiplicative effects of poor sleep with other health risk factors. Age may also modify the effects of sleep deprivation on health. For example, in an analysis data from the First National Health and Nutrition Examination Survey (NHANES-1) of nearly 5,000 adults followed for 8–10 years, a significant increased incidence of hypertension was observed in individuals 32–59 years of age reporting 5 or fewer hours of sleep per night compared to those reporting 7–8 h of sleep per night. In contrast, no associations were observed among those more than 60 years of age [19]. These data underscore the importance in quantifying thresholds for optimal sleep duration across the age span.

Age-Specific Sleep Characteristics

Infancy (Neonate to Twelve Months)

Circadian Rhythm

Prior to birth, the sleep-activity cycle is distributed across the 24-h period evenly. At birth, the day-night cycles are not yet entrained. As the central circadian pacemaker, the SCN, matures, external cues (zeitgebers) help to entrain the body into a day-night (wake-sleep) cycle. By about 6 weeks of life, the infant is more awake during the day and has more sleep during the typical night hours. By 4 months of age, most infants have "settled," meaning that they are sleeping most of the night. Additionally, at this time the two intrinsic processes that determine the timing of sleep and wakefulness, sleep homeostasis and circadian rhythm, are manifest. At 1 month of age, core body temperature displays a circadian rhythm, and at 3 months of age, melatonin and cortisol are secreted in a circadian manner. The 24-h day-night entrainment of the circadian cycle also is influenced by parents' activities and social customs.

Sleep Architecture Development

Sleep patterns in the brain start to develop at approximately 24-week post-conceptual age (PCA). This is evidenced by some neuronal electrical activity, but at this point it is very difficult to differentiate between sleep and wakefulness. Between 24- and 32-week PCA, a distinct EEG pattern called trace discontinue is seen [20–22]. Trace discontinue is characterized by bursts of high-voltage delta waves separated by prolonged episodes of electrical silence. After 32-week PCA trace discontinue matures into trace alternant, which is characterized by bursts of high-voltage delta waves interrupted by low-voltage mixed frequency activity on the EEG.

This pattern evolves into quiet sleep as the baby develops. Also around 32 weeks, active sleep can be seen on the EEG. By full term, three distinct sleep stages have developed: (1) active sleep, (2) quiet sleep, and (3) indeterminate sleep [23].

In the first few weeks of life, sleep can total up to 16 h in a 24-h period. Each cycle of sleep is 30–70 min in duration. During this time, individual sleep stages differ from that of adults. During active sleep, the infant may demonstrate some movements such as eye movements, facial grimaces, sucking, and myoclonic jerks, but these are on a background of mostly muscle atonia [20]. The hallmark of active sleep is an irregular breathing pattern. This stage is thought to develop into REM sleep as the infant gets older and the brain matures. At birth, active sleep accounts for up to 50 % of total sleep time, but this decreases to 20–25 % by 1 year of age [20, 21].

During quiet sleep, large muscle movements are generally not present, but the muscle tone on EEG is higher than seen in active sleep. The breathing pattern is regular and the EEG demonstrates trace alternant (bursts of high-voltage slow activity alternating with greatly attenuated activity). This stage develops into NREM sleep as the infant gets older and the brain matures. Trace alternant typically is not seen after about 6 weeks of life as it is replaced by stage N3 (slow-wave sleep) [20, 23].

Indeterminate sleep is the term used when polysomnography data do not clearly show changes that fit the definition of either active or quiet sleep. This usually disappears after the first month of life [20, 23].

Sometime around the second to third month of life, the EEG patterns of sleep start to take on the characteristics of adult sleep with evidence of more distinct features of stage N3 and emergence of characteristics of stage N2 sleep, namely, sleep spindles (bursts of oscillatory EEG activity) [20, 22, 23]. Although sleep architecture becomes more similar to adults, the proportion of time spent in each sleep stage differs in children and adults. As the brain matures and cortical synaptic density increases in the first year, the EEG pattern becomes more synchronized. This is an important period of neural reorganization with behavioral and physiological influences on sleep-wake patterns. By 3–4 months of age, the total sleep time starts to decrease to about 14–15 h per 24-h period, and the infant starts to show more attentive behavior during wakefulness. Also at approximately 6–8 weeks of age, the infant starts having more defined sleep and wakefulness throughout the 24-h period with more discrete daytime naps and a longer sleep period during the night. By age 6 months, this matures into the long wake period during the day and a more consolidated sleep period during the nights. In the first 8 weeks of life, the percentage of REM-active sleep and NREM-quiet sleep are about equal. Over the first 6 months of life, the percentage of REM sleep decreases and therefore the NREM percentage increases. Also, in the first few weeks of life, the infant enters sleep via REM, but this changes to NREM by about 3 months of age.

Both the sleep environment and genetic factors influence the nighttime sleep characteristics of infants. Gender does not seem to play a role in nighttime sleep duration. There is some evidence that sleep varies by ethnicity, but sorting out the effects of the environment or genetics is difficult. Sleep is also influenced by culture, such as the degree to which sleep routines are more or less structured, the occurrence of maternal-child co-sleeping, and use of sleep aids such as pacifiers.

Breathing During Sleep

Infants are particularly vulnerable to sleep disturbances, especially sleep-related breathing disorders, during the first 6 months of life. Vulnerability is likely due to anatomic risk factors (narrow, collapsible airway) and inappropriate responses to chemoreflexes. In NREM or quiet sleep, the breathing pattern is quite stable, but the respiratory rate is reduced, tidal volume is reduced, and therefore minute ventilation (respiratory rate x tidal volume) is diminished. REM or active sleep is notable for irregular breathing patterns. This is typically when periodic breathing of prematurity occurs. Infants also spend more time asleep in REM-active sleep relative to older children and adults, thus making sleep a more vulnerable time for infant's breathing [24, 25].

Sudden infant death syndrome (SIDS) is the most common cause of postneonatal infant death with approximately 2,300 deaths per year in the USA [26]. Rates are two- to threefold higher in the African-American and Native American communities. Other abnormalities of breathing during sleep in infants include apparent life-threatening event (ALTE), apnea of prematurity, and central congenital hypoventilation syndrome (CCHS) [27].

SIDS is defined as "the sudden death of any infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history." [26] It is more common in winter months, with infant boys, in lower socioeconomic areas and in children of parents who smoke tobacco [28, 29]. Infants born premature or with a family history of SIDS have a higher risk of SIDS. Also, infants who experience an ALTE have an increased risk. However, it is very important to note that the majority of infants who die from SIDS do not have any risk factors. The highest risk occurs between 2 and 3 months with 90 % of infants who die from SIDS being less than 6 months of age. One major risk factor that is preventable is sleep position. Since the start of the "Back to Sleep" campaign which educated parents to have the child sleep in the supine position, SIDS rates have plummeted. Other modifiable risk factors are loose bedding, soft sleep surface, bed sharing, and overheating [30]. Factors associated with reducing the risk of SIDS include use of a pacifier, breast feeding, room sharing (as opposed to bed sharing), and use of a fan in the bedroom [31, 32].

Apparent life-threatening event (ALTE) is a multifactorial paroxysmal event in an infant characterized by changes in tone, color, and breathing that is frightening to the caregiver [33]. Some descriptions include witnessed apnea, color change such as cyanosis, loss in muscle tone, and choking or gagging. The most common cause of these is gastrointestinal reflux, but may also be caused by seizures, infections, or intentional trauma. They are often benign and a link between ALTE and SIDS has not been confirmed. However, several case series documented a familial aggregation of SIDS, ALTE, and obstructive sleep apnea (in children and adults), suggesting that in some instances, each disorder may share common familial risk factors [34].

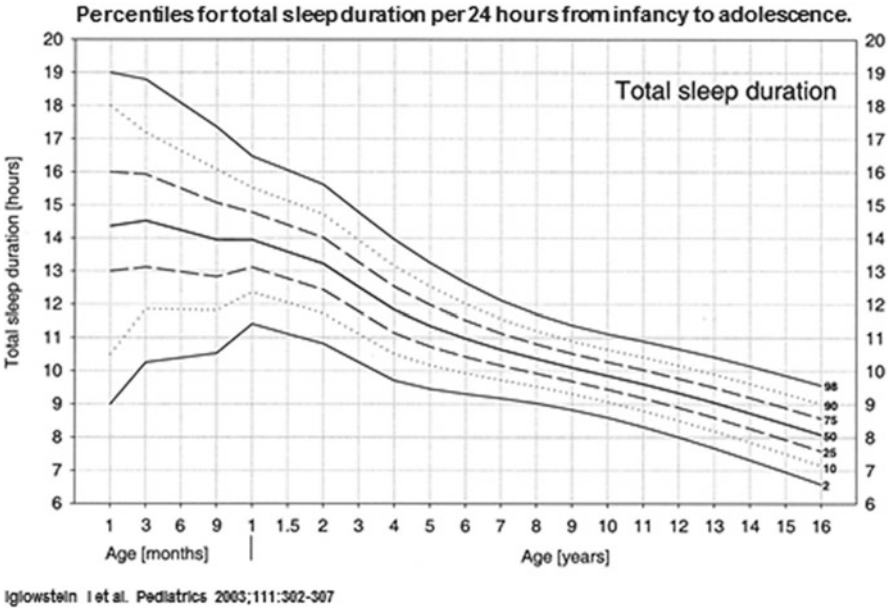

Fig. 1.1 Change in sleep duration across infancy and childhood (percentiles shown for each age, data from the Zurich Longitudinal Study; $n = 493$). The amount of time decreases as we age, with a large drop in the first year of life. A large variation among individuals is seen at all ages (From Iglowstein et al. [35])

Sleep in Early Childhood

Circadian Rhythm

In the first year of life, sleep duration averages 14 h in a 24-h period [35]. However, over the first year of life, sleep distribution changes from occurring across the 24-h period relatively regularly to, by 6 months of age, occurring predominantly at night, with approximately two naps during daytime. As children age beyond 1 year, the duration and frequency of naps reduces and thereby reduces total sleep time per 24 h to 10–13 h (Fig. 1.1). Circadian rhythm in early childhood is also influenced by external forces such as activity, exposure to light, and parental and cultural norms. In the USA, sleep duration is shorter in young children from minority ethnicity [36]. Daytime naps also differ by race and culture [37, 38]. Most children in the USA stop napping between ages 3 and 5 years. However, up to 39 % of African-American children still nap up to age 8 compared to only 4.9 % in white children [38]. The African-American children who napped had shorter nocturnal sleep duration. It is not clear whether differences in sleep patterns by race reflect genetic or environmental factors. However, shorter nocturnal sleep during infancy and early childhood is associated with increased weight at age 3 years, and thus sleep patterns in early

childhood may significantly contribute to obesity risk in minority and other children.

Sleep Architecture

In early childhood, the sleep stages are the same as adults, but the percentages are different. Young children have more stage N3 than older teenagers and adults [39, 40]. The sleep cycles are shorter than adults with each cycle occurring approximately every 40–60 min. This shorter cycle length may contribute to nocturnal arousals and awakenings. Abnormalities in sleep architecture during early childhood may contribute to daytime sleepiness and behavior and cognitive impairments.

Sleep-Disordered Breathing

Breathing is affected by sleep in early childhood and one of the more common problems is OSA. The peak age of OSA in children is in early childhood when the size of the lymphoid tissue (adenoids and tonsils) is largest compared to the size of the airway, thus leading to obstructive breathing. For children with congenital abnormalities, neuromuscular control of the upper airway is another important component. OSA is considered the severe end of a spectrum of related clinical conditions grouped together as "sleep-disordered breathing": primary snoring, upper airway resistance syndrome, and partial obstructive hypoventilation hypopneas. Seven to fifteen percent of children are habitual snorers, while 2–6 % may have frank OSA. Risk factors include enlarged adenoids and tonsils, craniofacial abnormalities, history of preterm birth, and African-American race [12]. However, obesity also increases risk of OSA in young children, and this factor may increase in relative importance as the prevalence of pediatric obesity grows [41]. Studies have also shown an increased risk of OSA in African-American children and those from lower socioeconomic status independent of obesity [14].

All of the conditions along this spectrum are associated with behavioral and cognitive impairments [42, 43]. Obstructive hypopneas and apneas with significant oxygen desaturations can lead to failure to thrive and cor pulmonale. Because of the developmental plasticity of the brain of young children, exposure to intermittent hypoxemia may be particularly deleterious [44].

Sleep in Older Children, the Influence of Puberty

Circadian Rhythm

As children enter school years, prior to the onset of puberty, the total sleep time per day decreases to 9–11 h on average and is almost exclusively during the night, with

little napping. Puberty appears to affect sleep and sleep patterns. A delayed circadian cycle is evident, corresponding to later secretion of melatonin (around 11 pm) [45]. Without societal demands, this would shift bedtime and wake times to later times. However, external factors such as early school start times require children to wake up earlier than would be set by their biological clock. This misalignment may contribute to significant sleep deprivation and sleepiness, which is further exacerbated by other societal demands (homework and school activities keeping the child up later in the night). In fact, between 50 % and 68 % of teens report sleepiness during the day, and a majority do not get the recommended 8–9 h of sleep per night [46]. These children may then attempt to make up for their sleep "debt" by sleeping longer on weekends. Increased day-to-day variability in sleep duration may further adversely affect health.

For girls, hormonal changes during puberty also affect the circadian rhythm and sleep overall [47]. Changes in sleep quality are reported to vary with phase of the menstrual cycle. The luteal phase of the menstrual cycle, when progesterone is high and the core body temperature is higher than normal, is reported to have longer onset to sleep and poorer quality of sleep.

Chronic sleep deprivation may contribute to poor school performance as well as to the neurohumoral effects associated with obesity and metabolic dysfunction. A study of adolescents (ages 13–16 years) showed that shorter sleep duration or reduced sleep efficiency was associated with higher fasting insulin levels and higher blood pressure [48, 49]. Shorter sleep is also associated with higher BMI in children and adolescents, with evidence that effects are stronger in the younger children [50]. Weight gain may be secondary to increased consumption of high fat foods and increased snacking that accompanies shorter sleep duration. There may be a stronger association between short sleep duration and obesity in boys compared to girls, although the association between increased caloric intake and short sleep appears to be stronger in girls [51].

Sleep Architecture

During the transition from adolescence to adult, several changes occur to the sleep architecture. Most notably is the significant reduction in stage N3 sleep by approximately 40 % as the child progresses through the teenage years (Fig. 1.2). This means that other stages of NREM (N1 and N2) take up more of the sleep time. Functionally this translates to the child having lighter sleep during the night and therefore is easier to arouse and awaken. Also, the biological influence of N3 on memory, learning, and hormonal control may vary across childhood as N3 decreases. Other changes in sleep architecture during this period include a longer latency to sleep onset and shorter latency to REM sleep.

At the end of puberty, the sleep cycle is very much like adults with 90-min NREM-REM sleep cycles. Menarche does not seem to substantively influence sleep architecture. Some studies, however, show that sleep spindle density is greater

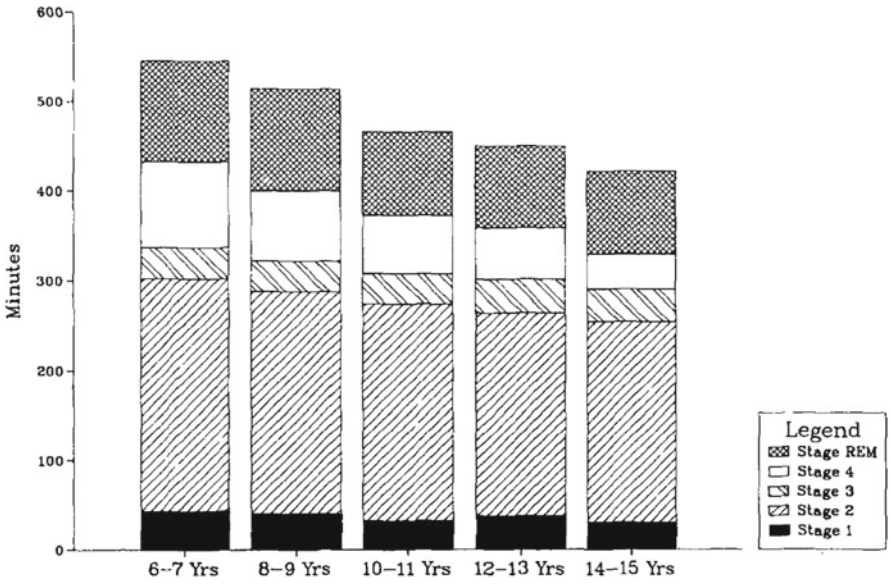

Fig. 1.2 Age-related changes in sleep architecture during childhood. Slow-wave sleep is particularly reduced during the teenage years (From Coble et al. [52])

during the luteal phase, when progesterone is highest and core body temperature is higher [53]. Since sleep spindles are considered to play a key role in modulating sleep and in sleep-dependent memory consolidation [54], this observation raises interesting hypotheses about differences in learning across the menstrual cycle.

Sleep-Disordered Breathing

Similar to SDB in the young child, SDB in the older child is a disorder characterized by repetitive episodes of upper airway obstruction, intermittent hypoxemia and hypercapnia, and snoring. However, older children may show patterns of SDB that may be more typical of that of adults (with clear apneas and hypopneas), in contrast to patterns in younger children who often may show prolonged periods of hypoventilation rather than discrete apneas. Prevalence of SDB in older children is approximately 2–3 %, but may be two- to sixfold higher in vulnerable populations such as blacks and children who were born preterm and in children from disadvantaged neighborhoods [12].

Premature birth (<36-week gestational age) may predispose to childhood SDB through in utero or early postnatal effects on craniofacial development or ventilatory chemosensitivity and load compensation. These effects may be facilitated by the plasticity of the neural control systems in infancy. In particular, in the first few days of life, maturation of respiratory chemoafferents occurs.

Exposure to hypoxia during this time, but not later, results in blunted ventilatory responses later in life [55].

Children exposed to maternal smoking are also at increased risk of SDB, possibly because of increased nasopharyngeal inflammation. Pediatric SDB also is associated with respiratory allergies and with asthma or asthma symptoms [56]. The basis for these associations is unclear, but may include increased nasal resistance causing increased negative pressure swings and collapsibility, generalized airway inflammation and narrowing, and common genetic mechanisms. Obesity is associated both with asthma and with SDB and, thus, may also partly, but not fully, explain this association.

Obesity appears to play an even stronger role in the older compared to the younger child as an SDB risk factor. Results from the Cleveland Family Study, which included children ages 4–18 years, indicate that children who are overweight are at a 4.6-fold increased risk for SDB than children who are of normal weight [11]. In contrast, in a cohort of children aged 8–11 years, risk for SDB given obesity was only 1.3 (95 % C.I: 0.55, 3.10) and not statistically significant [12]. A follow-up study of a sample of children from the latter cohort assessed at ages 13–16 years, however, showed a markedly different pattern, with an odds ratio for obesity greater than 9.0 [57]. These studies demonstrate marked differences in estimates of the influence of obesity depending on the age of the sample, with evidence of weaker associations in prepubertal children and strong associations, similar to what has been described in adults, in adolescents. Interestingly, obesity has also been associated with adenoid hypertrophy and velopharyngeal narrowing [58], suggesting that obesity may increase risk of SDB in children through several pathways.

Central obesity, as measured by the waist circumference or by visceral fat detected by specialized imaging of the abdomen, appears to be particularly important among adults as a risk factor both for SDB and for cardiovascular disease-associated comorbidities. In children, the role of body fat distribution as a risk factor for SDB has not been established. However, gender-specific patterns of body fat distribution begin to establish during adolescence, and these patterns may be useful for identifying high-risk subgroups.

The chronic comorbidities associated with untreated pediatric OSAS include cognitive deficits, behavioral problems (inattention, hyperactivity, aggression, conduct problems, attention-deficit/hyperactivity disorder [ADHD]), mood impairments, excessive daytime sleepiness, impaired school performance, and poor quality of life. However, SDB also has been associated with adverse cardiovascular and metabolic outcomes. Children with OSAS have higher levels of blood pressure, CRP, and increased insulin resistance. SDB increases risk of metabolic syndrome (characterized by dyslipidemia, central obesity, hypertension, and insulin resistance) by six- to sevenfold [57, 59]. Thus, SDB in the older child and adolescent is a potent risk factor for metabolic syndrome. Since metabolic syndrome in childhood is associated with diabetes and cardiovascular disease in adulthood, this observation underscores the importance of treating SDB early in life.

Sleep in Early to Mid-Adulthood

Circadian Rhythm

The circadian rhythm changes with age and one important change is a general shift to early sleep times (advanced sleep phase) with advancing age. While teenagers and college students have a tendency due to both intrinsic rhythm and external pressures to have later bedtimes, this starts to wane in young adulthood. This phase advance to an earlier sleep time has been referred to as "an end to adolescence" and happens at a younger age for women than for men [60]. External influences such as caffeine intake can lead the young adult to continue to have later bedtimes. However, once the person is in the adult workforce, earlier bedtimes typically are needed due to needing to wake up earlier for work (as opposed to college classes). Some studies have demonstrated that adults aged 16–54 years still get extra sleep on weekends or days off, indicating perhaps that they are not getting enough sleep on week nights. Overall, once in adulthood, most people will have a circadian rhythm such that they fall asleep in the nighttime and maintain wakefulness during the day. Notable exceptions are shift workers, comprising about 20 % of the work force (see Chap. 7).

Sleep Architecture/Duration/Stages

The sleep architecture of young adults is now solidly in a 90-min cycle with all sleep stages represented. The amount of stage N3 sleep continues to reduce at this time, at a rate of approximately 2 % per decade up to age 60 years. There is also a smaller reduction in REM sleep during early and mid-adulthood.

Once through puberty and into the 20s, most adults sleep approximately 7–8 h per night. This remains relatively constant through mid-adulthood. Young adults may still sleep a bit longer, 8–9 h for a few years. The need for sleep does not change as people progress to mid-adulthood, but the ability to maintain sleep may be affected by medical conditions and environmental influences. In fact, although average sleep duration does not change over adulthood, there is a large degree of inter- and intraindividual variability in sleep duration. Individuals who are consistently short sleepers (e.g., <6 h per night) and long sleepers (>9 h per night) and who demonstrate high between-day variability in sleep duration are at increased risk for weight gain, diabetes, and other metabolic dysfunction and chronic disease.

Pregnancy and Sleep

Pregnant women have frequent complaints related to their sleep. Many hormonal and physiological changes during pregnancy affect sleep and may be the reasons for these complaints. These can be divided up by the three trimesters of pregnancy.

During the first trimester, sleep symptoms are reported by between 13 % and 60 % of women [61, 62]. In addition, women also commonly report daytime fatigue. During the first trimester, progesterone increases and this can contribute to daytime sleepiness; increases in core body temperature also can worsen sleep quality. Changes in sleep, particularly a longer total sleep duration as well as increased awakenings and decrease in N3 sleep, have been reported to occur as early as 11–12-week gestation. Nocturia, which may interrupt sleep, may be a result of the effect of progesterone on bladder smooth muscle as well as to the effects of the growing uterus on the bladder.

Sleep often improves during the second trimester of pregnancy, but some women have persistent sleep complaints. Hormones like progesterone are leveling off during this trimester, and the uterus has now moved into the abdomen.

By the third trimester, the prevalence of sleep complaints increases to 66–97 % (Driver [61] and Lee [93]). Limited research suggests that overall objective sleep quality also is reduced, with poorer sleep efficiency, decreased REM sleep, and more awakenings at night as time in the third trimester lengthens. The uterus is now large and increases pressure on the bladder and the stomach, increasing the frequency of nocturia as well as gastroesophageal reflux, both of which may disrupt sleep. The gravid uterus also leads to significant low back pain and general discomfort while trying to sleep. During this trimester, women are at increased risk of developing sleep disorders such as restless legs syndrome (RLS) and OSA. RLS, a neurosensory disorder that often is accompanied by periodic leg movement disorder (recurrent kicks at night), likely occurs in association with iron and folate deficiency. Leg movements cause arousals, awakenings, and sympathetic surges which reduce sleep quality and can contribute to increased blood pressure. Obstructive sleep apnea may be particularly common, especially in women with high prepregnancy weights. OSA likely occurs secondary to further weight gain, body fluid redistribution, and increased nasal resistance. OSA in pregnancy is associated with an increased risk of preeclampsia and adverse fetal and maternal outcomes [63]. Gestational diabetes has been associated with OSA during pregnancy [64]. There is ongoing research on whether OSA during pregnancy contributes to persistent cardiometabolic disturbances in both mother and child.

Sleep-Disordered Breathing

SDB increases in prevalence across adulthood; however, some studies suggest a plateau may occur at approximately 65 years of age [65]. Obesity is the strongest SDB risk factor in adulthood, associated with an increased odds of SDB of four- to eightfold. Approximately 40 % of those with a BMI over 40 and 50 % of those with a BMI over 50 have been estimated to have SDB. The association between increasing BMI and SDB is shown for participants in the Sleep Heart Health Study in Fig. 1.3. Data from the Wisconsin Sleep Cohort, the Cleveland Family Study, and the Sleep Heart Health Study consistently have shown that weight gain is associated with increased severity of SDB; a 1 % increase in weight is estimated to be

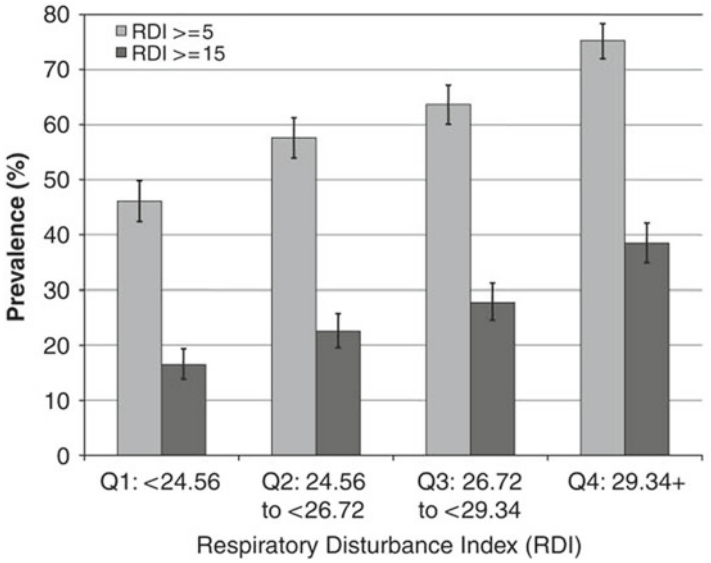

Fig. 1.3 Sleep-disordered breathing (*SDB*) prevalence estimates with 95 % confidence intervals are illustrated based upon respiratory disturbance index (*RDI*) cutoffs of 5 (*P*-value for trend <.001) and 15 (*P*-value for trend <.001) according to BMI quartile, Outcomes of Sleep Disorders in Older Men Study. Increasing SDB prevalence is seen with increasing BMI (From Mehra et al. [66])

associated with a 3 % increase in SDB severity [67–69]. Overall, the 5-year incidence of SDB is estimated to be 11 % in men and 4 % in women [67]. In middle-aged adults, visceral obesity, which is related to insulin resistance and hypercytokinemia, may be a more important determinant of SDB than total body fat or subcutaneous fat [70]. The rise in obesity in the population is expected to result in an increased prevalence of SDB. Other established risk factors for SDB include male gender, craniofacial risk factors (mandibular retrognathia, brachycephalic head form), alcohol consumption, and family history of OSA. SDB appears particularly prevalent in individuals of Asian ancestry, and this finding occurs despite the relatively low BMI in the populations studied [71]. A high prevalence of SDB in this population occurs in association with an increased prevalence of diabetes; whether the co-occurrence of these risk factors is independent or causal is not clear. However, together both conditions may increase risk for premature mortality and chronic diseases. Disease burden may be particularly great in populations at risk for both obesity and OSA related to craniofacial or soft tissue characteristics or other genetic factors, such as ethnic minorities.

Several large epidemiological studies have established that SDB is associated with significant increased incidence rates of hypertension, stroke, coronary artery disease, and heart failure [7–9, 72]. Diabetes is also associated with SDB and several moderate sized trials indicate improvement in insulin sensitivity after 1–3 months of SDB treatment with continuous positive airway pressure (CPAP) [73–76].

Meta-analyses also indicate that CPAP treatment reduces blood pressure by an average of 3 mmHg, with some evidence of larger effects in more severely affected individuals and those with higher levels of adherence [76]. A number of studies indicate that SDB is more strongly predictive of cardiovascular disease in middle-aged compared to older adults, underscoring the importance of SDB, and its key comorbidity, obesity, in middle-aged individuals.

Sleep in Older Age

Circadian Rhythm

The amplitude and timing of circadian rhythms change with advanced age [77]. Overall, amplitude is reduced and timing is advanced (sleep onset occurring earlier) by 40–60 min [78, 79]. These effects likely result from several factors, including decline in the output of SCN with neuronal aging and decreased secretion of melatonin. Also, with aging, retirement, and other lifestyle and health factors, there may be a reduced dichotomy between day- and nighttime activities, as well as inopportune light exposures, which may indirectly influence the biological clock. Visual problems such as those due to cataracts reduce the SCN's exposure to light, particularly short-wavelength frequencies which most potently influence the SCN, contributing to weakening of the circadian rhythm [80]. Sleep homeostatic pressure (process "S") responses also appear to differ with increasing age. Circadian rhythm disturbances also are common in association with neurodegenerative diseases that are common in the elderly [81]. In fact, "sun downing" is one of the most troubling symptoms of patients with Alzheimer's disease and a key reason for institutionalization. Treatment with light therapy, daytime exercise, and avoidance of daytime naps has been used with partial success for this problem [82].

Sleep Architecture

With aging, there are marked reductions in the proportion of N3 sleep, with concomitant increases in N1 and N2 sleep [83]. In addition, sleep of older individuals often is characterized by frequent arousals and awakenings and low sleep efficiency – all indications of poor sleep quality [84]. Bliwise has suggested that a reduction in percentage N3, which is correlated with many neurohumoral processes, may be a sensitive biomarker of aging [85]. Reductions in N3 may be due to age-related reductions in cortical mass, cortical metabolism, or neurotransmitter levels, changes in circadian rhythm, or other neuroendocrinological or nervous system activity. The somatotropic axis (secretory patterns of growth hormone and insulin-like growth factor) and the control mechanisms that affect stage N3 sleep are highly integrated systems that are interactive and affected by common neuroendocrinological control mechanisms. Selective reduction of N3 sleep has been associated with insulin

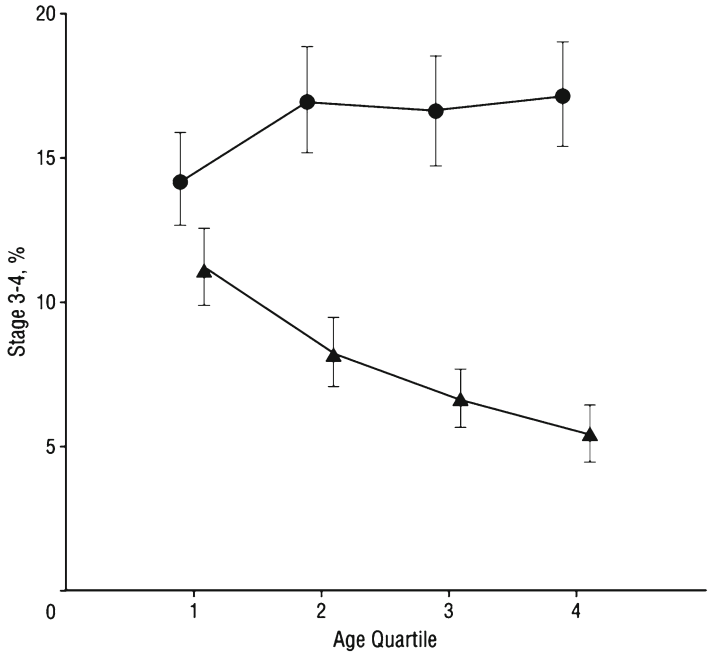

Fig. 1.4 Association between percentage stage N3 sleep in men and women in the Sleep Heart Health Study (*SHHS*) across age quartiles (≤54, >54 to ≤61, >61 to ≤70, and >70 years) for men (*triangles*) and women (*circles*). With increasing age, N3 drops markedly in men, but less so in women (From Redline et al. [83])

resistance and, in a group of older men, predictive of hypertension incidence [4, 5]. Decreased N3 also has been associated with central obesity in cohorts of older men and women, and this association was independent of total sleep duration [86]. Further understanding with changes in sleep architecture that are epiphenomena or causally contribute to the development of chronic diseases is of great importance.

Gender is a significant determinant of age-associated changes in sleep architecture. As shown in Fig. 1.4, with advancing age, N3 declines to a much larger extent in men than in women. In the Sleep Heart Health Study, after adjusting for a variety of confounders, including SDB, older women had an average 106 % higher proportion of N3 sleep and 23 % lower N1 (light) sleep [83]. Whether these dramatic differences reflect differences in cortical mass and neural connectivity or are biomarkers for other aspects of health that differentiate aging in men and women is not clear.

In addition to objective evidence of poor sleep, the prevalence of most sleep disorders increase with advancing age. Among adults over the age of 65, more than 50 % report difficulty in sleeping. In contrast to gender differences in objective sleep architecture, older women more commonly report symptoms of insomnia and poor sleep quality than older men. Sleep disturbance in older adults may be attributable to a number of factors. In addition to abnormalities in intrinsic processes related to circadian rhythm and the sleep homeostatic process, sleep is influenced by underlying

medical or psychiatric conditions, medication use, and specific sleep disorders such as insomnia, periodic leg movement disorder, and SDB. Furthermore, despite their frequency, sleep disorders are frequently undiagnosed and untreated.

Sleep-Disordered Breathing

SDB is highly prevalent in the elderly [84]; in addition to OSA, a large proportion of older individuals has central sleep apnea, i.e., more than 5 apneas per hour of sleep that are unassociated with respiratory effort and result from instability of breathing control, often due to cardiac dysfunction or cerebrovascular disease [87]. Both conditions can cause recurrent arousal, sleep disruption, and hypoxemia. A large community-based study of men more than 67 years of age, the Outcomes of Sleep Disorders in Older Men (MrOS) Cohort, estimated that the prevalence of moderate or more severe OSA was 25 % and prevalence of central sleep apnea was 7.5 % [66]. Results from this study indicate that across the age range of 67 to 90+ years, prevalence of both conditions increases with advancing age. CSA is almost twofold more prevalent in individuals with heart failure and is not associated with obesity. In contrast, OSA is associated with a 2.5-fold increased prevalence of OSA in this group – thus obesity is a significant risk factor of OSA in older individuals, although not as strong as in middle age. This may reflect the importance of other comorbidities that contribute to OSA in older individuals, including the more complex association of BMI with health as individuals age and unintentional weight loss and sarcopenia that occur in association with frailty. Like younger individuals, OSA in older individuals is associated with snoring, sleepiness, and hypertension [66]. OSA and CSA also are highly prevalent in older women; there is evidence that gender differences narrow but do not disappear with advancing age. The associations between SDB with cardiovascular disease and mortality appear to be weaker in older compared to middle-aged individuals [8]. Stroke risk is significantly increased in association with both OSA and CSA in older individuals [9].

Sleep and Menopause

Menopause has a broad range of effects on sleep [88, 89]. Some effects are associated with general physical and mental health issues experienced during the menopause transition, such as vasomotor symptoms which can be particularly disruptive to sleep. Other changes are likely due to the influence of changing hormone levels in areas of the brain that modulate sleep, many of which contain estrogen receptors. However, more consistent associations are seen between menopause and subjective as compared to objective sleep changes [90]. Because menopause is a time of frequent mood disturbance and weight gain, it is important to consider the role that sleep disruption may play in these conditions.

Estrogen and other hormonal factors may be protective for the development of SDB, and waning sex hormones likely contribute to an increase of SDB in

menopausal women. Estrogen and progesterone influence ventilatory control systems that modulate breathing during sleep. In addition, changes towards a more android (central) body fat distribution with menopause may increase airway collapsibility. In support of an importance for sex hormones in SDB is the finding that among older women, hormone replacement therapy (HRT) is associated with a lower apnea hypopnea index [91]. In addition, premenopausal women and postmenopausal women on HRT have a similar prevalence of SDB, whereas the prevalence is considerably higher among postmenopausal women not taking HRT [92]. Overall, the evidence suggests that sex hormones may influence the severity of SDB and that changes in sex hormones after menopause likely contribute to the higher prevalence of SDB in older compared to younger women.

Conclusions

Sleep is a key neurophysiological process that is manifest in utero and develops and changes across the lifespan. Brain maturation influences both sleep homeostatic and circadian rhythms which shape the timing, duration, and quality of sleep. These sleep characteristics have important influences on a wide variety of biological processes that influence weight, metabolism, and general health. These influences are notable in infancy and early childhood and have the potential to influence trajectories of weight and health across the lifespan. Sleep disorders, particularly SDB, which exposes the individual to a large number of physiological stresses that adversely affect insulin sensitivity and metabolism, also occur at all ages. Metabolic abnormalities are evident in association with even mild levels of SDB in children as well as in older populations. In considering the influence of sleep traits on health outcomes, it is important to appreciate how normative values differ by age and gender. It is also important to consider whether normal age-dependent changes in sleep traits contribute to the propensity to other age-dependent diseases, such as diabetes and cancer.

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Chapter 2
Effects of Sleep Deficiency on Hormones, Cytokines, and Metabolism

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Abstract What are the best approaches to reduce the staggering health and economic costs of the diabetes and obesity epidemics? Traditional efforts have centered on diet and exercise, which are key health behaviors during wakefulness. Yet, mounting evidence supports the addition of sleep as a third pillar of health. Increasingly, scientific research suggests insufficient sleep puts Americans at risk for weight gain and impaired glucose regulation. Synthesizing epidemiological studies with clinical experiments enables a more complete understanding of these relationships by tying population-level trends to underlying mechanisms and causes. Although the associations between sleep, obesity, and diabetes and their intertwined

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_2,

mechanisms are still emerging, the current "epidemic" of insufficient sleep seems to warrant individual, behavioral, and policy interventions.

Keywords Sleep • Sleep deficiency • Insomnia • Circadian disruption • Cytokines • Hormones • Glucose metabolism • Insulin sensitivity • Obesity • Diabetes

Pressing Public Health Concerns: The Obesity and Diabetes Epidemics

Twin epidemics of obesity and diabetes imperil public health in the United States and worldwide. Identifying and implementing strategies to mitigate these epidemics are critical to improving well-being and reducing healthcare expenditure.

The incidence and prevalence of obesity and diabetes have increased significantly over the past decades. According to 2010 Center for Disease Control data, 33.3 % of American adults are overweight (Body Mass Index (BMI) >25) and an additional 35.7 % are obese (BMI > 30), while 18 % of children over six are obese [1]. Obesity affects over 78 million adults and 12.5 million children in the United States. The prevalence of obesity has more than doubled in children and adults over the past decades, with a projected 33 % rise from today's levels by 2030 [2–4]. This epidemic is not limited to America. World Health Organization data from 2008 indicate that over 1.4 billion adults worldwide were overweight, 500 million of whom were obese [5].

Largely preventable, excess weight poses significant health problems, leading to increased morbidity and mortality [6]. The expense of obesity and overweight is also immense. Finkelstein et al. calculate costs of approximately $147 billion in 2008 or 9 % of annual United States healthcare expenditure [7]. Thorpe et al. conclude that related costs account for 12 % overall and 27 % of per capita healthcare spending growth from 1987 to 2001 [8].

Obesity is associated with a significant increase in different types of cancer and identification of the pathways through which obesity influences cancer risk is critical to primary and secondary prevention. Emerging evidence suggests that insulin resistance and hyperinsulinemic compensation that occurs in response to obesity-related insulin resistance represent an important pathway through which obesity influences cancer risk and disease progression [9]. To provide a better understanding of how sleep deficiency may stimulate cancer cell growth, this chapter will focus on the mechanisms through which sleep deficiency alters exercise, energy expenditure and dietary behavior, as well as insulin secretion, insulin resistance, and glucose metabolism.

Obesity and overweight have significantly contributed to the alarming rise of the diabetes epidemic. Comprising ~95 % of diagnosed cases, type 2 diabetes is primarily responsible for this increased incidence and prevalence [10]. Type 2 diabetes and excessive weight are frequently comorbid. The World Health Organization estimates that excessive weight accounts for 44 % of the global diabetes burden, and the Center

for Disease Control colorfully comments that "we are eating ourselves into a diabetes epidemic" [11]. As of 2010, the Center for Disease Control approximates that 25.8 million or 8.3 % of Americans had type 2 diabetes, a 160 % increase in prevalence since 1980 [12]. Moreover, a Center for Disease Control survey 2005–2008 reveals that about 35 % of Americans were prediabetic by assessing diagnostic measures including fasting blood glucose and hemoglobin A1c samples [12]. Like obesity, the diabetes epidemic is not unique to the United States, and the World Health Organization considers diabetes to be implicated in four million or 9 % of annual global deaths [11]. Since diabetes is often comorbid with obesity and overweight, costs generally reflect the impact from both conditions. In a 2008 study, the American Diabetes Association calculated the direct costs of diabetes and related complications as $116 billion and the associated diminished national productivity as $58 billion [10].

Given the scope and scale of obesity and diabetes, mitigating these epidemics is a prime public health priority.

Reconsidering Public Health Strategies to Combat Obesity and Diabetes: The Role of Insufficient Sleep

Traditional efforts to combat overweight and diabetes have centered on diet and exercise. Nevertheless, increasing scientific evidence suggests that a public health focus should move beyond diet and exercise to include sleep as a third pillar of health and well-being in the fight against obesity and diabetes.

American culture generally fails to recognize the importance of sleep. The introduction of electricity in the late twentieth century has fostered an attitude prioritizing work and leisure over sleep. Televisions, computers, smartphones, and tablets further facilitate 24/7 activity. Moreover, the popularity of coffee and energy drinks has skyrocketed over the past decade. Relying on caffeine and other stimulants to stay awake is only one of many reasons why (and signs that) Americans are not getting sufficient sleep. A workers' inadequate sleep can be related to an unsupportive supervisor in the workplace [13]. Noise and other environmental disturbances, as well as the demands of family life and childcare, compound this problem. Moreover, disorders such as sleep apnea, restless leg syndrome, and insomnia may further interfere with sleep (Figs. 2.1 and 2.2).

Modern lifestyles and work practices also disrupt circadian rhythms, which can be an additional challenge to adequate rest. Working in shifts around the clock, travel across time zones, and the reality of a global economy can profoundly disrupt the natural sleep cycle. Circadian misalignment not only affects the brain's central pacemaker in the suprachiasmatic nucleus [14] but also impacts peripheral organs and tissues that also have their own circadian clocks [15, 16].

Therefore, a range of contributing factors can lead to sleep deficiency, which the strategic planning group of the National Heart Lung and Blood Institute defines as an "insufficient quantity or inadequate quality of sleep obtained relative to that needed for optimal health, performance, and well-being" [17].

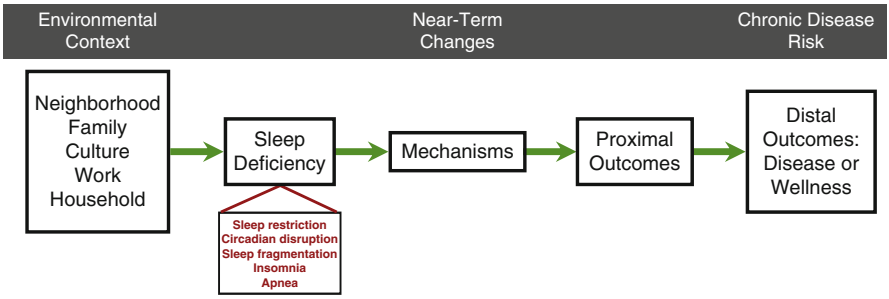

Fig. 2.1 General conceptual framework for evaluating the effects of insufficient sleep on health and wellness

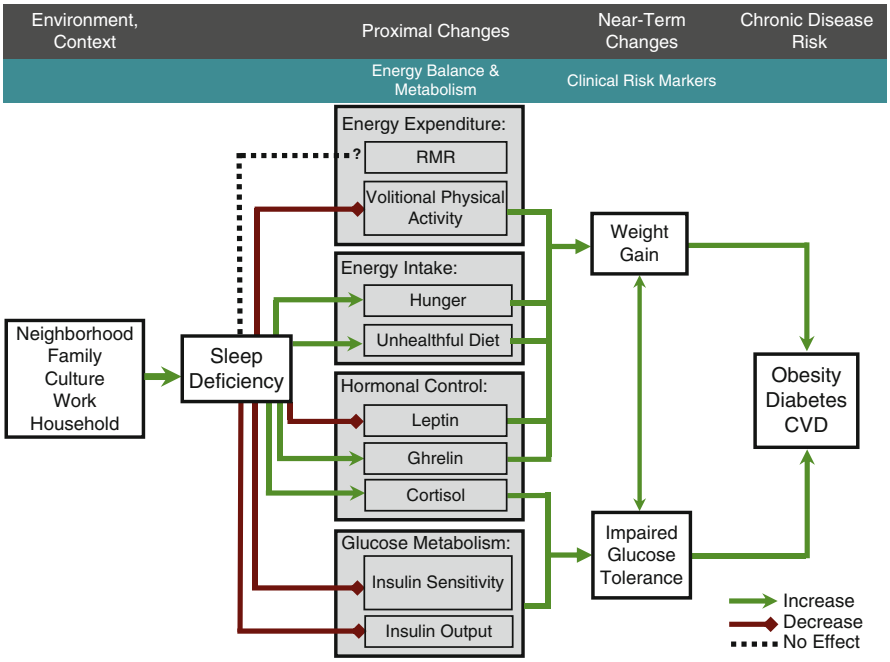

Fig. 2.2 Mechanistic conceptual framework for evaluating the effects of insufficient sleep on diabetes and obesity

Sleep insufficiency is an increasing problem in the United States. Americans report averaging 1.5–2 h less sleep than a century ago [18]. Recent surveys also suggest that more than one-third of American adults sleep less than 6 h each night, well below the recommended 7–9 h [19]. While approximately 30 % of adults report

symptoms of insomnia, many limit their sleep voluntarily to watch TV, surf the Internet, or complete work [20]. Similarly, Owens estimates that about one quarter of children experience sleep difficulties over the course of childhood [21].

Indeed, the Institute of Medicine has recognized sleep deprivation and sleep disorders as unmet public health problems [22].

Sleep and Metabolism: Epidemiological Evidence

From a population-level perspective, scientists have noted parallel increases in obesity, diabetes, and sleep deficiency over the past decades. Within the United States, the similarity in geographical distribution of all three conditions is visually compelling (Fig. 2.3). Given the scale of these conditions, epidemiological studies are valuable for identifying associations and trends in large groups of individuals. Cross-sectional studies examine exposure and disease status at one point in time, while longitudinal cohort trials can identify temporal relationships. Nevertheless, epidemiological observations cannot prove causality. The tendency to focus on sleep duration alone without consideration of quality or circadian shifts can further constrain the conclusions of epidemiological analysis. Within these limitations, cross-sectional and longitudinal studies provide a basis for establishing links between insufficient sleep, diabetes, and obesity.

Epidemiological Evidence in Pediatric and Adult Populations: Associations Among Insufficient Sleep, Overweight, and Obesity

Throughout the life course, insufficient sleep is often associated with overweight and obesity. A prospective study of over 900 infants in the United States found that 6-month-olds sleeping less than 12 h per day are at higher risk for overweight by age three [23]. A prospective study of 150 American children 3–5 years old indicates that sleeping 30 min less each night than recommended was positively correlated with overweight at 9.5 years of age [24, 25]. Similarly, by analyzing wrist actigraphy recordings of 383 American adolescents to assess sleep, Gupta et al. found an 80 % reduction in obesity risk for every hour of sleep gained per night [26] (Fig. 2.4).

While individual studies can be valuable in identifying patterns, reviews and meta-analyses can provide a broader sample size to generalize the relationship between sleep and weight in pediatric populations. Patel and Hu's review of 11 and Cappuccio et al.'s meta-analysis of 12 cross-sectional global pediatric studies show consistent patterns of increased obesity risk with insufficient sleep, particularly short sleep duration [27, 28]. Based on this evidence, Bell et al. speculate, "There is a critical window prior to age five, when nighttime sleep may be important for subsequent obesity status. Insufficient nighttime sleep among infants and preschool-aged

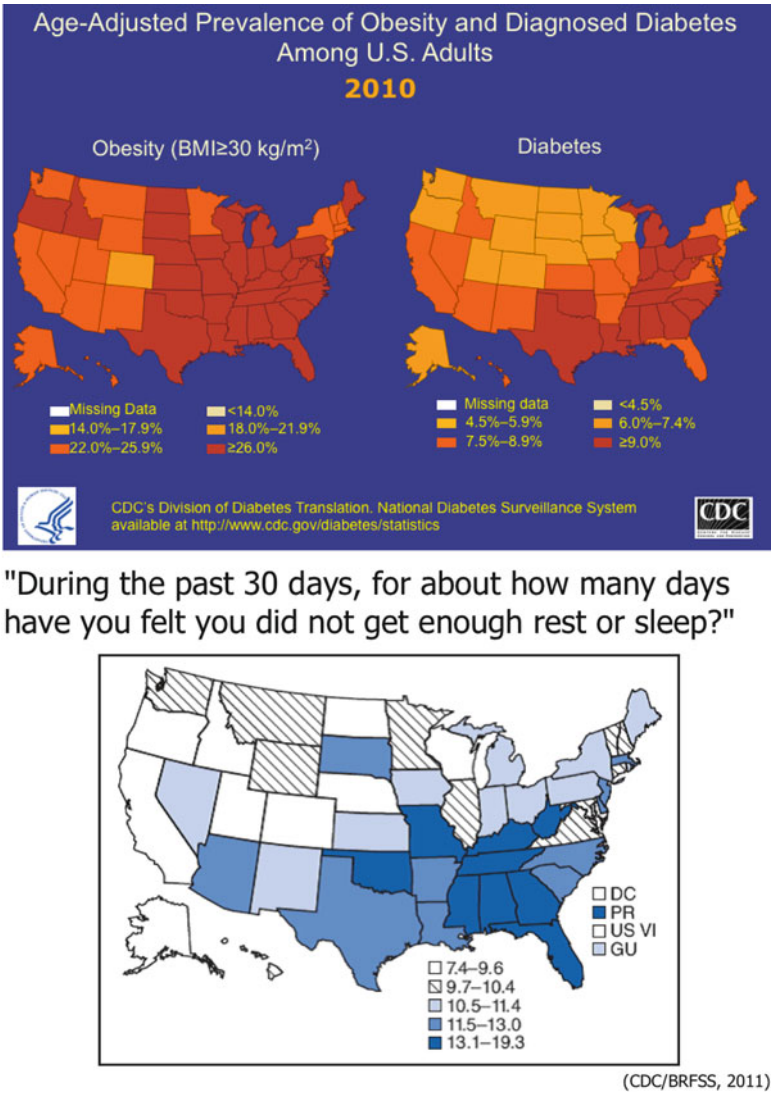

Fig. 2.3 Similarities between the geographic distribution of obesity, diabetes, and reported sleep insufficiency (Sources: CDC Data and Slides (2010–2011)

children appears to be a lasting risk factor for subsequent obesity, while contemporaneous sleep appears important to weight status in adolescents" [3].

Though apparently weaker, this relationship between weight and sleep continues into adulthood [28]. A U-shaped curve exists between sleep duration and weight with the lowest BMIs being associated with the recommended 7–8 h per night. Longitudinal studies surveyed support an independent positive association between

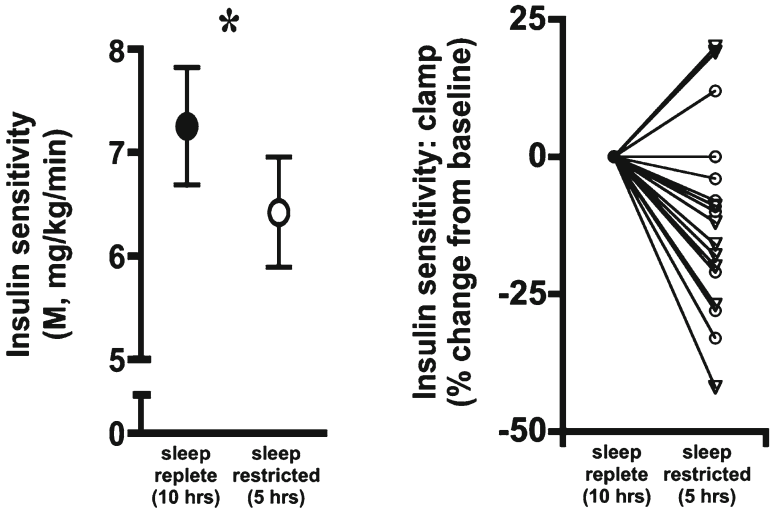

Fig. 2.4 (Insulin sensitivity in young adult men is reduced following 1 week of sleep restriction. Insulin sensitivity was measured using the euglycemic hyperinsulinemic clamp procedure at baseline during a sleep replete condition (10 hrs/night, filled circles) and compared to a sleep restriction condition (5 hours per night for 1 week; open circles). *Left panel*: mean ± SE. *Right panel*: individual values for change with sleep restriction relative to baseline sleep replete (Orfeu Buxton et al. [70])

insufficient sleep and weight gain. A systematic meta-analysis of short sleep duration and obesity in adult populations yields similar results [29]. In a pooled regression, a 0.35 kg/m^2 increase in BMI was associated with each 1 h less sleep per night, compared to a reference of 7 h per night of self-reported sleep.

Epidemiological Evidence in Pediatric and Adult Populations: Associations Between Insufficient Sleep and Diabetes in the Context of Overweight

The overlap between excessive weight and diabetes alone is significant. The American Diabetes Associate notes that "most patients with [type 2] diabetes are obese" [10], while overweight confers greater risk of insulin resistance. The concomitance of diabetes and excess weight is observed throughout the life course. In a survey of 3,953 diabetic and 7,666 nondiabetic youth (3–19 years) from diverse ethnic and racial backgrounds, the prevalence of overweight and obesity in subjects with type 2 diabetes was 10.4 % and 79.4 %, respectively [30]. It is, therefore, plausible that sleep insufficiency could increase risk for type 2 diabetes by predisposing children and adults to weight gain.

Many studies, however, report that sleep independently relates to diabetes risk, even after controlling for the confounding effects of obesity and overweight. A 2012 cross-sectional study of black and white adolescents by Matthews et al. reports

that short sleep duration correlates with higher insulin resistance independent of adiposity and other confounding factors [31]. Adolescents with greater sleep fragmentation, which may indicate poor sleep quality, tended to have higher glucose levels, another risk for diabetes [31]. A similar effect for short sleep duration and insulin resistance was observed in the Cleveland Sleep and Health Study of black and white adolescents, although results disappeared when the investigators adjusted for central adiposity [32]. Differences in sample characteristics likely contributed to these somewhat conflicting results; fewer adolescents in the Cleveland sample were obese and a greater proportion of these adolescents were long sleepers.

Again, meta-analyses and reviews are useful to gauge systematic trends. Cappuccio et al. [29] analyzed ten prospective studies with a pool of over 100,000 adults to ascertain the association of type 2 diabetes with sleep duration and quality. After controlling for BMI, age, and other confounding factors, they found results similar to those from their "Meta-Analysis of Short Sleep Duration and Obesity in Children and Adults" [27]. Specifically, sleeping less than 6 h per night conferred an RR of 1.28 in predicting the incidence of type 2 diabetes, and prolonged duration (>8–9 h) had a higher RR of 1.48. As for sleep quality, Cappuccio et al. found that difficulty falling and staying asleep were highly correlated with type 2 diabetes risk with RRs of 1.48 and 1.84, respectively. Knutson et al.'s review connects insufficient sleep with poor glucose control and type 2 diabetes, particularly in men [19]. Although some studies do not find a significant association between sleep and diabetes in women [33], a 10-year American Nurses Health Study [34] of exclusively female subjects found increased diabetes risk after controlling for confounding variables such as BMI, shift work, hypertension, exercise, and depression.

Buxton and Marcelli's study of data from the US National Health Interview Survey (2004–2005) also links insufficient sleep, diabetes, and obesity [35]. Using a range of four classes of predictors, the investigators employ a socio-geographic model to expand upon prior conceptual frameworks and detect often neglected social and behavioral effects on chronic diseases. As with prior cross-sectional analyses, the Buxton and Marcelli study reveals that short and long sleep duration are both directly and independently associated with increased risk for obesity and diabetes in a representative sample of the American adult population. Obtaining 7–8 h sleep per night was associated with the lowest risk profile for the adults surveyed. The analysis also indicates indirect relationships such as a significant association of diabetes, obesity, and hypertension with cardiovascular disease. Buxton and Marcelli's framework suggests that sleep is more strongly linked to obesity, diabetes, and cardiovascular disease than other sociodemographic or health behavior covariates.

Epidemiological Evidence: Associations Between Insufficient Sleep and Mortality

Given these associations with excess weight and diabetes, it is not surprising that insufficient sleep is also linked to higher mortality rates in epidemiological studies. Cappuccio's meta-analysis of 16 prospective studies including 27 independent

cohorts found that both short and long duration of sleep are significant predictors for all-cause mortality [36]. For individuals averaging less than 7 h of sleep per night, the risk of death increased by 12 %. As a result, epidemiological evidence suggests that insufficient sleep is associated with the more proximal outcomes of excessive weight and diabetes, as well as with the distal outcome of mortality [37].

Associations Between Insufficient Sleep and Obesity: Energy Intake and Hormones

Energy balance influences weight regulation and may explain associations between insufficient sleep and the current obesity and overweight epidemics. Positive balance suggests weight gain, while negative balance can lead to loss. Perceived hunger versus satiety, dietary selection, and calories ingested all influence energy intake. While sleep itself is an energy-conserving state, short duration can encourage weight gain by allowing more time to eat. But it is more complex than simply having more time to eat—many population and laboratory studies demonstrate that insufficient sleep affects physiological energy balance, resulting in weight gain.

Moreover, a spectrum of hormones and other signaling pathways influence caloric intake and utilization. Providing potential physiological links between short sleep and overweight, ghrelin, leptin, peptide YY, cortisol, and Glucagon-like peptide-1 (GLP-1) vary under different sleep conditions. The hormone leptin [38], produced by adipose cells; the peptide YY (PYY) [39], released by neuroendocrine cells in the ileum and colon after eating; and GLP-1 all signal satiety and reduce appetite. On the other hand, the hormone ghrelin, primarily produced by the gastric fundus, stimulates appetite [38]. Longer-acting cortisol, which has a wide range of effects throughout the body and is secreted by the adrenal cortex, is also linked to increased hunger and visceral adiposity [39]. Since these hormones may impact eating behavior and dietary preference, variations in levels may underlie energy balance changes observed during sleep insufficiency.

Epidemiological Evidence: Discerning Relationships Between Energy Intake and Sleep

Epidemiological research suggests that insufficient sleep may effect changes in energy balance that lead to excess weight but cannot prove causality. In the HELENA study, Garaulet et al. review the relationship between short sleep duration, physical activity, and dietary habits in 3,311 adolescents from nine European countries [40]. After adjusting for BMI, physical activity levels as measured by hip accelerometers were significantly reduced in adolescents with chronic partial sleep deprivation (<8 h/night). Short sleepers were more likely to consume unhealthy diets with more servings of junk and snack foods but fewer servings of fruits, vegetables, and dairy.

Epidemiological studies yield similar findings in adults. In a population of 542 male freight workers, Buxton et al. use a multivariable model to demonstrate that sleep adequacy, perceiving to usually getting enough sleep, is a mediator of healthful food selection [41]. Professional drivers typically experience more job strain, as well as disruption of sleep and mealtime schedules, than other freight workers because of lengthy and irregular work shifts. Compared to drivers who felt fatigued, those reporting adequate rest consumed more vegetables and fruit with less sugary drinks and snacks. This cross-sectional analysis was constrained by self-reported data, an exclusively male population, and a lack of information regarding stimulant use other than nicotine. Nevertheless, the study points to the possible role of adequate sleep, independent of other workplace factors, in maintaining a healthful diet.

Other cross-sectional studies reveal associations between sleep and hormones that may influence energy intake. Analysis of a Wisconsin Sleep Cohort Study of 1,024 adults found that short sleep was associated with lower leptin and higher ghrelin levels [42]. Comparing subjects averaging 5 h versus 8 h of sleep per night predicted 15.5 % lower leptin and 14.9 % higher ghrelin levels, respectively. The Québec Family Study, which includes 740 men and women, supports these observations regarding leptin and also reports lower physical activity levels in obese short sleepers [43]. Therefore, epidemiological studies suggest a range of possible interfaces between both sleep and energy balance.

Laboratory Evidence: Insufficient Sleep and Energy Intake

Controlled experiments can point to causality and reduce the influence of confounding factors. However, inconsistencies exist between various studies, which rely on data from small sample sizes and employ different protocols. It is especially important to consider differences in food availability. For example, Raynor and Wing report that doubling portion size of snack foods can increase consumption by 81 % [44]. Differences in study design include restrictive versus ad libitum feeding, trial duration, and the range of outcomes measured.

Laboratory studies of insufficient sleep vary with respect to observed effects on subjects' satiety, diet composition, and caloric consumption. Chapman et al.'s meta-analysis of five controlled trials found a cumulative effect of sleep insufficiency on food intake (Cohen's $d = 0.49$) [45]. Individual studies provide further detail. After one night of 4-h sleep curtailment, Brondel et al. found a 22 % increase in ad libitum energy intake in 12 subjects and increased preprandial hunger without particular predilections in food type [46]. On the other hand, Schmid et al.'s acute 4-h sleep restriction study does not indicate changes in ad libitum energy intake or hunger in 15 men over 2 days [47]. Participants in this trial exceeded their estimated required caloric needs by ~60 % and increased fat consumption on average. In a longer experiment comparing 5 days of 4-h sleep restriction to 9-h sleep in 30 adults, subjects showed a 15 % increase in ad libitum energy intake and a 39 % increase in dietary and saturated fat consumption, especially in women [48]. Differing effects

of sleep loss on energy intake with respect to gender, age, and phases of the menstrual cycle are areas for further investigation [48].

Studies over a longer duration indicate a similar spectrum of negative results for chronic partial sleep restriction. Nedeltcheva et al. report increased snacking activity generated higher energy intake for 11 participants during a 2-week trial of 5.5 h of sleep per night compared to 8.5 h [49]. The sleep-restricted state was associated with a 54 % increase in the consumption of high-carbohydrate snacks especially at night, while average energy intake from meals remained constant. It is important to note that again under ad libitum conditions, caloric intake of adequately rested subjects sometimes exceeded physiological requirements, likely reflecting non-homeostatic mechanisms [49].

On the other hand, in a natural environment outside the laboratory, Beebe et al.'s study of 41 adolescents (14–16 years old) also indicates that chronic partial sleep restriction (<6.5 h per night) affects dietary intake [50]. During sleep curtailment, participants preferred and consumed diets of higher glycemic load but did not alter fat and protein consumption on average. Beebe et al. note significantly increased sweet consumption with decreased sleep duration. Laboratory studies of both chronic and acute partial sleep restriction indicate that insufficient sleep can lead to increased hunger and caloric intake.

Laboratory Evidence: Total Sleep Deprivation, as well as Acute and Chronic Partial Sleep Restriction, May Alter Hormonal Regulation and Lead to Changes in Energy Intake

Hormonal regulation may play a role in observed changes in diet and appetite with insufficient sleep. Leptin and ghrelin both have 24-h profiles that interact with sleep, as shown by trials using total sleep deprivation to eliminate the confounding effects of meal response. Simon et al.'s study of subjects receiving continuous enteral nutrition demonstrates that leptin levels are independently related to sleep after one night of total sleep deprivation and a resulting 8-h circadian shift [51]. In subsequent research, Mullington et al. note a decrease in the diurnal amplitude of leptin variation in ten healthy men during 88 h of total sleep deprivation [52]. Insufficient sleep also seems to affect ghrelin levels. Dzaja et al. found a dampening of nocturnal ghrelin elevation during 24-h total sleep deprivation [53].

While these extreme sleep restrictions are necessary to establish definitive links between sleep and hormonal profiles, evaluating states of partial and acute sleep restriction can yield results that more closely match real-life conditions. Spiegel, Leproult, et al. limited 11 healthy young men to 4 h of sleep per night for six nights and found significant decreases in mean and maximum leptin levels compared to the rested state [54, 55]. Possible negative influences on these levels include elevated cortisol levels and autonomic dysfunction, as indicated by decreased heart rate variability. Since caloric intake was tightly controlled, the authors postulate that approximately 3 days of dietary restriction at 70 % of energy requirements would have

been necessary to cause this observed reduction in leptin. In sleep-restricted participants, the rhythm amplitude of leptin profiles was 20 % lower and acrophase occurred 2 h later on average, despite typical diurnal variation. Although they did not assess subjective hunger, these physiological changes could be expected to increase appetite because of leptin's role in signaling satiety [56].

In another study of 12 healthy young men, Spiegel, Tasali, et al. measured a broader range of variables that link acute restricted sleep to energy intake [57]. After two nights with 4-h sleep duration, leptin levels decreased by 18 % and ghrelin levels rose by 28 %. In this experiment, the investigators also assessed appetite by a visual analogue scale and found a 24 % increase in subjective hunger during short sleep duration. Like the participants in Nedeltcheva et al.'s study [49], sleep-restricted participants' desire for high-carbohydrate, calorie-dense foods intensified disproportionately. The strong correlation between increased hunger and ghrelin-to-leptin ratio further suggests an underlying physiological process that links insufficient sleep to energy balance via hormonal control.

In a study of 11 young and 12 older adults, Buxton et al. also found evidence of hormonal changes that could affect energy intake under chronic conditions of short sleep duration in conjunction with circadian desynchrony [58]. Endogenous rhythms are synchronized to 24-h days, and disruptions of oscillators have been shown to alter hormone secretion and regulation [14]. Buxton et al. administered a strictly controlled eucaloric diet in the laboratory setting and collected blood samples over a wide range of circadian phases. During a study of partial sleep restriction (5.6 h per 24 h) combined with experimenter-controlled 28-h "days" over a period of 3 weeks, leptin and ghrelin profiles were slightly lower and higher, respectively, when compared to baseline. Unlike Spiegel et al. [57], the investigators noticed less pronounced changes in these two hormones, possibly indicating that circadian disruption and short sleep duration together produce a different response than short sleep duration alone [58]. With respect to the two age groups, Buxton et al. found significant interactions between subject age and time. Specifically, there were higher levels of leptin and free ghrelin in younger compared to older subjects during sleep times. This result indicates that the effect of sleep on energy balance may change over the life course.

Since healthy, young lean men are the participants of most research evaluating the effects of acute and chronic partial sleep restriction, Omisade et al. conducted a study of acute short sleep in healthy young women to determine whether effects were gender specific [59]. After one night of a 10-h sleep opportunity, 15 participants in the follicular phase of the menstrual cycle were restricted to 3 h of sleep the following night. Sleep-restricted women had significant elevations in morning leptin levels without reported changes in subjective hunger. Therefore, acute short sleep duration seems to affect hormonal regulation in healthy young women as well.

It is important to note that several studies of chronic and acute sleep curtailment do not record changes in leptin and ghrelin profiles, even with altered appetite. For example, Nedeltcheva et al. did not observe changes in either leptin or ghrelin levels of subjects after 2 weeks of short sleep (5.5 h per night) despite increased

hunger and caloric consumption [60]. An ad libitum feeding study design may explain this and similar results because hormonal responses after eating can mask changes in ghrelin and leptin profiles on a controlled eucaloric, or negative energy balance, diet [58].

However, even studies without ad libitum eating sometimes reveal mixed results. St-Onge et al. conducted an experiment under strict laboratory conditions of partial sleep restriction and controlled diet with fixed meal times [61]. Four days of 4 h of sleep per night produced no effect on participants' leptin or peptide YY levels compared to the rested state. Underestimation of energy requirements using the Harris-Benedict equation, however, created a condition of slightly negative energy balance that could have influenced hormone levels [61]. Short sleep, however, induced significant gender-specific effects in the hormones GLP-1 and ghrelin. The authors postulate that different hormonal mechanisms may regulate appetite in women and men because male, but not female, participants exhibited increased fasting, morning, and total ghrelin levels. Women, but not men, showed lower afternoon levels of GLP-1. Unlike St-Onge et al. [61], Magee et al. found a statistically significant reduction in PYY levels and a corresponding decrease in subjective satiety following two nights of acute short sleep duration [62]. Diet and activity, however, were not stringently controlled, and the participants were limited to healthy young men. Given the wide range of experiment designs and findings, studies with analogous conditions would be needed to more accurately assess hormone regulation of energy intake on a broader scale.

Laboratory Evidence: Insufficient Sleep May Affect Neural Reactions to Food Stimuli and Promote Energy Intake

Altered brain response to food stimuli is another possible mechanism for increased energy intake and unhealthy diet during insufficient sleep [63]. In an effort to identify brain regions vital to these behaviors, Benedict et al. used functional magnetic resonance imaging in 12 male subjects to assess responses to food stimuli after total sleep deprivation [63]. When presented with pictures of food, subjects with one night of total sleep deprivation exhibited increased activation of the right anterior cingulate cortex. This response was positively correlated to subjective hunger ratings despite unchanged fasting glucose levels. In a larger study of 30 partially sleep-restricted men and women, St-Onge et al. also used functional magnetic resonance imaging to evaluate brain activation in response to food stimuli [64]. After a 6-day trial of 4 h per night in bed, participants demonstrated increased activation in the cingulate gyrus and other areas associated with reward systems in response to food images. Not only does sleep deficiency appear to increase the desirability of food by activating central reward systems, but it may also induce impairments in self-control. A study by Barber et al., using a multiple-mediator model to assess the effect of sleep on work engagement, suggests that decreased sleep quality and duration predicts poor self-control and ability to resist temptation [65].

Laboratory Evidence: Various Levels of Insufficient Sleep Link to Energy Expenditure

On the other side of the energy balance equation, sleep may also affect energy expenditure. Total energy expenditure (TEE) includes basal resting metabolic rate (RMR), the thermic effect of meals (TEM), and volitional activity-based energy expenditure (AEE) [66]. Studies indicate that short sleep has mixed effects on RMR and TEM, which account for about 60 % and 10 % of expenditure, respectively [66, 67]. Benedict et al. using indirect calorimetry found that one night of total sleep deprivation in healthy young men reduced resting and postprandial energy expenditure [68].

In chronic partial sleep restriction studies, Nedeltcheva et al. [60] did not find a similar impact on total energy expenditure as observed in Benedict et al. [68]. To study the effects of insufficient sleep on weight loss, Nedeltcheva et al. observed ten overweight adults subjected to caloric restriction during 2 weeks of 8.5 versus 5.5 h sleep duration [60]. Although shorter sleep duration reduced weight loss by 55 % in sleep-restricted subjects, the investigators did not observe changes in total energy expenditure. In order to determine caloric output, Nedeltcheva et al. used doubly labeled water to gauge metabolic rate. In a subsequent report, Nedeltcheva et al. [69] found comparable weight loss in overweight and obese subjects with hypocaloric intake under conditions of short and adequate sleep. Indicating a metabolic difference between sleep conditions, subjects' respiratory quotients were elevated with 2 weeks of short sleep restriction (5.5 h per night) compared to the rested state (8.5 h). The authors postulate that this increase in respiratory quotient during the trial signaled the utilization of more carbohydrate energy. Under conditions of short sleep, overweight and obese participants did not preferentially burn fat but used carbohydrates instead. Although weight loss was comparable in sleep-restricted participants, fat again contributed much less to the weight loss (25 %) than in the rested state (56 %) as the subjects disproportionately lost muscle.

Buxton et al. found that fasting RMR remained unchanged from baseline in subjects provided with an isocaloric and nutrient-controlled diet under conditions of partial sleep restriction for 1 week and controlled activity [70]. In contrast, after adding circadian rhythm disruption to a prolonged restricted sleep challenge, Buxton et al. found that RMR decreased by 8 % [58]. Circadian desynchrony may have interfered with food metabolism and caused nutrients to be excreted unchanged [60]. Circadian misalignment of central and peripheral oscillators may have desynchronized metabolic signals, which, along with altered hormone levels and glucose metabolism, could have caused the decrease in RMR and energy expenditure.

Therefore, sleep deficiency may contribute to the current rise in overweight and obesity by inducing positive energy balance that leads to weight gain.

Explaining Associations Between Insufficient Sleep and Diabetes: Glucose Homeostasis and Hormonal Regulation

Laboratory studies may also help explain the relationship between insufficient sleep and diabetes. Trials of sleep restriction demonstrate adverse effects on glucose homeostasis, insulin sensitivity, and pancreatic secretion [19]. Again, hormones may underpin these very proximal sleep restriction outcomes. A wide range of tests are available to assess the effects of insufficient sleep on glucose homeostasis (Table 2.1).

Laboratory Evidence: The Impact of Total Sleep Deprivation on Glucose Homeostasis

In an early experiment to assess the effects of sleep deprivation on glucose homeostasis, Kuhn et al. found that 72–126 h of total sleep deprivation induced higher levels of plasma glucose in response to an OGTT [71, 72]. Similarly, Benedict et al.'s trial of one night of total sleep deprivation in young healthy male participants with strictly controlled dietary intake reveals elevated post-breakfast plasma glucose concentrations [68]. Increased insulin levels did not accompany the significantly higher glucose values, indicating reduced pancreatic beta-cell responsiveness [68]. Although disturbances induced by total sleep deprivation trials generally correct quickly, abnormalities sometimes persist beyond recovery periods [19].

Laboratory Evidence: The Impact of Recurring Partial Sleep Restriction on Glucose Homeostasis

Spiegel et al. investigated the impact of recurrent short sleep on metabolism and endocrine function [73]. After a trial of 4 h of sleep for six consecutive nights, healthy young men exhibited impaired glucose tolerance in response to a tolbutamide-modified IVGTT and controlled carbohydrate-rich meals. Relative to the recovery state, sleep-deficient subjects cleared an intravenous bolus of glucose at a 40 % slower rate, which was similar to that of older adults with impaired glucose tolerance. Minimal model analysis demonstrates a 30 % decrease in glucose effectiveness and acute insulin response to glucose. Since glucose effectiveness is a measure of non-insulin-dependent glucose utilization, a lower level can indicate decreased uptake of glucose by the brain, whose metabolism does not require insulin [73]. The authors postulate that decreased cerebral glucose uptake may have caused the subjective sleepiness reported on the fifth day of the short sleep trial.

Table 2.1 An overview of tests used to evaluate glucose homeostasis

Type	Test	Test description	Interpretation	Op. Cit.
Retrospective, cumulative measurement of chronic glycemia	Hemoglobin A1c	The percent of glycated hemoglobin in a blood sample	Historical indication of blood sugar regulation over the prior 2 months. Diagnostic of diabetes Normal: <5/6 % Prediabetic: 5.6–6.5 % Diabetic ≥6.5 %	ADA, *Diabetes Care* January 2012; Broussard et al., *AIM* 2012 [82, 87]
Glycemic response to fasting: indicative of hormonal control	Fasting plasma glucose	Plasma glucose levels after a ≥8 h fast	Fasting lowers blood glucose levels, stimulating glucagon release which elevates blood glucose. Insufficient release of and/or sensitivity to insulin results in hyperglycemia Prediabetic: 100–125 mg/dL Diabetic ≥126 mg/dL	ADA, *Diabetes Care* January 2012; Spiegel and Lancet, 1999; Matthews et al., *Sleep* 2012; Broussard et al., *AIM* 2012 [31, 73, 80, 85]
Hormonal response to fasting	Fasting insulin	Serum insulin (and c-peptide) levels after an ≥8 h fast	Insulin production is elevated in response to fasting which causes the release of glucagon to raise blood glucose levels Hyperinsulinemia: >20 uU/mL insulin and >4.6 ng.mL c-peptide	Buxton et al., *STM* 2012; Nedeltcheva et al., *JCEM* Sept 2009; Buxton, *Diabetes* 2012 [58, 70, 80]
Mathematical approximation	HOMA (homeostasis model assessment index)	HOMA-IR = (Fasting Insulin*Fasting Glucose)/22.5	Mathematical model that approximates steady-state insulin sensitivity and beta-cell function based on fasting insulin and glucose levels	Spiegel et al., *JCEM* 2004 [55]
		HOMA-Beta = (20*Insulin)/(Glucose−3.5) %	Useful in larger-scale clinical studies	

Response to standardized challenge	OGTT (oral glucose tolerance test)	Standard 75 g oral glucose dose administered after an 8–12 h fast. Blood glucose and insulin levels tested at time intervals after ingestion	After 2 h: normal (<140 mg/dL diabetic) Indicates the effectiveness of glucose removal from the bloodstream. Insulin resistance can be gauged from calculating glucose-AUC (Muniyappa)	Nedeltcheva et al. JCEM 2009; Broussard AIM 2012; Pamidi et al., *Diabetes Care* 2012 [80, 82, 88]
Response to a more ecologically valid challenge	Meal response	Standard meal administered, sometimes after an 8–12 h fast. Blood glucose and insulin levels tested at time intervals and after ingestion	After 2 h: normal (<140 mg/dL diabetic) Indicates the effectiveness of glucose removal from the bloodstream in response to a more ecologically accurate glucose challenge. Insulin response can be gauged from calculating glucose-AUC (Muniyappa)	Buxton et al., *STM* 2012 [58]
Response to precise, high-dose challenge	IV glucose tolerance test	IV glucose (.3 g/kg) bolus administered after an 8–12 h fast. Blood samples for plasma glucose and insulin levels tested frequently after injection up to 180 min	Minimal model analyses (MINMOD) indicate insulin sensitivity (Si) and glucose effectiveness. *Glucose tolerance is the slope of the natural log of glucose values from minute 5 to 19 after dose*	Buxton et al., *Diabetes* 2010; Spiegel and Lancet, 1999; Broussard et al., *AIM* 2012 [70, 73, 82]
Gold standard	Hyperinsulinemic euglycemic clamp	IV insulin is infused at a high and then lower steady rate to maintain euglycemia (90 mg/dL). At steady state, the glucose infusion rate in mg/kg body weight • min is recorded	The rate of glucose infused every minute per kg of patient body weight needed to maintain euglycemic measures the rate of peripheral glucose utilization and indicates tissue insulin sensitivity	Buxton et al., *Diabetes* 2010 [70]

The sleep-restricted participants' lower acute insulin response, an early marker of diabetes, was in the range seen in older adults and gestational diabetes. There was no significant difference in insulin sensitivity between the short sleep and recovery intervals in the trial.

Concordant with the impaired glucose tolerance indicated by the IVGTT, sleep-restricted participants showed higher post-breakfast glucose levels than in the sleep-replete state [73]. In a subsequent experiment in 2004, Spiegel et al. examine the effects of recurrent partial sleep debt on glucose homeostasis after a carbohydrate-rich breakfast [57]. They use the HOMA model as an indication of beta-cell function and as an integrated measure of the glucose and insulin responses to meals, rather than an index of insulin sensitivity. As in the 1999 experiment, post-breakfast glucose levels were elevated with short sleep, and insulin concentrations were higher but not significantly so when compared to the sleep-replete condition (a week of 10-h time in bed). Sleep-restricted participants showed a 56 % increase in HOMA values over the adequately rested state.

Buxton et al.'s double-blind, randomized study further demonstrates short sleep's negative effect on insulin sensitivity in healthy young men [70]. The investigators used an IVGTT to provide an accurate measure of insulin sensitivity and also employed a euglycemic hyperinsulinemic clamp technique, considered the gold standard for insulin sensitivity assessment. The conditions of this experiment include a confirmed baseline sleep-replete state, confinement to the laboratory setting, eucaloric controlled diets, and monitored minimal activity.

After 1 week of 5 h of sleep per night, results of both the IVGTT and euglycemic hyperinsulinemic clamp evaluations correlated with each other, revealing significantly reduced insulin sensitivity compared to the rested state [70]. Minimal model analysis of IVGTT data showed a decrease in mean insulin sensitivity, although the acute insulin response did not significantly change across conditions. Sleep-restricted subjects had a reduced disposition index, indicating increased diabetes risk, and glucose tolerance was significantly decreased. Moreover, decreased insulin sensitivity was not offset by increased pancreatic insulin secretion.

These results were essentially similar to Spiegel et al.'s findings which, on later reexamination, revealed indices of HOMA levels and glucose disposition that indicated insulin resistance during conditions of short sleep [73]. As Buxton et al. note, this finding also concurs with data from Nedeltcheva et al.'s study which demonstrate increased insulin resistance and impaired glucose tolerance in sleep-restricted subjects under conditions of high caloric consumption and sedentary activity [60]. In a randomized crossover investigation conducted in a laboratory setting, Nedeltcheva et al. assessed the effects of chronic partial sleep restriction (5.5 h per night for a 2 week period) on male and female middle-aged adults. Participants were given ad libitum access to food, while activity was maintained at a low level. It is important to note that this increase in insulin resistance occurred under laboratory protocols more analogous to real-life conditions.

Laboratory Evidence: The Impact of Various Levels of Insufficient Sleep on Inflammatory Markers

Pro-inflammatory cytokines are also increased by sleep restriction. For example, 24-h levels of IL-6 are increased by sleep restriction in men and women [74, 75], whereas TNF alpha has been shown to increase with sleep restriction only in men [75]. CRP levels have been shown to be elevated in one study of both acute total sleep deprivation and 10 days of partial sleep restriction to 4.2 h/night [76] but have not always replicated, for example, in a study of 4 h/night of sleep restriction [74]. More recently CRP has been associated in NHANES with extremes of sleep duration (short or long), but this effect varies by both gender and ethno-racial categories and is not present in all categories [77]. Far more work is needed to understand the role of inflammation due to sleep loss and its subsequent effects on glucose homeostasis.

Epidemiological and Laboratory Evidence: The Impact of Chronic Partial Sleep Restriction Combined with Circadian Disruption on Glucose Homeostasis

Given the evidence for impaired glucose homeostasis during total sleep deprivation and chronic short sleep duration, Buxton et al. investigated the consequences of prolonged sleep restriction combined with circadian disruption [58]. This study is important because cross-sectional and prospective epidemiological evidence indicate an increased risk of obesity and diabetes in shift workers whose schedules disrupt circadian rhythms. These disruptions usually diminish the duration and quality of sleep because the central circadian pacemaker makes it difficult to maintain sleep during the day when it exerts its greatest homeostatic drive for alertness [14]. Increased noise from routine daily activities can also disturb daytime sleep, as Buxton et al. document in a study of hospital sounds' impact on sleep [78]. In light of these endogenous and external factors interfering with daytime sleep, it is not surprising that jobs which disrupt circadian rhythms predispose at-risk populations to adverse health effects. Indeed, a 3-year prospective study shows that of workers with prediabetic indices, such as elevated fasting glucose, night-shift workers are at fivefold risk for developing overt diabetes compared to day workers [79].

To test these epidemiological observations in a controlled laboratory setting, Buxton et al. employed a forced desynchrony protocol that manipulates light/dark, feeding/fasting conditions to allow participants' biological pacemakers to oscillate according to inherent circadian rhythms [14]. Forced desynchrony permits the separation of endogenous homeostatic mechanisms from the "sleep-wake" and "fasting-feeding cycles" [58]. In order to avoid the possibility of entrainment,

the investigators imposed a 28-h "day" for the trial, and sleep times were equivalent to 5.6 h per night in a 24-h day. Buxton et al. hypothesized that circadian disruption would augment the relationships of short sleep duration to impaired glucose tolerance.

After 3 weeks of sleep restriction combined with circadian disruption, participants exhibited fasting and post-breakfast peak plasma glucose concentrations that were significantly elevated compared to the rested state [58]. Three of 21 participants exhibited postprandial glucose concentrations in the prediabetic range. Despite this hyperglycemia, fasting plasma and integrated insulin levels were significantly lower, and postprandial insulin secretion was reduced by 32 %. Prior studies such as Buxton et al.'s 2010 evaluation [70] of sleep restriction without circadian disruption and Nedeltcheva et al.'s 2009 assessment [80] of short sleep duration under conditions of high caloric consumption and sedentary activity revealed increased peripheral insulin resistance with elevated glucose levels despite slightly elevated or unchanged insulin profiles. Under conditions of recurrent sleep restriction combined with circadian disruption, participants' low insulin levels, concomitant with high plasma glucose, seem to indicate insufficient pancreatic beta-cell secretion of insulin [58]. Signaling that short sleep may lead to even more generalized islet cell dysfunction, Schmid et al. found evidence of impaired alpha-cell glucagon secretion in young healthy men with sleep debt in response to hypoglycemia [81].

In addition to possible pancreatic dysfunction, a recent study by Broussard et al. has shown a direct metabolic tissue dysfunction following sleep loss [82]. In this study, participants underwent an IVGTT followed by fat biopsy after a period of both four nights of 8.5 h in bed and four nights of 4.5 h in bed in a randomized crossover design. Sleep restriction induced a reduction in insulin signaling in the fat cells taken from participants after short sleep, resulting in an overall decrease of cellular insulin sensitivity by 30 % as compared to "normal" sleep. This is in contrast to a whole body insulin sensitivity reduction of 16 %, suggesting that the fat cell, like the pancreatic β-cell, may be a particularly vulnerable cell type to the effects of sleep loss.

Laboratory Evidence: The Impact of Insufficient Sleep on Glucose Homeostasis via Cortisol Regulation

Other studies also demonstrate an impact of insufficient sleep on cortisol in response to range of sleep challenges. Cortisol plays an important role in glucose homeostasis by stimulating gluconeogenesis in the liver to raise blood sugar and by counteracting insulin.

Total sleep deprivation and acute partial sleep restriction elevate cortisol levels. Leproult et al. evaluated the effect of one night of total sleep loss and of partial restriction on healthy young men, whose caloric intake was restricted to a constant intravenous glucose infusion. This protocol disrupted the hypothalamic-pituitary-adrenal axis [83]. Total sleep deprivation raised participants' mean cortisol levels by 45 % on the following day, whereas a short sleep of 4 h yielded a more modest 37 %

increase. The investigators note that increased amplitudes of secretion and a slower rate of cortisol decline may indicate impaired glucocorticoid feedback mechanisms. Omisade et al.'s study in healthy young women shows similar results after one night of 3-h sleep restriction [59]. Afternoon and evening cortisol levels were elevated, resulting in altered 24-h cortisol profiles.

Spiegel et al.'s longer trial of partial sleep restriction of 4 h per night for 6 days also shows changes in cortisol [54, 55]. Nevertheless, 24-h mean cortisol levels were similar in trials of sleep insufficiency and sleep extension. Like Leproult et al. and Omisade et al.'s findings, sleep-restricted participants in Spiegel et al.'s study also demonstrated higher late afternoon and evening cortisol levels with the nadir occurring about 1.5 h later than in the rested state. As in prior studies, they propose that the slower decline in cortisol from the morning acrophase throughout the day resulted in elevated evening values. Buxton et al.'s study of 20 healthy, nonobese men who underwent restricted sleep for 5 h per night over a 1-week period reveals similar changes in cortisol under conditions of controlled diet and activity [70]. In sleep-restricted subjects, late afternoon and evening levels of salivary free cortisol were significantly elevated compared to the sleep-replete condition but did not show linear correlation to insulin sensitivity. The sleep-deficient participants experiencing 28-h "days" in Buxton et al.'s study of prolonged sleep restriction combined with circadian disruption also exhibited higher plasma cortisol levels compared to the rested state [60]. These hormonal changes persisted throughout the 3-week exposure in all circadian phases.

Overall, studies suggest a strong relationship between insufficient sleep and impaired glucose homeostasis and cortisol regulation. These proximal outcomes may explain observed associations between sleep and the diabetes epidemic.

Laboratory Evidence: The Impact of Insufficient Sleep on Glucose Homeostasis via Sympathetic Nervous System Activation

Studies have shown links between increased sympathetic output and obesity, insulin resistance, obstructive sleep apnea, hypertension, and leptin resistance. Many studies also suggest a role of the sympathetic nervous system (SNS) in the alteration of glucose regulation following sleep loss. The SNS is regulated by sleep-wake cycles and its activity is highest during REM sleep and wakefulness and gradually decreases during non-REM sleep [84]. Sleep onset is associated with a significant decline of circulating concentrations of catecholamines, which serve as direct readouts of sympathetic activity. In contrast, nocturnal and morning awakenings are associated with increases in these hormones [85]. One study by Marangou and colleagues administered catecholamines before an IVGTT to test their effects on glucose regulation in healthy humans [86]. Norepinephrine infusion resulted in a significant increase in blood glucose and circulating free fatty acids during the IVGTT, as well

as a marked decrease in insulin sensitivity and disposition index, suggesting a significant increase in diabetes risk with increased levels of catecholamines [86].

Additionally, sleep disturbances have been shown to increase sympathetic output. In a study comparing 5.5 h with 8.5 h of time in bed in 11 healthy middle-aged volunteers, a significant increase was observed in nighttime and 24-h epinephrine levels during sleep restriction [80]. Furthermore, heart rate variability (HRV), a read-out of cardiac sympathetic nervous system activity, has been shown to be impaired during short sleep [55, 73], suggesting an increase in sympathetic drive during sleep restriction.

The relationship suggested between sleep loss and sympathetic nervous system dysfunction proposes another likely mediator of several of the negative metabolic effects of sleep loss and sleep disorders, including insulin resistance, decreased glucose tolerance, and reduced leptin signaling, all of which can predispose an individual to obesity.

Conclusions and Policy Implications

Mounting evidence from both epidemiological and laboratory investigations indicates the deleterious and complex effects of insufficient sleep. In view of the morbidity and mortality associated with the global obesity and diabetes epidemics, the relationships between inadequate sleep, excess weight, and impaired glucose regulation are particularly troubling. The burgeoning "epidemic" of inadequate sleep seems cause for concern. Indeed, rising sleep insufficiency in both pediatric and adult populations has paralleled the surge in obesity and diabetes. These epidemics and associated disorders, such as hypertension, cardiovascular disease, and cancer, generate enormous healthcare and economic burdens. While public policy efforts tend to focus on waking health behaviors such as diet and exercise, it seems crucial to highlight sleep as a third pillar of health and well-being.

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Chapter 3
Sleep Disorders and Melatonin

Katherine A. Dudley and Sanjay R. Patel

Abstract Melatonin is an endogenously produced neurohormone that plays a key role in the signaling of daily rhythms and the coordination of these rhythms with the external world. It serves as a marker of darkness and also modulates circadian phase, or timing, through feedback mechanisms on the intrinsic circadian rhythm generated by the suprachiasmatic nucleus. Melatonin and its metabolites can be readily measured in plasma, saliva, and urine. Measurement of melatonin profiles, particularly, the timing of the sharp rise in melatonin levels during the biological night, can be used to assess circadian phase which is useful in the diagnosis of sleep/circadian pathology as well as determining the optimal timing of treatment. Therapeutically, melatonin can be used to manipulate circadian phase and promote sleep in a circadian rhythm-dependent fashion. Randomized trials have demonstrated that exogenous melatonin can be of benefit in a number of sleep disease states including delayed sleep phase syndrome, non-24-hour sleep-wake syndrome, jet lag, and insomnia.

Keywords Melatonin • Sleep • Circadian rhythm • Dim-light melatonin onset • Pineal gland • Circadian rhythm sleep disorders • Phase response curve • Advanced sleep phase syndrome • Delayed sleep phase syndrome • Non-24-hour sleep-wake syndrome • Jet lag • Insomnia

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_3,

Basics of Melatonin

Living organisms make use of a complex, yet adaptable, system that allows for timekeeping within the body and entraining to external light signals, which provides a determination of season from day length. One of the most basic components of this timekeeping system is melatonin, which regulates the sleep-wake cycle and serves as a marker of darkness. Melatonin is a neurohormone, synthesized by pinealocytes within the pineal gland. The pineal gland is located in the brain, between the two thalamic bodies and behind the third ventricle. Though pinealocytes are responsible for production of circulating melatonin, other organs including the retina, gut, bone marrow, and lymphocytes are known to produce melatonin locally [1, 2].

The steps involved in melatonin synthesis are displayed in Fig. 3.1. Formation of melatonin begins with the amino acid tryptophan, which is hydroxylated to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase [3]. Through the enzyme 5-HTP decarboxylase (also known as L-aromatic amino acid decarboxylase), serotonin is formed. Melatonin is created from serotonin through a two-step

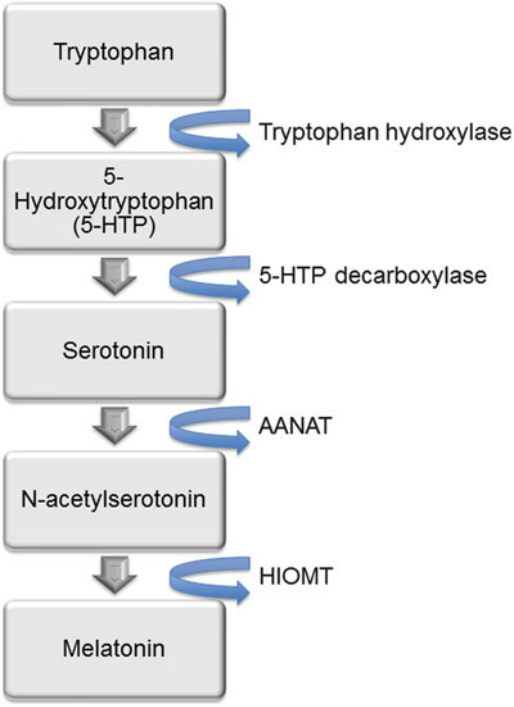

Fig. 3.1 Melatonin synthesis. Melatonin synthesis starts with the amino acid tryptophan. Tryptophan is first converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. 5-HTP is converted to serotonin by 5-HTP decarboxylase (also called L-aromatic amino acid decarboxylase). Next, serotonin is made into *N*-acetylserotonin by *N*-acetyltransferase (AANAT, also referred to as serotonin-N-acetyl transferase or NAT). Finally, melatonin is produced after hydroxyl indole-*O*-methyl transferase (HIOMT) transfers a methyl group onto *N*-acetylserotonin, creating *N*-acetyl-5-methoxytryptamine, also known as melatonin

process, first by *N*-acetyltransferase (AANAT, also called serotonin-*N*-acetyl transferase or NAT), which creates *N*-acetylserotonin. Next, hydroxyindole-*O*-methyl transferase (HIOMT), an enzyme highly localized within the brain to the pineal gland [4], transfers the methyl group of *S*-adenosylmethionine to the hydroxyl group of *N*-acetylserotonin, to form *N*-acetyl-5-methoxytryptamine, or melatonin.

The two strongest regulators of melatonin production are the underlying circadian rhythm and ambient light. The circadian rhythm is generated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which acts as a master pacemaker. This rhythm produces a host of physiological and biological processes that follow a self-repeating pattern over a regular period. The endogenous rhythm of the SCN has a period that is typically slightly greater than 24 h [5], garnering the description "circadian" coming from the Latin words circa, meaning "around," and diem, meaning "day." Besides the period, it is also useful to describe the phase of a rhythm, which refers to the position of the rhythm within the self-repeating pattern. Convenient markers of position, or phase, of the circadian rhythm include reference points within physiological outputs of the rhythm such as the body temperature nadir or the onset of melatonin rise.

While the endogenous SCN period is typically longer than 24 h, through input from the external environment, the SCN is able to synchronize to the 24-h daily cycle. Light is the most powerful synchronizer or zeitgeber for the SCN. Light-sensitive retinal ganglion cells sense light through the photopigment melanopsin [6]. Light information is thus received by the retinal cells and subsequently relayed via the retinohypothalamic tract (RHT) to the SCN. The SCN transmits information via the paraventricular nucleus (PVN) of the hypothalamus and then via a multi-synapse pathway which includes the superior cervical ganglia in the spinal cord to the pineal gland. In some patients with cervical spinal cord injuries, and thus interruption of this pathway, melatonin production has been found to be absent [7].

Due to the circadian influence of the SCN, when a normally entrained individual is kept in constant darkness, levels of melatonin begin to rise in the evening between 8:00 p.m. and 11:00 p.m., peak between 2:00 a.m. and 4:00 a.m., and then return to baseline levels around 8:00 a.m. to 10:00 a.m., with a rather abrupt offset of production. Levels during the day are typically very low. On top of this underlying circadian rhythm, light has an acute inhibitory effect on melatonin production, independent of any changes caused to the circadian rhythm. In normally entrained individuals who sleep during the night and are awake during the day, the inhibitory effect of light synergizes with the underlying circadian rhythm leading to elevated melatonin levels at night and barely detectable levels during the day.

During the day, while exposed to light, photoreceptor cells of the retina are hyperpolarized [8]. The hyperpolarized state ultimately results in inhibition of neurons in the dorsal parvocellular area of the PVN. During darkness, when this inhibition is lifted, a tonic adrenergic stimulation is applied to beta-1-receptors on the pinealocytes through a multi-synapse pathway [9]. Despite the presence of both serotonin and norepinephrine in the adrenergic nerves controlling pinealocyte stimulation, norepinephrine has been established as the critical neurotransmitter regulating melatonin secretion [10]. Norepinephrine thus drives control of synthesis and activation of AANAT through a cyclic adenosine monophosphate (cAMP)-mediated process [10, 11], which makes activation of AANAT the rate-limiting step in melatonin production [12, 13].

Levels of melatonin and serotonin within pinealocytes vary depending on degree of light and dark exposure and are 180° out of phase [12]. Additionally, the size, activity, and composition of other cellular components such as the Golgi apparatus and granulated vesicles within pinealocytes also vary significantly by light exposure, highlighting the light-dependent nature of this gland's activity. Although light is the most powerful influence, additional factors can modulate pineal melatonin synthesis, including insulin-induced hypoglycemia and physical activity which stimulate catecholamine release [14]. Similarly, medications such as beta-adrenergic agonists and antagonists can impact melatonin production.

After synthesis in the pinealocytes, melatonin passively diffuses into the bloodstream. Downstream from the pineal gland, there are abundant binding sites throughout the body. Three melatonin receptors have been identified: MT_1, MT_2, and, more recently, MT_3 [15, 16]. Melatonin receptors have been identified in nearly every organ in mammals, from retina, liver, adrenal glands, heart, gastrointestinal tract, blood cells, and the central nervous system, including within the SCN, allowing for feedback. Melatonin is able to cross the blood-brain barrier as well as across the placenta [9].

Metabolism of melatonin takes place primarily in the liver, where it is rapidly broken down to 6-hydroxymelatonin. After conjugation with sulfuric acid, it is excreted from the body via urine predominantly as 6-sulfatoxymelatonin (a6MTs, also referred to as 6-SMT) and secondarily as a glucuronide. The half-life of melatonin once it enters the bloodstream is quite short, on the order of 0.5–5.6 min [17].

Measurement of Melatonin

Melatonin and its metabolites may be measured from several different locations, including plasma, saliva, or urine. This makes it one of the most widely utilized biomarkers for determining circadian phase or otherwise determining abnormalities in circadian rhythm. This can be useful in diagnosing circadian rhythm sleep disorders as well as in investigations of the role of circadian biology in the pathophysiology of other disease states.

During the biological night, melatonin production typically starts abruptly, appearing as more of a square wave than a sine wave in shape when graphed against time (Fig. 3.2) [18]. As a result, the time of onset of production can be fairly accurately identified through serial measurements and this can be used as a marker of circadian phase. Since light has a profound inhibitory effect on melatonin production [19], samples should be collected under dim-light conditions, typically less than 10 lux. With sampling of either plasma or saliva, care should be taken to avoid exercise and changes in posture, as these can interfere with timing and amount of melatonin secretion [20, 21]. Some medications, such as beta-blockers and nonsteroidal anti-inflammatory agents, may also interfere with melatonin production [22–24]. Testing completed in this fashion, under dim light, allows for determination of the dim-light melatonin onset (DLMO), which is typically defined as the first time that melatonin level is greater than 10 pg/mL in plasma or 3 pg/mL in saliva, after which point the levels continue to rise [18, 25, 26]. An alternative is to use a threshold of two standard deviations above the baseline level [27].

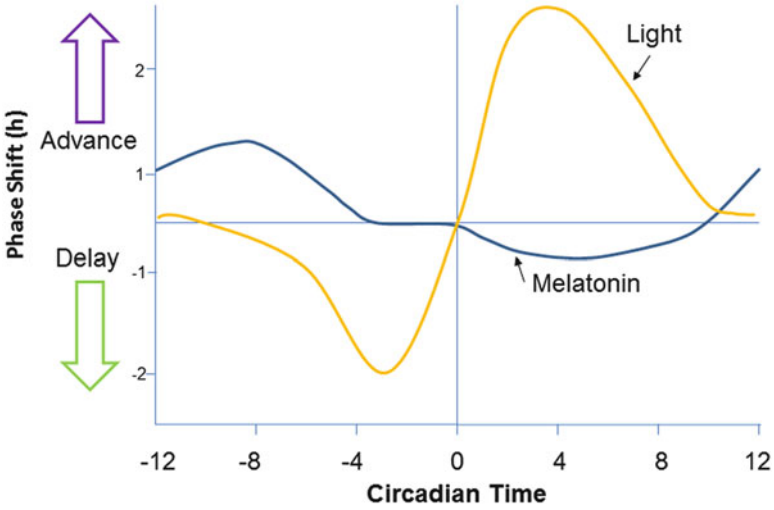

Fig. 3.2 Phase response curve to melatonin and light. A human phase response curve to melatonin (*blue line*) and light (*yellow line*). Circadian time (CT) 0 = core body temperature minimum. Melatonin administered before this time will create a phase advance (positive direction on y-axis), while after this time, a phase delay (negative direction on y-axis). Light, in contrast, will create a phase delay when exposure is before CBTmin. After CBTmin, light will create a phase advance. Amplitude of phase change depends on circadian time. (Modified from [25, 28, 81], Burgess 2008)

DLMO has been evaluated in normally entrained individuals as well as those with sleep disorders and can be tracked when manipulations of phase are made through light exposures, medications, or other interventions. Typically, DLMO occurs 2–3 h before sleep onset [29–31]. In general, melatonin is considered a better marker of circadian phase than core body temperature or cortisol, in that it is less sensitive to non-circadian inputs [32].

To capture DLMO, when collecting plasma or saliva, sampling should ideally occur frequently, as much as every 30 min, beginning at least 4 h before habitual bedtime and continuing for at least 2 h after usual bedtime [26, 33, 34]. For example, in a normally entrained individual with a stable sleep-wake cycle of at least a week and a typical bedtime of 10 p.m., samples might be collected from 6 p.m. to midnight [18]. In those whose sleep onset is variable or irregular, sampling over a longer period of time may be needed to not miss the DLMO. Measurement of duration of melatonin production, as well as total amount, can be used as markers of seasonality. Total secretion of melatonin can be assessed by the area under the curve profile of serum melatonin over time or alternatively by measuring 24-h total urinary excretion of aMT6s [35]. Additionally, in disease states, such as pineal tumors or after pineal surgery, total melatonin amounts can be useful to identify pathology or assess surgical success.

In plasma and saliva, melatonin may be measured by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA), while in urine, aMT6s is typically measured by RIA. Although salivary samples are noninvasive and readily

collected, melatonin levels are approximately 10–30 % of plasma levels. Nevertheless, studies have demonstrated that patterns in melatonin secretion are identical [36, 37].

Measurement of urine aMT6s offers the advantage of home-based, noninvasive testing that can be performed in real-world settings and can be collected over longer periods of time. The 24-h pattern of urine aMT6s excretion mirrors serum melatonin patterns [38, 39], though phase assessment can be less accurate due to less frequent sampling. Urine samples are typically collected every 4 h while awake. Additional data, including collection period, urine creatinine, and volume of urine, must also be noted in order to calculate 24-h output and timing of peak values [33].

Functional Effects of Melatonin

As outlined in the last section, melatonin allows for the chemical coding of light signal and, thus, provides a measure of day length and seasonality. In addition, melatonin acts as a positive feedback mechanism on the SCN to reinforce timing of the circadian clock. High-affinity melatonin receptors, both MT1 and MT2 subtypes, have been identified in the SCN [40]. Binding of these receptors leads to activation of various signaling pathways, resulting in inhibition of SCN neuronal firing. The downstream result is modulation of the circadian rhythm generated by the SCN. As a result, melatonin can be utilized to advance or delay circadian phase. The MT2 receptor appears to be the primary pathway by which this modulation of circadian phase is mediated [41]. Melatonin also has a sleep-promoting effect. MT1 receptors within the SCN appear to play an important role in this capacity, as their activation is associated with inhibition of neuronal activity [42]. Exogenous melatonin administration is associated with a time-dependent hypnotic effect, with maximal effect around onset of biological night [43].

Despite these important feedback roles in sleep and phase modulation, however, melatonin is not necessary for generation of sleep or to maintain circadian rhythm. Patients with undetectable levels of melatonin, such as those with high cervical spine injuries, exhibit normal sleep/wake and cortisol rhythms as well as normal sleep architecture. Thus, the effects of melatonin on normal sleep and circadian biology are to a large extent redundant.

Beyond its timekeeping properties, melatonin also has a number of non-circadian properties, such as a modifier of endocrine function. Melatonin serves as a signal of seasonality and thus has a modulating role for animals that exhibit photoperiod-dependent seasonal breeding. Though this role is not prominent in humans, seasonal variation of conception and births in some geographic areas has been reported [44]. In humans, a substantial drop in melatonin levels occurs around age 9–10 years, which may act as a stimulating signal for release of gonadotropin-releasing hormone (GnRH) [45, 46]. Once melatonin levels decline, GnRH pulses become more frequent and larger in amplitude, ultimately resulting in start of puberty. In women, after puberty, melatonin production and effect may fluctuate depending on phase of

menstrual cycle [47–49], though this has not been consistently found in all studies [50–52]. Abnormalities in melatonin levels are linked to disease states such as functional amenorrhea [52, 53]. Melatonin is also involved in other hormonal circuits, including oxytocin, vasopressin, and growth hormone [54, 55]. Melatonin also has an inhibitory effect on insulin secretion from β-cells in the pancreas [56, 57]. A polymorphism in the MTNR1B gene which encodes the MT2 receptor has been identified as a risk factor for type 2 diabetes mellitus in several genome wide association (GWA) studies [58, 59].

Melatonin also has immune-enhancing functions. Both animal and human studies demonstrate that melatonin increases the number and activation of circulating CD4+ T-lymphocytes [60–62]. Activation is dose dependent and appears to be mediated by IL-2 and IFN-gamma [63, 64]. In addition, melatonin induces monocyte proliferation as well as activation with increased production of cytokines including IL-1, IL-6, and TNF-alpha [65]. Natural killer (NK) cells are another cell type activated by melatonin [66].

Independent of its receptor binding effects, melatonin has direct effects as an antioxidant [67–69]. Its antioxidant properties come from its electron-rich aromatic indole ring, which is able to function as an electron donor. Additionally, melatonin exhibits oncostatic activity, which may be mediated through effects on angiogenesis, tumor proliferation, and metastasis [70–73]. Proposed mechanisms by which this occurs include the inhibition of fatty acid growth-factor uptake by cancer cells, apoptosis of cancer cells via inhibition of telomerase activity, inhibition of endothelin-1 synthesis, and modulation of the expression of the tumor suppressor gene TP53 [74–76].

Melatonin and the Phase Response Curve

Circadian phase can be manipulated through melatonin, which can be administered exogenously. After light, melatonin has perhaps the strongest influence on circadian phase. Experiments assessing the direction and magnitude of change in circadian phase as assessed by DLMO to exogenous melatonin administered at different times have allowed for the creation of a phase response curve (PRC) for melatonin (Fig. 3.3). Similar curves have been generated for response to light [77, 78].

Though labeled variably in the literature, circadian time (CT 0) is often defined by the circadian phase marker of core body temperature (CBT) minimum. On average, DLMO occurs around 14 h after lights on and onset of activity, with bedtime about 2 h afterward [25]. CBT minimum is approximately 7 h after DLMO [32]. Typically, a phase advance occurs when melatonin is administered before CBT minimum and a phase delay if given after. There are two points in the day considered crossover times, at which time the direction of phase effect of melatonin changes [79]; there is also a period of reduced response to melatonin during the night.

The PRC for melatonin is 12 h out of phase with the light PRC [79], with similar crossover points for light stimulus and reduced responsiveness during the day.

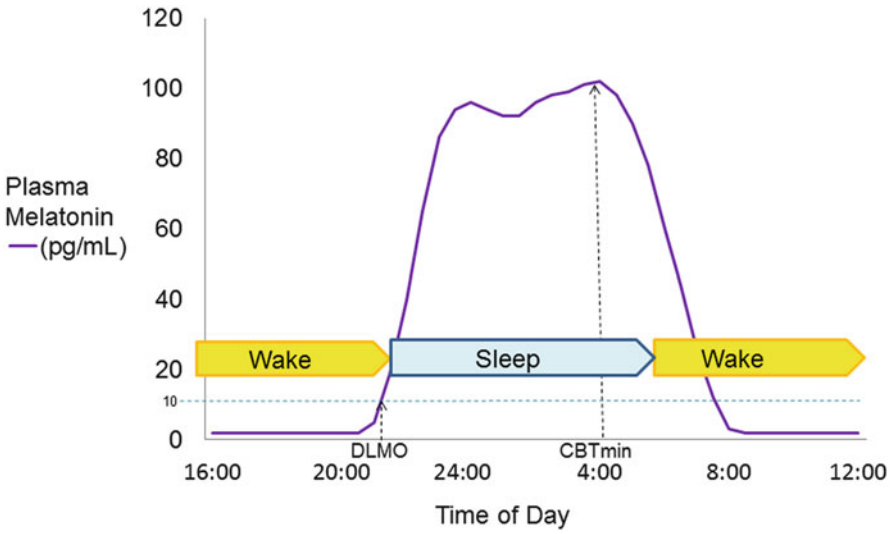

Fig. 3.3 Melatonin production in dim light. Plasma melatonin levels in a normally entrained individual sleeping from 22:00 until 6:00. Onset of melatonin production is around 20:00, prior to initiation of sleep. Dim-light melatonin onset (DLMO) is defined by the point at which levels rise above 10 pg/mL or two standard deviations above baseline level and is often used as a marker of circadian phase. Melatonin production rises sharply, peaks around core body temperature minimum (CBTmin) which is typically around 4:00 for normally entrained individuals, and then declines rapidly to baseline levels shortly after wake (Modified from [33])

Though there is variable degree of effect based on intensity of stimulus, the magnitude of phase shift for light and melatonin is largest a few hours before and after the crossover point, which occurs around CBT minimum [80, 81]. Melatonin administered before this time will create a phase advance, while light a phase delay. After CBT minimum, they will have the opposite—melatonin will induce a phase delay while light a phase advance. Though light does appear to be the more powerful stimulus, melatonin remains important due to the availability of exogenous melatonin and the inability to use light in some cases.

Melatonin and Circadian Rhythm Sleep Disorders

There are a number of circadian rhythm sleep disorders recognized by the International Classification of Sleep Disorders (ICSD-2) including delayed sleep phase type, advanced sleep phase type, irregular sleep-wake phase type, free-running sleep type, jet lag type, and shift work type [82]. All of these share the common feature of alterations in the endogenous circadian rhythm or misalignment with the external 24-h light-dark rhythm that impact the timing or duration of sleep and result in impairment in social, occupational, or other domains [82].

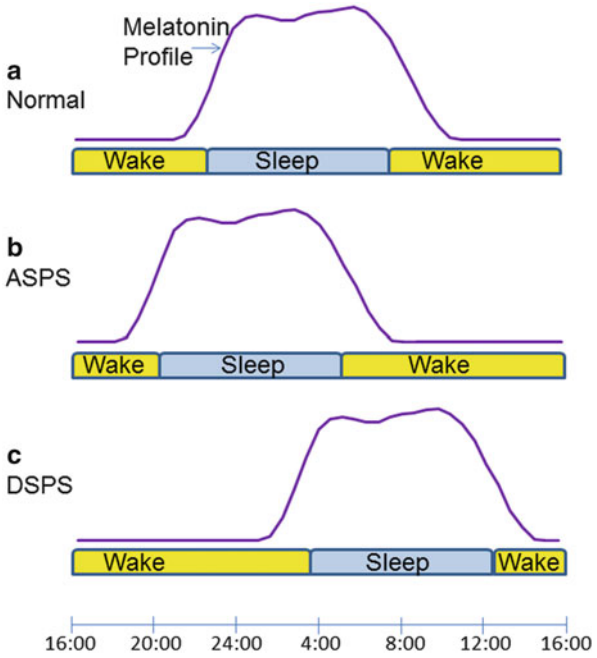

Fig. 3.4 Melatonin profiles in normal entrainment and advanced and delayed phase. (**a**) For a normally entrained individual, melatonin levels start to rise just before sleep initiation and rapidly decline after wake in the morning. (**b**) In comparison, for an individual with advanced sleep phase syndrome (ASPS), melatonin levels rise and fall several hours earlier, with sleep period similarly advanced by several hours. (**c**) For an individual with delayed sleep phase syndrome (DSPS), melatonin levels and sleep are delayed by several hours as compared to a normally entrained individual

Advanced Sleep Phase Syndrome

Individuals with advanced sleep phase syndrome (ASPS) exhibit an internal circadian rhythm that is advanced, or early, as compared to local 24-h light-dark signals. As a result, patients with ASPS endorse bothersome sleepiness in the afternoon or early evening hours and early termination of sleep. Awakening in the early morning hours results in difficulty sleeping until desired wake time. Increased age is one of the strongest risk factors for an advanced sleep phase [83], though in the majority of individuals, it does not create impairment in functioning or bothersome symptoms. It has been documented that in some individuals with a familial form of ASPS, the circadian clock period is less than 24 h, thus perpetuating the cycle of phase advancement relative to the 24-h day light-dark cycle [84].

Studies have confirmed an early DLMO in those with ASPS, as much as 4 h earlier than controls (Fig. 3.4) [84, 85]. Thus, measurement of DLMO can be used to confirm the diagnosis of ASPS in cases where the etiology of symptoms is not

clear. In addition, measurement of DLMO can be useful in determining the optimal time for treatment. Exogenous melatonin in the morning after CBT minimum should theoretically delay circadian phase and help ameliorate symptoms based on effects of melatonin in healthy controls. However, there are no clinical trials demonstrating the efficacy of this strategy in ASPS patients. Instead treatment of ASPS typically focuses on bright light exposure in the afternoon to induce a phase delay [86]. Although they are not available for use in clinical practice, experimental studies in mice with melatonin antagonists suggest this class of drugs may be a promising treatment strategy in the future [87].

Delayed Phase Sleep Syndrome

Patients with delayed sleep phase syndrome (DSPS) commonly endorse difficulty falling asleep as a chief complaint; however, they are distinct from other types of insomnia in that sleep maintenance is normal and sleep duration is normal or even longer as compared to controls [88]. In addition to difficulty falling asleep at their desired bedtime, patients with DSPS commonly report sleepiness at their desired time of awakening. When allowed to sleep without external restrictions on timing, such as on weekends or school holidays, sleep is perceived as normal, though bedtimes are often as late as 2–6 a.m., with wake times of 10 a.m. or later [89]. The etiology of the disorder is not understood, though a longer than average circadian period and increased sensitivity to evening light have been proposed as possible mechanisms [90].

DLMO has been found to be delayed in individuals with DSPS (Fig. 3.4) [91–93]. As compared to normal sleeping controls, when assessed at various different time points, including both weekdays and weekends, individuals with DSPS who were allowed to sleep ad lib consistently had a significantly delayed DLMO [92]. Though not routinely used in clinical practice, measurement of DLMO can be useful to confirm the diagnosis of DSPS when the etiology is unclear, as well as to accurately assess circadian phase in order to determine the best timing for light or melatonin interventions. In one study, the sensitivity and specificity for using DLMO for the diagnosis of DSPS was 90.3 % and 84 %, respectively [93].

Melatonin therapy has been evaluated in DSPS in addition to light therapy. In randomized, double-blind, placebo-controlled studies using 5 mg of melatonin in the evening for several weeks, sleep latency is consistently reduced with an earlier sleep onset time as compared to placebo [94–97]. In addition, improvements have been reported in daytime sleepiness, fatigue, and sense of feeling refreshed [95, 96, 98]. Timing of melatonin administration has been variable in controlled studies limiting comparison, though a larger effect was suggested with earlier administration, as much as 6–7 h before sleep time, and doses as low as 0.3 mg have been found to be efficacious [99]. DLMO has been measured in response to evening melatonin therapy, with the expected phase advancement seen. In these studies, DLMO measurement was used to guide timing of melatonin administration [95, 100]. There are

no trials evaluating the role of melatonin agonists in the treatment of DSPS; however, at least one agonist, ramelteon, administered in the evening, has been found to induce phase advancement in healthy volunteers, suggesting that it may be of benefit in this condition [101].

Non-24-Hour Sleep-Wake Syndrome

Free-running-type or non-24-hour sleep-wake syndrome is characterized by a continuous drift in sleep and wake times across days due to a period length that is typically greater than 24 h. This is thought to be due to a lack of entrainment of the endogenous circadian rhythm of the SCN (which is typically slightly greater than 24 h) by environmental cues to remain on a 24-h cycle. While rare among sighted individuals, free running is relatively common among the blind [102]. Approximately 50 % of completely blind individuals have circadian rhythms that are not entrained to the local 24-h light-dark cycle [103]. Melatonin has been measured in individuals with free-running type syndrome, with good correlation found with cortisol levels and activity, suggesting usefulness of DLMO in assessing circadian phase in this population [104]. Because free-running individuals typically have irregular sleep-wake patterns, DLMO measurement is especially useful in this population to determine the timing of chronotherapeutic interventions. While light again has a greater impact than melatonin on phase shifting and resetting, in blind patients who cannot sense light, melatonin becomes the most important therapy. Melatonin, in a variety of doses from 0.5 to 10 mg, has been reported as useful in this disorder both in entraining patients to a 24-h day and in improving sleep symptoms [105–108].

Irregular Sleep-Wake Type Disorder

This disorder is characterized by the absence of a clearly identifiable circadian rhythm of sleep and wake and can be associated with neurocognitive disorders such as dementia in older adults, mental retardation in children, and brain injury [109]. Melatonin secretion has been evaluated in certain populations with this disorder, such as Alzheimer's patients, without abnormal phase detected. Given the heterogeneous nature of this disorder, studies evaluating melatonin administration are difficult to interpret, but do not appear to show substantial benefit.

Shift Work Sleep Disorder

Shift work is increasingly prevalent in the United States and other industrialized nations, as the Internet and other technological advances have increasingly created

a 24-h business day. As much as 20 % of the US workforce may work during nonstandard hours, including night or rotating schedules. Shift work is particularly common among part-time workers [110]. Despite the large number of Americans working nonstandard shifts, shift work sleep disorder characterizes those who have impairments in sleep as a result of their work schedule [82]. Survey estimates suggest around 32 % of night shift workers and 26 % of rotating shift workers could fulfill minimal criteria for diagnosis [111].

Melatonin production has been interrogated in this population to assess degree of circadian pathology, as well as response to various treatment modalities. Interestingly, despite misalignment in shift work individuals based on circadian phase markers such as body temperature, some individuals do not exhibit perturbed sleep or other symptoms [112]. Some intrinsic differences may exist between the internal circadian phase of night workers who are symptomatic as opposed to those who are not. One study demonstrated that those with shift work sleep disorder maintain a circadian phase similar to day workers while those who are asymptomatic exhibit a phase delay [113].

Melatonin may have a role as a therapy in shift workers. Melatonin and melatonin receptor agonists can improve subjective quality of sleep during daytime hours, including improvements in total sleep time and reduced wake after sleep [114–116], though not all studies have demonstrated this benefit [117]. Despite improvements in sleep, no benefits have been observed on nighttime alertness after melatonin usage for daytime sleep [118]. Melatonin receptor agonists may impact psychomotor vigilance task and cognitive performance up to 12 h after administration in night shift workers [119]. Although there have been conflicting reports on neurocognitive function, these results raise concerns about the use of melatonin agonists in shift work patients.

Jet Lag

Travel of long distances east or west across time zones can result in dyssynchrony between the body's internal clock and the local 24-h light-dark cycle. This can result in disruption of timing and quality of sleep. In general, travel westward results in excessive evening sleepiness and premature awakening in the morning as related to the local time, similar to ASPS. Eastward travel has the opposite effect with insomnia at the time of desired sleep onset and morning hypersomnolence, similar to DSPS. Other symptoms such as malaise, gastrointestinal distress, headaches, changes in appetite, and decreased concentration are also frequently reported with more severe symptoms associated with eastbound travel.

Melatonin has been investigated as a marker of circadian phase and potential treatment in jet lag disorder. The underlying pathology in jet lag disorder is a consequence of travel across time zones. Therefore, melatonin levels reflect that forced dyssynchrony and are not the primary pathology. Urinary 6-sulphatoxymelatonin (6-aMTs) and free cortisol have been measured in pilots undergoing both east- and westbound transmeridian flights, confirming internal desynchronization of circadian

rhythm as compared to external 24-h light-dark cycles [120]. Re-entrainment after acute phase advance was markedly delayed in studies of mice that are either melatonin deficient or lacking functional type 2 melatonin receptors, pointing to the key role melatonin may play in extent and duration of jet lag symptoms [121].

Several studies have reported benefits in a number of jet lag symptoms with exogenous melatonin administration. These trials have been performed nearly exclusively in individuals undergoing either real or simulated eastward travel. Benefits of melatonin in these trials include fewer days to establish a normal sleep pattern, quicker return to normal energy levels, and quicker resolution of daytime sleepiness [122–124]. Randomized, placebo-controlled studies have more formally evaluated use of melatonin in treatment of jet lag. Though they are not uniform in their dosage or timing of administration, most studies have demonstrated improvements in various measurements of jet lag symptoms, tiredness, and drowsiness [125–127]. Melatonin has been well tolerated, without some of the bothersome side effects associated with other medications, such as sedative hypnotics [124]. Melatonin at a dose of 5 mg has been found to provide greater hypnotic effects and greater improvements in sleep quality and sleep latency as compared to 0.5 mg, in several studies, although the difference between the doses was small [127]. Administration time of exogenous melatonin is generally at "bedtime" which corresponds to the nocturnal sleep period at the travel location. While some studies have examined usage prior to or during travel, others have only evaluated usage after return from travel, with benefit seen when used upon arrival in randomized studies [124, 127]. Melatonin agonists such as ramelteon may also have a role in treatment of jet lag, suggested by a laboratory-imposed advancement of phase aided by ramelteon as well as a reduction in sleep latency with ramelteon usage after eastward travel [101, 128].

Melatonin and Insomnia

The term insomnia may be used to describe a number of different sleep complaints, including difficulty falling asleep, difficulty maintaining sleep due to frequent or prolonged awakenings, and a sense of poor quality or non-restorative sleep after adequate opportunity [129]. In patients with primary insomnia, melatonin levels are reduced compared to controls [130, 131]. Whether low nocturnal melatonin levels are a cause of insomnia or a consequence (due to light exposure from not being able to sleep at night) is not completely clear. However, the abnormality in absolute values of melatonin in primary insomnia is in distinct contrast to the abnormality in timing seen in circadian sleep disorders. There is a limited role for measurement of DLMO or melatonin levels in patients with primary insomnia unless a circadian disorder is suspected.

Exogenous melatonin administration has hypnotic effects, which are dependent on time of administration. This timing dependency may minimize the side effect of daytime sedation making melatonin an attractive option for treating insomnia [43, 132]. Studies in healthy volunteers demonstrate decreases in sleep latency, improved

sleep efficiency, and reduced intermittent wakefulness with exogenous melatonin without effects on mood, reaction time, or sleepiness the following morning [133].

Melatonin supplementation has theoretical benefits in the elderly due to age-related reductions in melatonin secretion and in those individuals on beta-blockers, given the inhibitory role this medication may have on physiologic melatonin production [134]. Additionally, in several patient populations where sedative or other effects of benzodiazepines may be undesirable, melatonin has a role as a sleep aid. This includes children, the elderly, and those with respiratory disorders or history of alcohol abuse [135–138].

Melatonin has been evaluated as therapy for primary insomnia in a number of randomized, placebo-controlled trials. In adults with primary insomnia over 55 years of age, melatonin usage resulted in improvements in sleep quality, sleep efficiency, sleep onset latency, morning alertness, and quality of life as compared to placebo [139–143]. In contrast, studies have generally failed to demonstrate an increase in total sleep time with melatonin [144, 145]. Of note, the magnitude of benefit from exogenous melatonin in primary insomnia is not correlated with the magnitude of depression in endogenous melatonin levels [146].

Melatonin receptor agonists have also been studied as treatments for insomnia. Two are currently available, ramelteon, which is FDA approved, and agomelatine, which is available outside of the United States. Ramelteon has high affinity for both MT1 and MT2 receptors, with 3–16 times the affinity of endogenous melatonin, but notably without any significant binding to other receptors, specifically those in the opioid, benzodiazepine, and dopamine family [147]. The elimination half-life is about 2–4 h [148]. Unlike other medications often used for insomnia, such as benzodiazepines, ramelteon administration was not associated with impairment in learning or memory tasks in animal studies, nor was any behavior seen that might suggest abuse potential [149].

In humans, ramelteon has been demonstrated as effective in reducing sleep latency and increasing total sleep time in adults with transient insomnia related to sleeping in a novel sleep environment [150]. Similarly, randomized studies of patients with chronic primary insomnia have shown reductions in sleep latency and increases in total sleep time, without any next-day effects and no increase in adverse events as compared to placebo [151–154]. Sustained efficacy is observed with use over weeks to months [155–158].

Comparison of melatonin and melatonin receptor agonists to benzodiazepines and other sedative hypnotics is limited by the absence of studies directly comparing these agents. In general, the effect of melatonin and melatonin receptor agonists on insomnia is smaller compared to benzodiazepines and benzodiazepine receptor agonists such as zolpidem, with benefit generally seen in shortening of sleep onset latency and not in sleep maintenance [159]. Melatonin and melatonin receptor agonists, however, do have a more favorable side effect profile, with less impairment of psychomotor function, memory, and driving skills [160, 161], no evidence of rebound insomnia or withdrawal effect, and no respiratory depression [155–158, 162, 163]. Melatonin has also been used to facilitate discontinuation of benzodiazepines and other sleep aids successfully [164, 165].

Melatonin and Sleep Apnea

Melatonin levels and melatonin therapy have been studied to a limited degree in patients with obstructive sleep apnea (OSA). Patients with obstructive sleep apnea have been found to have a normal melatonin rhythm as measured in both plasma and saliva [166, 167]. In addition, treatment of OSA does not appear to change melatonin levels [168]. As opposed to sedative-hypnotic agents that have muscle relaxant and respiratory depressant properties that might worsen OSA, both melatonin and ramelteon have been shown to not worsen disease severity among patients with OSA [169, 170]. As a result, these drugs may be useful agents as adjunctive therapy in OSA patients with prominent insomnia symptoms. In addition, case reports suggest that by improving sleep continuity, melatonin could have a role in treating central sleep apnea [171].

Melatonin and Restless Legs Syndrome

There has been little research surrounding the area of restless legs syndrome and melatonin, either as a therapeutic agent or as playing a role in the pathology. Symptoms of restless legs syndrome follow a circadian rhythm with worsening in the evening and night time hours. Changes in salivary melatonin may precede both the motor and sensory symptoms of restless legs syndrome [172]. However, no cumulative differences in melatonin production are seen in patients with RLS as compared to controls [173]. Treatment of restless legs syndrome with L-DOPA resulted in earlier DLMO in one small study [174]. Another study found that administration of exogenous melatonin worsened sensory and motor manifestations of restless legs syndrome while bright light provides a small decrease in sensory symptoms [175].

Melatonin and Hypersomnias

Several studies evaluating melatonin levels in patients with narcolepsy have demonstrated levels of melatonin similar to those found in non-narcoleptic individuals [176]. However, one study examining the pattern of melatonin secretion in narcolepsy with cataplexy found that though mean concentrations were similar to controls, there was a significantly higher percentage of melatonin secreted during the day in those with narcolepsy [177]. This is consistent with another study demonstrating increased salivary melatonin during the day in narcoleptics with more severe daytime sleepiness [178]. These findings may simply reflect disorganized sleep-wake schedules with daytime napping secondary to narcolepsy as opposed to a primary pathogenic role of melatonin.

There is very little literature published on the relationship between melatonin and idiopathic hypersomnia. In one small study, as compared to control individuals, those with idiopathic hypersomnia had delayed peak of melatonin secretion and prolonged secretion as measured by salivary samples [179].

Melatonin and REM Behavior Disorder

REM behavior disorder (RBD) is a rare disorder characterized by absence of muscle atonia in rapid eye movement (REM) sleep, with motor activation during often vivid and violent dreaming, which can lead to patient or bed-partner injury. Although benzodiazepines such as clonazepam are regarded as first-line treatment in RBD, melatonin has been widely used in REM behavior disorder as a second-line therapy [180, 181]. The mechanism by which melatonin works is unclear, though re-entrainment of internal dyssynchrony of circadian rhythm is one proposed mechanism. Several studies have documented an improvement in degree of REM without atonia as well, including one small, placebo-controlled, randomized study [181–183]. The efficacy of melatonin has been found to persist beyond 1 year in a small case series [184], and it is well tolerated with fewer adverse effects as compared to clonazepam [185].

Melatonin and Cancer

Melatonin has been widely used for a variety of sleep disorders as noted above. With its widespread usage, there has been no evidence that melatonin causes cancer or cancer progression. To the contrary, in part due to its antioxidant effects and anti-angiogenic activity, melatonin may play a role in attenuation of cancer progression and symptoms.

Animal studies have demonstrated that removal of the pineal gland can result in accelerated growth of some malignancies such as melanoma, while replacement with exogenous melatonin blunts this effect [72, 73]. To further evaluate this potential link, melatonin levels have been measured in a number of human malignancy states. Low levels of melatonin have been found in patients with breast, endometrial, prostate, lung, gastric, and colorectal cancers, as compared to healthy patients [186–188]. Additionally, low levels of melatonin have been associated with progression of the underlying malignancy [70]. However, the impact of cancer symptoms such as pain and depression, medication effects, and resulting sleep disturbance, which could impact melatonin levels, has not been fully quantified in these studies.

Aside from its potential link to malignancy progression, several studies have evaluated the use of melatonin as a therapeutic agent for cancer or chemotherapy-related symptoms. Melatonin has been found to improve asthenia, fatigue, stomatitis, thrombocytopenia, cardiotoxicity, and neurotoxicity when given alongside

chemotherapy in advanced solid malignancies [189–191]. Treatment with exogenous melatonin may also improve performance status in patients with metastatic disease resistant to first-line chemotherapy, such as non-small cell lung cancer treated with cisplatin [192]. Melatonin may also improve life expectancy in patients with cancer. A meta-analysis of randomized controlled trials in solid cancer patients found a consistent treatment effect on 1-year survival, with a pooled relative risk of 0.66 (95 % CI: 0.59–0.73) [193]. Dosage was typically 20 mg of melatonin, either with standard chemotherapy or, in some cases, as compared to supportive care alone. Several metastatic malignancies have been studied, including non-small cell lung cancer, breast cancer, melanoma, and renal cell cancer. The largest trial, which included 250 patients with metastatic solid tumors and poor clinical status, demonstrated a reduction in disease progression and improvement in survival at 1 year with melatonin in addition to standard chemotherapy, as compared to chemotherapy alone [190]. One possible mechanism may be through synchronization of circadian rhythms in those with advanced malignancies [194]. On the other hand, other studies have not found a treatment effect with melatonin [195]. Thus, overall, while results are not yet definitive, there is support for the notion that exogenous melatonin may have a beneficial role as an adjuvant therapy in the management of cancer patients.

Conclusion

Melatonin plays a role in synchronizing the internal timekeeping system to the local light-dark environment aiding in normal sleep-wake rhythms. Measurement of melatonin may be used to diagnose sleep pathology and better understand the physiology of sleep and circadian biology. Exogenous melatonin has become a useful therapeutic agent in the treatment of a number of sleep and circadian disorders in part because of its efficacy but also because of its favorable side effect profile. As further research reveals the mechanisms by which melatonin functions in normal and diseased states, the application of melatonin measurement as well as its therapeutic use will likely expand including perhaps a role in the treatment of cancer.

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Chapter 4
Biomedical Effects of Circadian Rhythm Disturbances

Keith C. Summa and Fred W. Turek

Abstract Circadian rhythms are biological processes that recur on a daily basis and exist to appropriately organize physiology, metabolism, and behavior relative to the 24-h light/dark cycle created by the rotation of the Earth. These rhythms are controlled by a genetically encoded molecular clock active in most, if not all, cells in the body. In mammals, these cell-autonomous oscillators are regulated and synchronized by the master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus through a variety of direct and indirect pathways. The circadian timekeeping system imposes integrated temporal organization to ongoing biochemical and physiological processes throughout the body, ensuring optimal functioning in the context of repeated environmental changes driven by the solar cycle. It is well known that shift workers are at greater risk for development of a large number of chronic diseases and recent experimental evidence has shown that disruption of circadian organization leads to physiological impairments and dysfunction that are relevant for disease development and pathology. In particular, circadian disturbances yield metabolic derangements capable of predisposing individuals to diabetes, obesity, gastrointestinal and cardiovascular disease, and to disease states which have been linked to increases in risk for various cancers. In addition, the molecular circadian machinery has been linked to regulators of the cell cycle and other prominent pathways involved in cancer, including DNA repair and apoptosis. An understanding of the circadian timekeeping system and recognition of its fundamental role in temporal organization of biochemical pathways and physiological processes enables a framework

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_4,

upon which the concept of time on a 24-h basis can be applied to translational research and brought into the realm of clinical medicine in order to improve diagnostics, therapeutics and, ultimately, patient outcomes.

Keywords Circadian rhythms • Physiology • Metabolism • Obesity • Cancer • Circadian disturbances • Cell-autonomous oscillators • Master clock • Suprachiasmatic nucleus (SCN) • Cell-autonomous molecular pacemaker • Night eating syndrome (NES) • CLOCK • BMAL1 • Per1/Per2/ • Cry1/Cry2 • Clock-controlled genes (CCGs) • Chronotherapy

Introduction

Circadian rhythms, from the Latin *circa dies* ("about a day"), are biological rhythms with a length of about 24-h that persist in the absence of any external environmental timing signals. These innate and self-sustaining oscillations, nearly ubiquitous in living systems, exhibit several fundamental properties: they are temperature compensated, meaning that the rhythm length is consistent across a physiologically relevant range of ambient temperatures; they are entrained by, or synchronized to, specific periodic environmental signals such as light, humidity, and food availability; and they have a remarkably small variance in cycle length (i.e., the circadian system is characterized by extreme precision) [1]. Circadian rhythms are generated by a cell-autonomous molecular pacemaker, active in nearly all cells of the body [2]. In mammals, the master circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [3]. The SCN consists of a bilateral pair of neuronal clusters containing about 10,000 neurons, which are organized into coupled topographical networks that fire synchronously [3]. The circadian system integrates timing signals from the environment (cycles of light and dark, temperature, food availability, etc.) to organize internal rhythms in the appropriate phase relationships to one another and the external environment. The circadian system thus imposes temporal organization to behavior and ongoing physiological and biochemical processes, which results in enhanced fitness by enabling organisms to anticipate and prepare for predictable daily environmental changes, as well as to optimize functionality in the context of an environment shaped by the rotation of the Earth about its axis every 24-h.

Given the fundamental role of circadian clocks in biological processes, it is perhaps not surprising that disruption of overall circadian organization results in physiological aberrations, alterations, and dysfunctions that are relevant for the maintenance of health and development of disease. Indeed, there is a growing body of evidence that circadian misalignment is associated with, and possibly contributes to, numerous diseases and disorders affecting nearly all systems of the body. Much of this evidence comes from studies of shift workers, individuals who must perform both cognitively and physically at the wrong time of day according to their internal circadian clock. These individuals suffer from chronic circadian disruption and are

an important study population for many investigators in the circadian rhythms field. As discussed in Chap. 7, Shift Work and Cancer Risk, shift workers have an increased risk for the development of several cancers. In addition, shift workers are more likely to suffer from metabolic, cardiovascular, and gastrointestinal diseases, among others [4–12].

Epidemiological evidence also links sleep loss and sleep disruption with cancer (see Chap. 8, Sleep Disorders and Cancer Risk, and Chap. 9, "Sleep Deprivation/ Insomnia and Cancer Risk") and cardiometabolic disease (see Chap. 2, "Effects of Sleep Disorders on Cytokines, Hormones and Metabolism"). The regulation of the sleep-wake cycle is a major output of the circadian clock [13], and sleep-wake physiology has strong, bidirectional interactions with circadian clock genes [14–17]. Thus, sleep disorders and sleep disruption likely represent a form of chronic circadian disruption. In the laboratory setting, clinical studies of humans have revealed that short-term misalignment of internal circadian rhythms causes immediate and substantial dysfunction of metabolic and endocrine physiology at a magnitude consistent with increased disease risk [18]. The generation, characterization, and utilization of animal models of chronic circadian disorganization have enabled translational studies aimed at identifying the specific adverse consequences of circadian disruption. Taken together, these lines of evidence all support the emerging consensus that circadian misalignment has significant, sustained, and relevant biomedical effects that contribute to disease pathophysiology and warrants consideration for the promotion and maintenance of health.

This chapter will begin with a brief overview of the molecular machinery driving the circadian clock. This description will highlight the role of metabolic genes in the functioning and regulation of the circadian system, leading into a discussion of how metabolism and the circadian clock are intimately intertwined and bidirectionally interacting. In addition to these interactions at the molecular and biochemical levels, environmental feeding-fasting cycles have recently been demonstrated to be critically important links between the circadian clock and metabolism. Studies exploring the role of time-restricted food availability on metabolism will be reviewed and presented alongside a description of night eating syndrome (NES), a disorder in humans that may potentially represent an extreme and pathologic example of mistimed feeding rhythms. Next, this chapter will discuss evidence linking circadian disruption to cardiovascular disease and gastrointestinal disease. We have focused on metabolic, cardiovascular, and gastrointestinal diseases and circadian misalignment in this chapter because of the links between these and cancer. A separate section will examine the role of circadian misalignment and circadian clock genes in cancer. For all of these sections, emphasis will be placed on translational studies using animal models and clinical experiments with humans. Epidemiological studies will be mentioned and discussed where appropriate, but for comprehensive reviews and in-depth analysis on the association between shift work and cancer, the reader is referred to Chap. 7, "Shift Work and Cancer Risk." This chapter will conclude with the argument that the incorporation of biological timing on a 24-h basis into clinical medicine and our understanding of disease pathogenesis has transformative potential across a broad spectrum of disease states, including cancer.

The Molecular Pacemaker

The molecular circadian clock is composed of interlocked autoregulatory feedback loops that give rise to characteristic 24-h cycles of gene expression and protein activity (see [2, 19] for detailed recent reviews of the core molecular mechanism of the circadian clock). Briefly, the proteins CLOCK and BMAL1 form a heterodimer that drives the expression of the circadian clock components *Per1/Per2* and *Cry1/Cry2*. The products of these genes form a repressor complex, regulated by *casein kinase 1ε/δ* and E3 ubiquitin ligase complexes, which colocalizes to the nucleus and inhibits CLOCK-BMAL1-mediated expression. This negative limb of the circadian pacemaker thus reduces the expression of *Per1/Per2* and *Cry1/Cry2*, resulting in reduced PER-CRY-mediated repression and subsequent reactivation of the positive CLOCK-BMAL1 limb of the pacemaker. CLOCK-BMAL1 also promotes the expression of *RORα* and *Rev-erbα*, which primarily modulate rhythmic *Bmal1* expression, which exhibits a peak about 12 h out of phase with the *Pers* and *Crys*.

Taken together, this self-sustaining feedback cycle takes about 24 h and is active in nearly all cells of the body [20–22]. CLOCK-BMAL1 also drives the expression of numerous additional genes, termed *Clock-controlled genes* (CCGs), which are ultimately responsible for establishing overt rhythms. Microarray studies have revealed that approximately 3–10 % of genes in any given tissue are expressed on a rhythmic basis under constant environmental conditions [23–28]. Interestingly, there is little overlap in the circadian transcriptome between different tissues [19], suggesting that the sets of CCGs have tissue-specific roles critical for the function of the organ and, more broadly, that diverse physiological processes in different cells and tissues are rhythmic. The identification and characterization of the core circadian clock genes was originally achieved primarily through conventional molecular genetics and biochemical techniques, such as mutagenesis and mapping. More recently, the advent and widespread adoption of high-throughput screening and advanced computational techniques have enabled a rapid expansion in the list of molecules known to influence circadian rhythmicity [29–31]. In our view, the circadian clock system can be considered an integrator and organizer that imposes temporal structure and coordination to ongoing physiological processes spatially separated within the body, thus ensuring optimal functioning of the organism in the context of behavior and predictable daily environmental change.

Another integral lesson of recent studies examining the molecular circadian clock is the profound degree of interconnection and bidirectional interaction between core circadian components and metabolism (discussed in detail in sections "Circadian Clock Components and the Regulation of Metabolism" and "Environmental Metabolic Input Affects Circadian Rhythms and Energy Balance"). At the molecular level, perhaps the first indication that the molecular clock system is linked to metabolism came from the observation that the activity of the core clock transcription factors is sensitive to the redox state of the cell [32]. Since then, the recognition of the tight association between circadian clocks and metabolism at the molecular level has grown appreciably (Fig. 4.1, see [33] and [34] for excellent recent reviews).

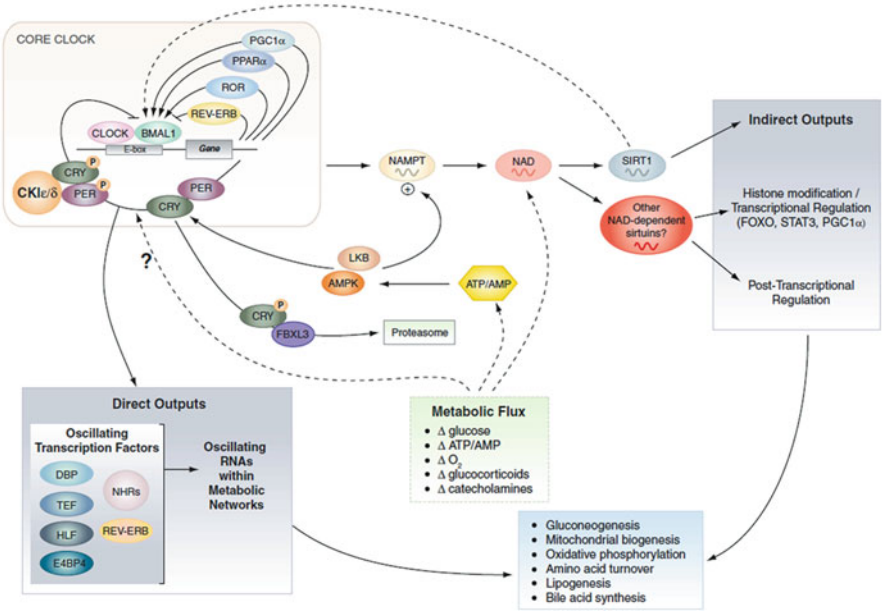


Fig. 4.1 The molecular circadian clockwork integrates and bidirectionally interacts with cellular metabolism. The core circadian clock mechanism consists of a positive limb, the CLOCK-BMAL1 transactivating complex; a negative limb, the PER-CRY repressor complex; and an accessory limb, the REV-ERB and ROR loop. Together, these integrated, autoregulatory, and self-sustaining feedback loops generate cycles of approximately 24 h that persist under constant environmental conditions. The CLOCK-BMAL1 heterodimer activates transcription of a number of target genes, including *Pers* and *Crys*. Translation of these gene products precedes complex formation in the cytoplasm, which then translocates to the nucleus where it inhibits CLOCK-BMAL1 (thus, repressing the expression of the *Per* and *Cry* genes, among others). Removal of the PER-CRY complex (via several mechanisms) derepresses transcription, enabling activation of the positive limb and initiation of another cycle. The core clock mechanism regulates metabolic processes both directly by regulating the expression of critical genes in metabolic pathways in a rhythmic manner—essentially controlling the timing of activity of those pathways—and indirectly by generating rhythms in NAD+ availability, which drive rhythmic deacetylase activity by SIRT1 and possibly other enzymes, as well as rhythms in other cellular processes, including translation and histone modification. Metabolic activity and flux within the cell reciprocally regulates the circadian clock through nutrient sensors, such as AMPK, LKB, and other rhythmically transcribed nuclear hormone receptors that can bind metabolites and other relevant ligands. The intimate interactions between the circadian clock system and metabolism at the molecular and biochemical levels highlight the key role of circadian organization in orchestrating cellular metabolism. Disruption of circadian organization thus has the potential to perturb many critically important cellular pathways, which may contribute to disease states (Reprinted, with permission from [33])

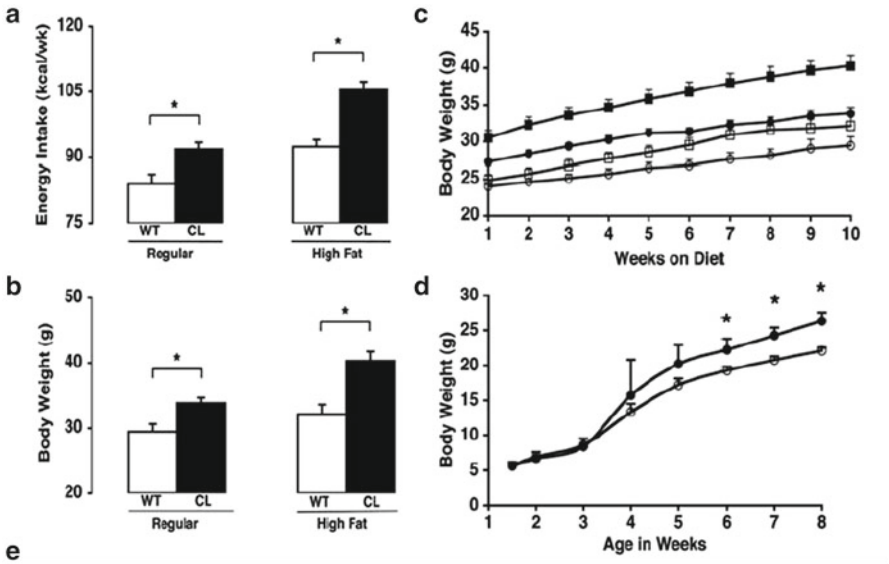
Indeed, a rhythm of peroxiredoxin oxidation was recently reported in the absence of transcription in eukaryotes [35, 36] and shown to be highly conserved across diverse phyla, even Archaea [37]. This apparently universal rhythm presumably represents the output of a non-transcription-based metabolic oscillator (i.e., normally coupled to

the genetically encoded pacemaker). This exciting finding has led to the hypothesis that circadian rhythms ultimately arose and evolved in the context of oxidative respiration and metabolism. Although the clinical implications of these exciting findings remain to be uncovered and worked out, the growing evidence that the circadian clock system serves an absolutely fundamental role in cellular metabolism underscores the relevance of circadian biology in regulating key signaling pathways, the activity of which are crucial in determining the balance between health and disease.

Circadian Clock Components and the Regulation of Metabolism

The first circadian gene identified in mammals, termed *Clock*, was initially discovered in a screen of mutagenized mice nearly 20 years ago [38]. Characterization of the $Clock^{\Delta 19}$ mutation [39–41] ushered in a rapid and profound revolution in our understanding of the molecular basis of circadian rhythms [30]. It is perhaps fitting, therefore, that examination of $Clock^{\Delta 19/\Delta 19}$ mutant mice has contributed substantially to the development of widespread interest in the connection between circadian rhythms and metabolic disease. $Clock^{\Delta 19/\Delta 19}$ mutant mice gain significantly more weight than wild-type littermates on a high-fat diet and exhibit broad metabolic dysfunction (Fig. 4.2, adapted from [42]). Mutant mice have blunted diurnal feeding and activity rhythms and consume a greater proportion of their daily calorie intake during the light phase [42]. Furthermore, mutants have altered expression of energy-regulating genes in the hypothalamus [42]. These findings linked the circadian clock to energy balance and systemic metabolism regulation at the genetic level for the first time, and paved the way for additional studies exploring the role of specific circadian clock components in different peripheral tissues involved in metabolic regulation. These initial studies in $Clock^{\Delta 19/\Delta 19}$ mutant mice included animals harboring the mutation in every cell of the body from birth onward. Due to the potential for developmental compensation and/or pleiotropic effects, a critical next step involved the generation and characterization of tissue-specific circadian clock mutants and knockouts in order to study the role of the molecular pacemaker in different tissues.

In contrast to the master clock in the SCN, clocks in peripheral tissues rapidly and stably entrain to feeding cycles [43, 44], supporting an important role in metabolic regulation. Deletion of the molecular clock in the liver (achieved via liver-specific deletion of the critical clock component *Bmal1*) resulted in hypoglycemia during the fasted state of the daily cycle (i.e., in the light phase of the light/dark (LD) cycle when mice normally are not consuming much food [45]), indicating that the molecular clock in the liver works to maintain normoglycemia by promoting hepatic glucose export during the extended daily fasting phase. This counterbalances the rhythm of circulating glucose induced by feeding patterns (in ad libitum-fed mice, about 75–80 % of caloric intake occurs during the dark, or active, phase of the LD cycle [46, 47]). The loss of the liver clock also dampens the expression rhythms of hepatic transcripts, including glucoregulatory genes [45, 48], further supporting the



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Metabolic parameter	WT	*Clock*	*P* value
Triglyceride (mg/dl)	136 ± 8	164 ± 8	<0.05
Cholesterol (mg/dl)	141 ± 9	163 ± 6	<0.05
Glucose (mg/dl)	130 ± 5	161 ± 7	<0.01
Insulin (ng/ml)	1.7 ± 0.3	1.1 ± 0.1	n.s.
Leptin (ng/ml)	3.4 ± 0.4	4.6 ± 0.3	<0.05

Fig. 4.2 The *Clock*$^{\Delta 19/\Delta 19}$ mutant mouse, a model of genetic disruption of the circadian pacemaker, develops obesity and metabolic syndrome. (**a**) *Clock*$^{\Delta 19/\Delta 19}$ mutant mice (CL, n = 10) have significantly elevated food intake compared to wild-type littermates (WT, n = 8) on both regular chow and high-fat diets. (**b**) *Clock*$^{\Delta 19/\Delta 19}$ mutant mice (CL) weigh significantly greater than wild-type littermates (WT) after 10 weeks on either a high-fat or regular chow diet. (**c**) Body weight gain is greater in *Clock*$^{\Delta 19/\Delta 19}$ mutant mice on both the regular chow (*closed circles*) and high-fat diet (*closed squares*) than in wild-type littermates (*open circles* and *open squares*, respectively). (**d**) Growth trajectories after weaning are significantly higher in *Clock*$^{\Delta 19/\Delta 19}$ mutant mice compared to controls. (**e**) *Clock*$^{\Delta 19/\Delta 19}$ mutant mice exhibit significant alterations in metabolic parameters, including higher triglycerides, cholesterol, glucose, and leptin, as well as a trend for reduced insulin compared to wild-type littermates (Adapted, with permission, from [42])

hypothesis that the liver clock is critical for proper hepatic function and maintenance of circulating glucose levels. More recently, it has been demonstrated that the core circadian clock gene *Rev-erbα* directs a rhythm of HDAC3 (histone deacetylase 3) recruitment to the genome in the liver in mice. These dramatic genome-wide patterns of HDAC3 binding and release across the day are associated with rhythmic histone acetylation and marked rhythms in expression of genes involved in lipid metabolism [49]. Importantly, loss of the interaction between *Rev-erbα* and HDAC3 abrogates rhythmic HDAC DNA binding and results in hepatic steatosis [49], indicating that the proper circadian and temporal organization of gene expression networks is necessary to protect against the development of fatty liver.

The characterization of global HDAC3 binding and subsequent acetylation rhythms in the mouse liver stemmed from previous work examining epigenetic changes at the intersection of circadian and metabolic physiology [50]. Indeed, there is much excitement in linking the circadian clock, metabolism, and epigenome [51, 52]. Although metabolic diseases remain a primary research target, it seems likely that such fundamental molecular findings linking the circadian clock and epigenetic regulation may pave the way to a deeper and more fundamental understanding of many diseases from various biomedical disciplines, including cancer, neurodegenerative disease, and psychiatric disease, among others [53]. The molecular clock system has been linked to critical cellular processes and biochemical pathways, including chromatin remodeling, NAD+ regulation and SIRT1 [54–57], and the expression of nutrient-sensitive nuclear hormone receptors has been shown to be regulated by the clock [58]. These and other dramatic advances in our understanding of the molecular mechanisms of the circadian clock and their intimate, bidirectional links to crucial metabolic processes underscore the fundamental impact of the circadian clock system in pathways critically important for cell function and, therefore, the maintenance of health and disease. Although the specific clinical implications of some of these findings may not be perfectly clear at present, increasing our understanding of the ways in which the circadian clock is linked to metabolism opens up a novel way of thinking about, and potentially treating, metabolic diseases associated with circadian disruption. For example, two recent studies in mice suggested that pharmacological approaches may be used to consolidate and increase the robustness of circadian rhythms (by activating the core circadian clock genes *Rev-erbα* and/or *Rev-erbβ*), as well as potentially alleviate metabolic dysfunction [59, 60].

In the initial characterization of the metabolic phenotype of $Clock^{\Delta 19/\Delta 19}$ mutant mice, it was discovered that mutants exhibit hyperglycemia and hypoinsulinemia [42], suggestive of a defect along the insulin axis. Careful examination revealed that isolated murine pancreatic islets had self-sustaining oscillations of core circadian clock genes and proteins, including *Clock* and *Bmal1*, which were altered in mutants [61]. Circadian clock mutants also exhibited impaired glucose tolerance, hypoinsulinemia, and alterations in size, growth, and function of pancreatic islets. In order to test the hypothesis that the molecular clock in the pancreas itself underlies these metabolic abnormalities, conditional, pancreas-specific *Bmal1* knockout mice (i.e., animals lacking a circadian clock in the pancreas, with intact clocks elsewhere) were generated. These animals developed frank diabetes at an early age due to defective insulin secretion by pancreatic islets [61], indicating a critical role for the pancreatic clock in regulating and coordinating insulin release in the context of the sleep-wake and feeding-fasting cycles. Importantly, loss of the pancreatic cell clock was sufficient to cause diabetes, suggesting that circadian disruption within the pancreas may hasten the onset and/or progression of diabetes.

More recently, specific deletion of *Bmal1* in adipocytes was shown to cause obesity in mice [62]. Mice lacking an adipocyte clock shifted their diurnal food intake rhythm, consuming more food in the light phase. This effect on feeding rhythms was not observed in mice with hepatocyte-specific or pancreatic islet-specific

Bmal1 mutations and was associated with altered expression of hypothalamic energy-regulating neuropeptides [62], suggesting that the clock in the adipocyte works in conjunction with hypothalamic feeding centers to regulate the timing of energy intake, which in turn influences energy balance. Taken together, these findings support the hypothesis that the circadian clock system acts as an integrator of signals between different tissues to optimize physiology and behavior, in this case, leading to coordinated feeding behavior and hypothalamic energy regulation in order to maintain homeostasis.

The examples presented above demonstrate the impact that genetic disruption of circadian organization can have on metabolism and, in particular, on the function of peripheral organs critical for metabolic health and homeostasis. The utilization of genetic mouse models of circadian disruption has enabled great strides in our understanding of the role of the molecular clock in disease-relevant pathways. A major long-term goal of many investigators in the circadian research community is to translate these findings into the realm of clinical medicine in order to improve the diagnosis and/or treatment of disease. Thus, it is particularly important to continue studying humans at risk for chronic circadian disruption (see Chap. 7, "Shift Work and Cancer Risk"), as well as to supplement the studies in animal models with clinical studies in humans. Using a "forced desynchrony" protocol to separate the sleep-wake cycle from the internal circadian clock, it was recently shown that circadian misalignment (i.e., when the circadian clock is out of sync with the sleep-wake cycle) acutely induces substantial metabolic, endocrine, and cardiovascular abnormalities [18]. Maximal misalignment (i.e., when the sleep-wake cycle is completely out of phase with respect to the circadian clock) resulted in impaired postprandial glucose clearance consistent with a prediabetic state in 3 of 8 young, lean male subjects [18], indicating that circadian disruption may be sufficient to push susceptible individuals into the disease state.

Environmental Metabolic Input Affects Circadian Rhythms and Energy Balance

Under ad libitum conditions in the laboratory, the master pacemaker in the SCN entrains to the LD cycle and synchronizes rhythms in peripheral tissues throughout the body through a variety of direct and indirect mechanisms including neural neural projections, endocrine signaling, body temperature rhythms, and behavioral rhythms, such as feeding-fasting and sleep-wake cycles [19]. Loss of the SCN causes widespread desynchronization of rhythms in peripheral tissues [22]. Although experiments demonstrated that circadian clocks in peripheral tissues involved in metabolic regulation rapidly and stably entrain to windows of temporally restricted food availability over 10 years ago [43, 44], it has only recently become appreciated that the timing of food intake may exert a significant influence on metabolic physiology as well. Wild-type mice given access to a high-fat diet at the "wrong" time of day—exclusively during the light phase of a 12:12 LD cycle—gain significantly

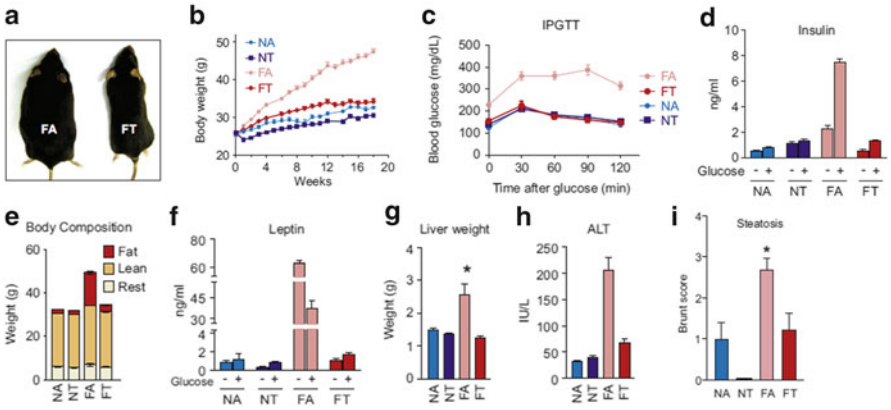

Fig. 4.3 Restricting feeding to 8-h of the dark phase prevents diet-induced obesity and metabolic syndrome without decreasing caloric intake. (**a**) Forced time (FT) feeding regimens prevent diet-induced obesity in mice. Mice were given access to high-fat diet (F) or a normal, regular chow diet (N) either ad libitum (A) or only during an 8-h window during the dark phase (T). Despite similar overall intake levels, the FT group failed to gain weight as the ad libitum did. FT feeding regimens prevented high-fat diet-induced obesity (**b**), glucose intolerance (**c**), hyperinsulinemia (**d**), fat mass gain (**e**), hyperleptinemia (**f**), and fatty liver disease (**g–i**) despite similar overall caloric intake between time-restricted and ad libitum feeding groups. With the exception of steatosis score (**i**), no differences were observed between ad libitum normal chow-fed (NA) and timerestricted normal chow-fed (NT) mice (Adapted, with permission, from [64])

more weight than mice given access to the same food at the "right" time of day (i.e., exclusively during the dark phase), despite similar overall caloric intake and physical activity levels [63]. Also, as discussed above, *Clock*$^{\Delta 19/\Delta 19}$ mutant mice and mice lacking an intact molecular clock in adipocytes have increased light-phase feeding and develop obesity [42, 62], further supporting a role for the timing of food intake in energy balance. More recently, mice given limited access to a high-fat diet for only 8-h of the dark phase (i.e., the "right" time of day, from 1-h after lights off until 3-h before lights on) were compared to mice on the same diet fed ad libitum [64]. The mice on the temporally restricted feeding regimen exhibited more robust circadian and metabolic cycles of a higher amplitude than the ad libitum-fed mice [64]. Most impressively, without any reduction in caloric intake, the temporally restricted feeding regimen prevented obesity, insulin resistance, fatty liver and inflammation, and improved motor coordination (Fig. 4.3, [64]). Presumably, the protection from diet-induced obesity and metabolic syndrome arose, at least in part, from increased activation of key metabolic pathways, including CREB, mTOR, and AMPK, and more robust and coordinated expression of circadian clock genes and clock-controlled genes [64]. These provocative findings highlight a potentially beneficial non-pharmacologic approach for the treatment of obesity and metabolic syndrome. In addition, they demonstrate the physiological benefit of synchronized, high-amplitude circadian cycles in peripheral target tissues related to metabolism and energy balance.

More generally, the finding that restricting food intake to the "right" time of day prevents weight gain and metabolic disease lends credence to the dictum that one should

eat "breakfast like a king, lunch like a prince, and dinner like a pauper." These findings invite clinical studies comparing food intake at different times of day in individuals in order to determine whether manipulation of feeding time can impact body weight regulation and energy balance. Such studies are necessary to provide evidence-based recommendations for strategies to prevent and/or alleviate the adverse sequelae of diet-induced obesity and metabolic dysfunction based on the principles and properties of the circadian clock system and its profound association with metabolic regulation.

These findings that link the timing of food intake to body weight regulation may have relevance for a clinical condition called night eating syndrome (NES), in which affected individuals consume a large portion of their daily calories during the night (often in binges), as well as frequently suffer from insomnia, anxiety, emotional distress and, occasionally, depression [65, 66]. Although NES lacks official diagnostic criteria and is not presently listed in the *Diagnostic and Statistical Manual of Mental Disorders*, it warrants consideration in a discussion of diurnal feeding rhythms and energy balance. It is associated with obesity clinically: NES is more prevalent in obese individuals than the general population, and individuals with NES frequently experience significant weight gain [65]. Although much remains to be learned about NES, one hypothesis is that it represents a primary disorder of circadian organization, in particular the feeding rhythm. When appropriate feeding-fasting cycles are not observed, genes regulating metabolism may become dysregulated and contribute to positive energy balance and increased weight gain.

Although the impact of feeding time and feeding rhythms in metabolic regulation is clear, it is important to recognize that the interaction is bidirectional. It has been demonstrated that a high-fat diet leads to altered circadian rhythms and disrupted circadian organization at both behavioral and molecular levels in mice [46]. Although the mechanism(s) of the effects of specific dietary components on the molecular clock are not understood, the ability of constituents of food to alter and impair overall circadian organization illustrates how a vicious cycle could easily be established, leading to worsened metabolic outcomes and even greater circadian desynchrony. Given that many nutrient-sensing nuclear hormones and energy regulators are controlled by the circadian clock or feed back to impact the core clock itself (or both) [33, 34], it is perhaps not surprising that specific dietary components can elicit significant effects on the properties of the circadian clock. Further work needs to be done to characterize the impact of different dietary components on the circadian clock system and to elucidate the resulting effects on disease-relevant molecular pathways.

Circadian Disruption and Cardiovascular Disease

For many years, it has been known that the timing of onset of severe adverse cardiovascular events, such as myocardial infarction, sudden cardiac death, cardiac arrest, angina, stroke, and arrhythmias, exhibits a diurnal rhythm with peak levels occurring between 6 am and noon (see [67] and references therein). It is clear that many

variables and parameters within the cardiovascular system are under substantial regulation by the circadian clock, highlighting the relevance of circadian organization for cardiovascular disease. Shift work has consistently been associated with increased cardiovascular disease risk [68–71]. The use of animal models to test the hypothesis that chronic circadian disruption exacerbates or augments cardiovascular disease began with a study of hamsters carrying a genetic predisposition to develop cardiomyopathy [72]. In that study, hamsters were randomized into one of two groups, the first of which was maintained on a constant LD cycle and the other was subjected to weekly phase shifts of the LD cycle. The animals exposed to chronic circadian disruption exhibited a significant increase in mortality, with an 11 % reduction in median lifespan [72]. Exposure to repeated phase shifts of the LD cycle has become a widely used model by researchers in the circadian rhythms field to examine the impact of environmental disruption of circadian rhythms, such as might occur with shift work or chronic jet lag. Studies utilizing variations of this model have shown that circadian misalignment increases mortality in aged mice [73], reduces reproductive success in mice [74], and alters immune responses [75]. Studies such as these and others support a model in which the adverse effects of circadian disruption become evident or apparent in the context of a physiological "challenge," such as genetic predisposition to disease, aging, pregnancy, immune challenge, or a high-fat diet. In this scenario, circadian disruption acts as a "second hit" to push susceptible individuals into the diseased or pathological state, or to exacerbate the severity of existing disease.

Recently, a study of hamsters carrying mutant alleles of the circadian clock gene *casein kinase 1ε* (termed *tau* mutants) provided an elegant demonstration of the role that global circadian dysregulation can have in the development of cardiovascular and renal disease [76]. Hamsters with one mutant *tau* allele have a faster circadian clock with a free-running period of about 22-h. Homozygous *tau* mutants have an even faster clock, with a free-running period of about 20-h. The investigators took advantage of the observation that hamsters with one mutant allele will try (unsuccessfully) to entrain to a 24-h LD cycle, whereas homozygous mutants do not and simply free-run throughout the LD cycle (i.e., the clock runs at its endogenous speed without attempting to synchronize to the LD cycle). Thus, heterozygotes experience chronic circadian disruption as they continually try to entrain, whereas wild-type and homozygous *tau* mutant hamsters do not experience such internal circadian disorganization. Heterozygotes develop significant age-related cardiomyopathy, cardiac fibrosis, and renal disease presumably due to chronic disorganization between the internal circadian clock and external LD cycle [76]. Importantly, heterozygotes on a 22-h LD cycle (that matches their endogenous circadian clock length) and SCN-lesioned heterozygotes (that cannot entrain and thus do not experience internal circadian desynchronization) on a 24-h LD cycle fail to develop cardiomyopathy and renal disease, strongly implicating chronic circadian disruption, as opposed to pleiotropic effects of the mutation, as the underlying cause of the pathology. These results complement previous work examining disruptions of the clock in specific tissues by showing that disorganization between tissues (and the environment) also contributes to pathologic transformation, at least in the cardiovascular and renal systems.

In addition to these studies of circadian disorganization at organismal level, rodent models have also been used to scrutinize the impact of genetic circadian disruption on cardiovascular tissue function and pathology. Circadian mutant mice exhibit increased pathological remodeling of vascular tissue and experience greater pathological damage in models of vascular injury. Isolated aortas from circadian mutant mice are characterized by endothelial dysfunction and reduced signaling in the Akt- and nitric oxide pathways, which are critical for normal arterial function [77]. The use of a vascular transplant model has enabled the study of wild-type mice with arterial-specific circadian clock mutations (and vice versa—circadian mutant mice with wild-type aortas) in order to assess the role of the molecular pacemaker in vascular function. When aortic grafts from circadian mutant mice (*Bmal1* knockout or *Per1/2* double knockout) were transplanted to wild-type hosts, severe arteriosclerotic disease and inflammation developed (Fig. 4.4, [78]), highlighting the role of intrinsic clocks in vascular tissue for immune regulation and proper physiological function. In addition to clinical relevance for classical cardiovascular diseases, including arteriosclerosis and atherosclerosis, these findings suggest that circadian clocks in transplanted tissues (particularly the endothelium) may also contribute to graft acceptance/rejection.

Although the diurnal variation in sudden cardiac death has been known for many years (see [67]), until recently the molecular mechanism for this rhythm was unclear. Sudden cardiac death is often precipitated by sustained ventricular arrhythmias, the risk of which is heavily influenced by the rate and pattern of cardiac repolarization. A recently published comprehensive study in mice demonstrated that the rhythmic expression of a clock-controlled transcription factor, *Klf15*, endogenously imparts a rhythm in the expression of a potassium channel subunit that controls the transient outward potassium current. This series of regulatory steps confers circadian rhythmicity to the QT interval duration on the electrocardiogram (the QT interval measures cardiac repolarization) [79]. Thus, circadian organization in cardiomyocytes generates rhythmic variation in the QT segment duration due to temporal regulation of critical ion channel components. Alteration of *Klf15* impacts cardiac repolarization, leading to dampened rhythms in QT segment variation and increased susceptibility to arrhythmias [79]. Taken together, these findings indicate that circadian disruption at the level of cardiomyocytes may contribute to arrhythmogenesis in humans. With an understanding of the molecular mechanisms involved, it becomes possible to design and deploy preventative and therapeutic strategies based upon the principles and properties of the circadian clock, which has an instrumental role in the physiology and function of the organs involved in disease pathogenesis.

Circadian Disruption and Gastrointestinal Disease

Circadian rhythms regulate many aspects of gastrointestinal physiology and function [80]. The signals controlling gut function originate from peripheral oscillators in cells throughout the GI tract as well as from CNS-mediated autonomic nervous

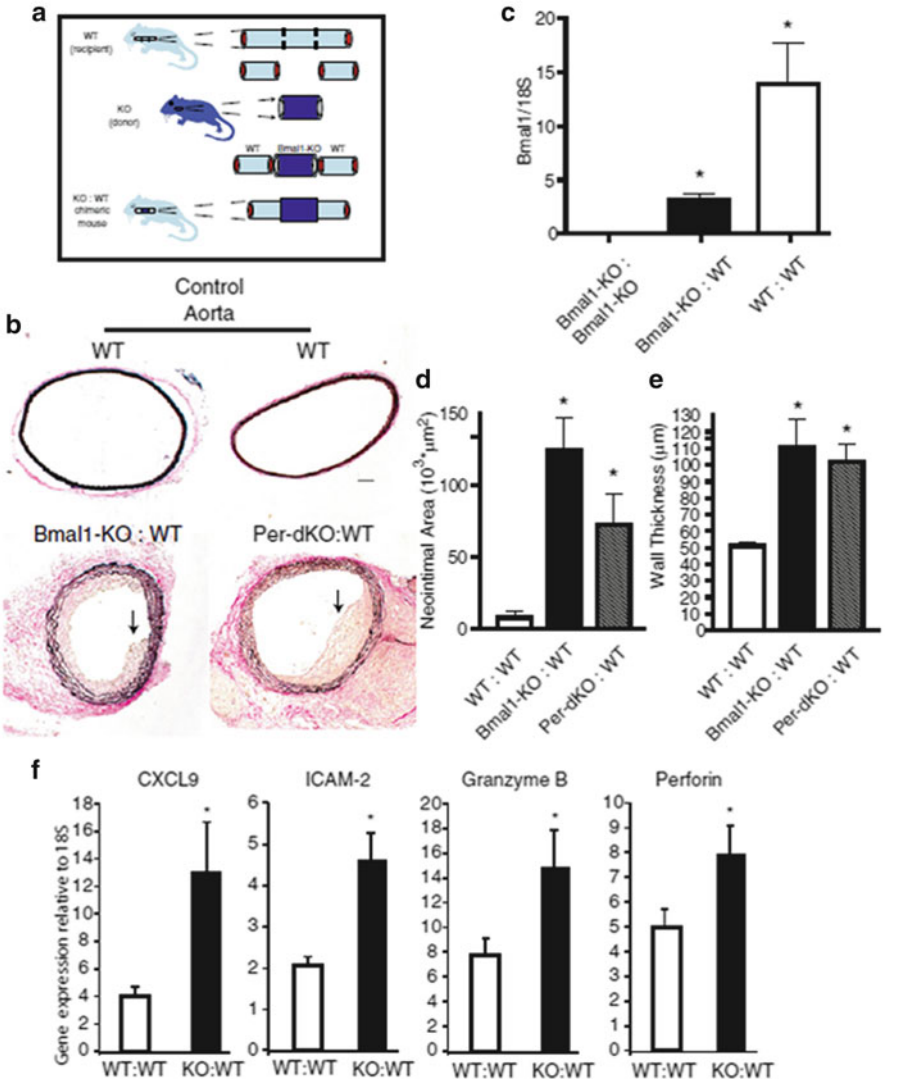

Fig. 4.4 Local genetic circadian disruption in transplanted arteries results in arteriosclerosis and inflammation. (**a**) Sections of aorta were transplanted between wild-type and circadian clock mutant mice (Bmal1-KO or Per1/Per2 double-KO, termed Per-dKO), generating chimeric mice used to determine whether local clock dysfunction in the transplanted artery influences the development of cardiovascular disease. (**b**) *Bmal1* expression is absent from Bmal1-KO host and recipient mice, markedly reduced in chimeras, and present at normal levels in wild-type mice. (**c**) Bmal1-KO:WT (Bmal1 KO donor tissue to WT recipient) and Per-dKO:WT (Per-dKO donor tissue to WT recipient) chimeras exhibit arteriosclerosis, consisting of neointimal hyperplasia (**d**) and increased vessel wall thickness (**e**). (**f**) Inflammatory responses are exaggerated in circadian mutant:WT chimeras, suggesting that the genetically disrupted local clock within the transplanted tissue contributes to inflammation and the development of vessel wall injury and arteriosclerosis (Adapted, with permission, from [78])

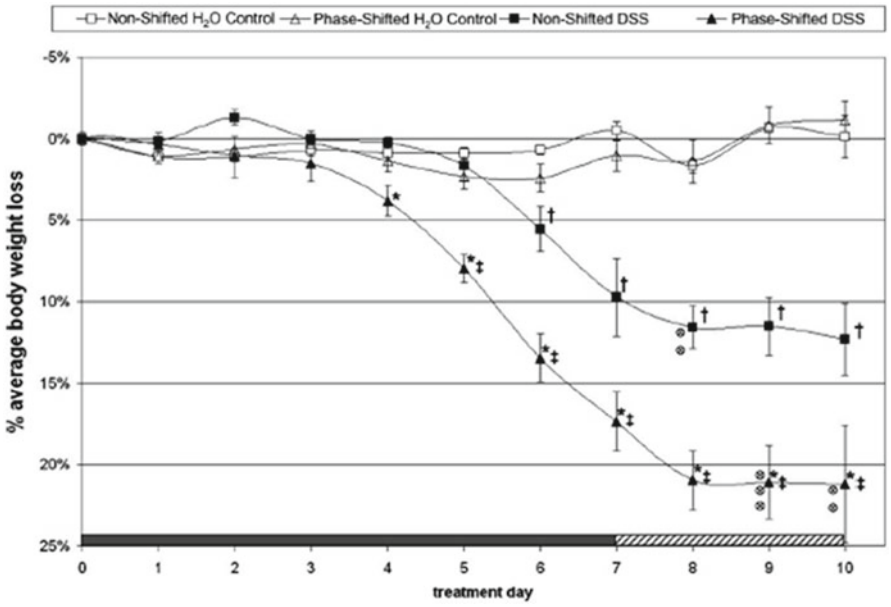

Fig. 4.5 Chronic disruption of circadian organization increased susceptibility to DSS-induced colitis in mice. Mice subjected to 3 months of weekly 12-h phase shifts of the light/dark (LD) cycle were administered with either dextran sodium sulfate (DSS), a compound toxic to the intestinal epithelial cells used to model colitis in mice, or a vehicle control in the drinking water. Two separate age-matched control groups were maintained on a constant 12:12 LD cycle and tested with either DSS or vehicle. To assess the severity of injury, body weight was monitored daily during and immediately following DSS administration. DSS-treated mice previously exposed to chronic circadian disruption (*filled triangles*) experienced an earlier onset and greater severity of the disease, including higher mortality, compared to non-shifted DSS-treated animals. In addition, DSS-treated mice that had been subjected to chronic circadian disruption exhibited greater histopathological damage and inflammation in the colon [83]. Taken together, these findings suggest that chronic circadian disorganization increases the sensitivity of intestinal epithelial cells to injury. In other words, circadian disruption may be a "second hit" that pushes certain individuals across a threshold into active disease (Reprinted, with permission, from [83])

system input [81]. One of the most common complaints associated with jet lag is gastrointestinal discomfort [82], presumably due to transient misalignment between rhythms in the GI tract and other internal clocks. Beyond jet lag, chronic circadian disruption, using the LD cycle phase shift model in mice, has been shown to sensitize intestinal epithelial cells to injury in a mouse model of colitis induced by dextran sodium sulfate (DSS) [83]. Animals exposed to phase shifts of the LD cycle experience an earlier onset of DSS-induced disease, with higher mortality, greater disease severity, and increased inflammation and histopathological damage (Fig. 4.5, [83]). These results support the "two hit" model wherein circadian disruption exacerbates the adverse effect of a physiological "challenge," in this case, DSS-induced intestinal injury and colitis.

A key function of the intestine is to maintain an epithelial barrier separating the proinflammatory contents of the gut lumen from circulation [84]. Disruption of the mucosal barrier permits translocation of bacterial endotoxin across the intestine wall into circulation and has been linked to numerous pathologies characterized by non-pathogen-mediated inflammation, including alcoholic steatohepatitis [85], metabolic syndrome [86, 87], cardiovascular disease [88], Parkinson's disease [89], and amyotrophic lateral sclerosis [90], among others. In an in vitro model of intestinal barrier function, using cultured human intestinal epithelial cells (i.e., Caco-2 monolayers), circadian clock genes were shown to be required for alcohol-induced increases in permeability across the monolayer [91], implicating the molecular clock in the development of barrier dysfunction in response to environmental insults such as alcohol. Further work is clearly warranted to characterize the role of circadian clock genes and circadian organization in maintaining intestinal epithelial barrier integrity, which is critical in promoting health and resisting disease.

Circadian Disruption and Cancer

Arguably, a field in which little progress has been made in linking circadian rhythms to pathology, disease pathogenesis, and/or clinical medicine at the molecular and genetic levels is cancer. This is unfortunate given that a diurnal rhythm in efficacy and sensitivity to chemotherapeutic agents was reported in mice over 40 years ago [92]. More recently, screening studies in rodents have demonstrated clear circadian rhythmicity in the antitumor activity and side effect profile of many anticancer agents, although at present, it is not possible to predict a priori at which time of day a given drug will be maximally effective (i.e., although rhythms are clearly present, little is known of their mechanistic underpinnings) [93]. Results such as these have given rise to the concept of "chronotherapeutics," in which the time of drug administration is taken into consideration in the treatment plan in order to maximize efficacy and minimize toxicity (Fig. 4.6, [93, 94]). Although some progress has been made, by and large, this approach has not made significant inroads into clinical oncology, especially in the United States. Increasing our understanding of chronotherapy and how it may be applied and used in clinical practice may represent a unique opportunity to improve patient outcomes by optimizing treatment strategies and modalities already in clinical use.

In addition to the impact of time of day on chemotherapy administration, there are indications that the molecular circadian clock directly interacts with and regulates pathways heavily implicated in many cancers. Perhaps most exciting are the lines of evidence that circadian clock proteins interact with the molecular regulators of the cell cycle [95]. Circadian clock gene targets include key molecules such as *p21*, *c-myc*, *Wee1,* and certain *cyclins*, which all contribute to the regulation of cell cycle phase transitions. Furthermore, disruption of the circadian clock and/or circadian clock genes induces dysfunction of the cell cycle (see [95] and references therein). It has also become evident in recent studies that the circadian clock

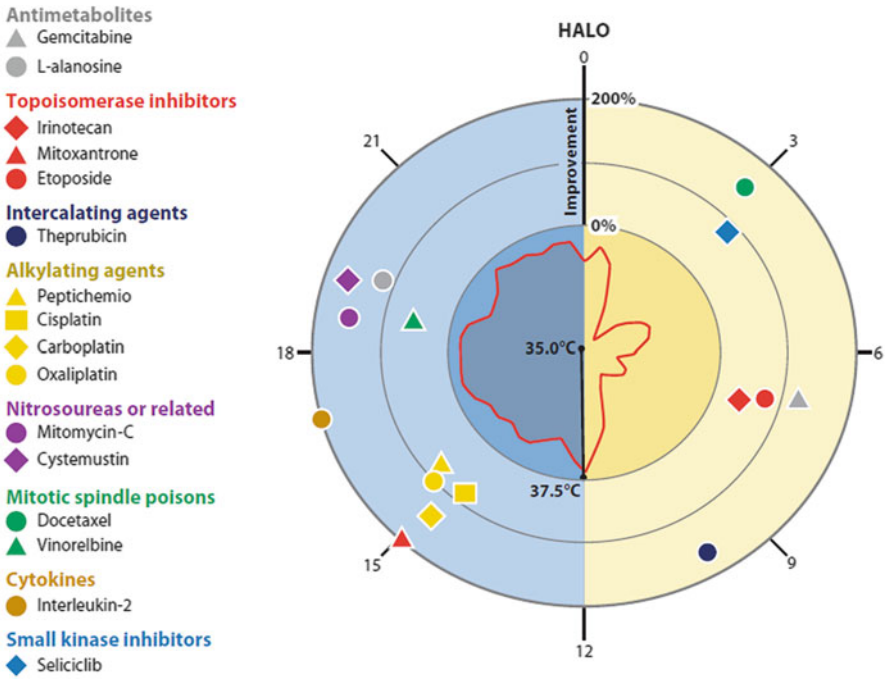

Fig. 4.6 Many commonly used chemotherapeutic agents exhibit significant rhythmicity in efficacy and tolerability. Sixteen anticancer drugs were tested across the diurnal cycle in male B6D2F1 mice housed in standard 12:12 LD conditions in the laboratory. The circadian time of maximal tolerability is plotted around the circle (HALO, hours after light onset). The distance outward from the center of the circle indicates the magnitude of the survival benefit provided by administration at the optimal time. Anticancer drugs from various classes exhibit circadian rhythms in tolerability and efficacy, and not all drugs from the same class have the same peak efficacy (Reprinted, with permission from [94])

machinery influences the rate and quality of DNA damage repair responses and pathways [96]. For example, the XPA protein, which plays a role in nucleotide excision repair, exhibits robust circadian rhythms of activity at both transcriptional and posttranslational levels in mouse hepatocytes, a finding that may have relevance for chemotherapeutic agents that induce damage amenable to nucleotide excision repair strategies [97]. Recently, mice were reported to have a diurnal variation in sensitivity to UVB radiation, with maximal vulnerability occurring during the night. Presumably this variation in sensitivity is due to coordinated progression through cell cycle states by groups of aligned skin cells throughout the day, with the most susceptible phase—S phase—occurring at night [98]. In addition, the circadian clock appears to contribute to the regulation of apoptosis [99, 100], which has obvious relevance for cancer. Despite these intriguing examples, it is important to point out that this field remains in its infancy and much detail remains to be worked out. For example, some effects may be due to functions of circadian genes that are

independent of their role in the clock mechanism [101], and it will be critically important to verify that observed effects in tissue samples and cultured cells are maintained in vivo [102].

It is clear that more work needs to be done to link the molecular clock to cancer biology at the molecular and genetic levels. Although, at present, the field has largely struggled to take advantage of the rapid revolutions in our understanding of the molecular mechanism of the circadian pacemaker and the physiology of the circadian timekeeping system, there is tremendous potential for the future. As detailed in Chap. 7, "Shift Work and Cancer Risk," and Chaps. 8 and 9, "Sleep Disorders and Cancer Risk" and "Sleep Deprivation/Insomnia and Cancer Risk," respectively, a substantial body of epidemiological data now links disruption of circadian rhythms and sleep to cancer. It will be up to physician-scientists and researchers in the cancer field to address these results and incorporate the vast increases in our knowledge about molecular and organismal circadian biology into their research programs. The dramatic advances in computational power and sequencing ability have opened up new avenues to interrogate and mine large datasets in which gene expression is altered in, and possibly even causal to, cancer. It is now critically important to mine these datasets in the context of circadian clock genes and clock-controlled genes. It is clear that meaningful gains in patient outcomes for the seemingly intractable forms of cancer will require large, multidisciplinary, highly coordinated, and rapidly adapting teams of professionals that leverage vast group knowledge, experience, and technical abilities for the benefit of patients. In our view, circadian biologists have an important role in such teams by encouraging and facilitating the incorporation of timing and circadian biology in our understanding of cancer pathogenesis and in our approaches to treatment.

Conclusions

There is now substantial evidence that circadian misalignment results in clinically relevant physiological abnormalities. The epidemiological data continue to support the hypothesis that chronic circadian disruption contributes to the pathogenesis of numerous diseases and indicate that it may represent an important risk factor to be routinely taken under consideration. Clinical and translational studies have begun to elucidate the molecular mechanisms linking circadian clock genes to pathways involved in various diseases and disorders. Future work will refine and improve our understanding of how alterations in the circadian system result in downstream dysfunction, disease risk, pathogenesis, and progression. Although this chapter has focused on medical disorders, including metabolic, cardiovascular and gastrointestinal diseases, and cancer, there is also ample evidence that circadian disruption is involved in psychiatric disease as well [103]. Continued research and further insights will be instrumental for ushering in a new era in clinical medicine—one in which the concept of biological time on the circadian scale is incorporated to enrich our understanding of disease pathophysiology broadly across biomedical and clinical disciplines and exploited to improve clinical care.

Fig. 4.7 Composite view of the United States from space at night. The relatively recent advent and widespread dissemination of electrical lighting has fundamentally transformed our relationship with day and night. The biological implications of these drastic changes are only beginning to be recognized. Given that the powers of modernization and globalization are unlikely to reverse course, it will be important for clinical medicine to incorporate our understanding of circadian rhythms and their relevance for health and disease. The shift work population is no longer the only target patient population for those who hope to practice "Circadian Medicine." In reality, the immense pressure against maintaining natural cycles of light and darkness and sleep and wake posed by modern society creates a scenario in which many of us are chronically subjected to circadian disruption. One metric of this phenomenon is the concept of "social jetlag," which refers to the weekly shifts that arise from changing bed and wake times between work days and free days [105]. "Social jetlag" has been linked to obesity [106] and, yet, may represent only the tip of the iceberg with respect to the impact of widespread circadian disorganization on health and disease (Image from NASA (www.nasa.gov/images/content/712129main_8247975848_88635d38a1_o.jpg))

Although the shift work population will remain an important group to study, the application of the dramatic scientific improvements in our understanding of circadian biology to the realm of clinical medicine has much more broad and widespread implications. Given the increasing modernization of our world and environment (Fig. 4.7), circadian disruption and sleep loss are becoming hallmarks of society. We live in a world increasingly divorced from the natural cycles of light and darkness that have served as the primary, defining geophysical feature of life on this planet. With the flick of a switch, we can override the solar cycle and, in so doing, dramatically disrupt our internal clocks. Indeed, it was recently reported that exposure to dim light at night in mice caused increased weight gain by shifting feeding rhythms towards more consumption during the light phase of the LD cycle [104]. With the click of a mouse (i.e., a computer one), we can purchase airplane tickets capable of rapidly carrying us to the far corners of the globe, drastically divorcing our internal

clocks and rhythms from the environmental day. As a consequence of our work and school schedules, we frequently alter the timing and quantity of our sleep every week, creating repeated internal circadian desynchrony, termed "social jetlag" [105], which has been linked to obesity [106]. These evolutionarily recent changes to our environment and behavior are not likely to stop or reverse course, thus it will be important to fully understand the impact of these changes on our circadian clocks and subsequent disease risk. Only with an understanding of the underlying biological pathways involved will it be possible to design and deploy preventative and/or therapeutic strategies based on the principles and properties of the circadian clock system.

In considering the specific effects of circadian misalignment on biological pathways involved in various diseases and disorders, it is important to recognize the levels at which circadian disruption can occur. The circadian clock machinery within an individual cell can become altered and disorganized. Within a tissue, the rhythms of different cells can become disrupted and desynchronized from one another, resulting in tissue-level dysfunction. This may be the result of altered phase relationships and/or miscommunication between cells of the same type within a tissue or between different cell types (or both). At the systems level, rhythms of one tissue may become desynchronized from those of other tissues, resulting in higher order dysfunction. For example, this may occur in a condition of chronic jet lag when the cells of the SCN rapidly re-entrain to the new light schedule, whereas the cells in other tissues of the body respond more slowly and variably, leading to a prolonged period of internal misalignment. Another example is chronically mistimed feeding-fasting rhythms, which can entrain clocks in peripheral organs associated with digestion and metabolism at an altered phase relationship(s) to the SCN, which remains tightly linked to the LD cycle irrespective to feeding time [44]. Finally, there may be an abnormal relationship between the phase of the circadian clock and the external environment, leading to chronic circadian disruption. This appears to be the case in the advanced and delayed sleep phase syndromes (ASPS and DSPS, respectively): the circadian clock is permanently shifted relative to the range of expected times based on the solar day. Such a situation may have important social and emotional ramifications, in addition to the physiological and biochemical alterations associated with the circadian disruption. The complexities of the roles that circadian disruption can play in the development and/or progression of disease indicate that continued research is necessary to narrow down the specific pathological effects of circadian disruption, identify the affected pathways, and attempt to mitigate and/or alleviate the adverse effects.

The past 20 years have witnessed profound and dramatic improvements in our understanding of the circadian system from a scientific standpoint. Indeed, it is difficult to fully appreciate just how far the field has come in such a relatively short period of time. Despite these successes however, little of the new information has been applied to the benefit of patients suffering from the diseases linked to circadian disruption, which is particularly relevant for cancer since many of the diseases linked to circadian misalignment are comorbid with cancer, and cancer itself has been associated with circadian disorganization. The upcoming translation of these

scientific findings to the realm of clinical medicine yields significant transformative potential in opening up an entire new avenue for the conceptualization and understanding of disease risk and pathogenesis. The insights gleaned from the scientific world are expected to contribute to the development of novel, biologically based therapeutic strategies based on the principles and properties of the circadian system. Such an approach, which we propose to refer to as "Circadian Medicine," incorporates and fully appreciates the concept of biological time as a critical biological determinant of health and, conversely, disease. The dramatic scientific advances of the field offer a blueprint upon which a foundation of clinical understanding can be built. Whether the vast potential of "Circadian Medicine" is ultimately realized remains to be seen and depends upon the continued dedication of scientists and researchers at the forefront of integrating our understanding of circadian biology with that of disease pathophysiology and treatment.

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Chapter 5
Intermittent Hypoxia: Mechanistic Pathways Influencing Cancer

Jayasri Nanduri and Nanduri R. Prabhakar

Abstract Sleep-disordered breathing with recurrent apnea is a major clinical problem affecting 4–5 % of middle-aged men, 2 % of women after menopause [1, 2], and nearly 50 % of premature infants [3]. Recurrent apneas are characterized by transient, repetitive cessations of breathing (10–60 s), which arise either as a consequence of obstruction of the upper airway leading to cessation of airflow (obstructive sleep apnea or OSA) or due to defective respiratory rhythm generation in the brain stem (central apnea). Recurrent apnea produces periodic decreases in arterial blood oxygen or chronic intermittent hypoxia (IH). In severely affected patients, arterial blood O_2 saturation can drop as much as 50 %. Comorbidities associated with recurrent apnea include hypertension, elevated sympathetic activity, myocardial infarction, stroke, ventilatory abnormalities, and sudden death in elderly individuals [2].

Association of cancer incidence with sleep disturbances has been documented. For instance, longer sleep duration was shown to be associated with higher incidence colorectal cancer [4–8]. In the recent past, there have been few studies linking OSA and the ensuing IH with cancer [5, 9–11]. The purpose of this chapter is to summarize studies describing the signaling pathways triggered by chronic IH, which may potentially contribute to cancer progression in recurrent apnea patients.

Keywords Hypoxia-inducible factors • Intermittent hypoxia • Obstructive sleep apnea • Reactive oxygen species • Sleep-disordered breathing

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_5,

Apneas and Cancer

A recent study by Nieto et al. reported that sleep-disordered breathing with apnea is a significant contributor to cancer-related mortality [9]. These investigators followed 1,500 subjects over a period of 20 years. The severity of sleep-disordered breathing was determined by polysomnography, and the data were adjusted for potential confounding factors such as tobacco use, alcohol, and physical activity as well as sleep duration. Participants who used continuous positive airway pressure therapy were excluded in this study. Remarkably, a total of 112 deaths were identified over a 20-year period and 50 of them were related to cancer. A statistically significant trend was noticed between the incidence of increased cancer mortality and severity of sleep-disordered breathing as determined by apnea-hypopnea index or degree of overnight hypoxemia. However, this study did not provide any data on cancer incidence. Thus, it remains uncertain whether the observed incidence of cancer-related mortality is due to higher incidence of cancer or aggressive cancer biology resulting from severity of apnea. Furthermore, the study was also underpowered to detect whether cancer mortality differed among types of cancer as noted by authors. Nonetheless, this is an important study that provides evidence for potential contribution of sleep-disordered breathing to cancer.

Association of OSA with increased incidence of cancer was also reported in a large multicenter Spanish cohort [5]. The authors found that hypoxemia index was a stronger predictor of cancer incidence than AHI. The association between OSA and cancer incidence differed according to sex and age. A strong relationship was found between OSA severity and cancer incidence in patients younger than 65 years but not in older patients. These age differences may simply reflect a survival bias and activation of protective and adaptive mechanism against IH which may explain decline in cardiovascular effects and cancer development with OSA with increasing age. Although the data suggest an intriguing link between sleep-disordered breathing and cancer incidence in males compared to women, additional adequately powered cohort studies are needed to further address the sex differences observed.

Apneas are associated with intermittent hypoxia (IH) as well as hypercapnia. A major advance in the field of apnea research is the demonstration that exposing experimental animals to chronic IH mimicking O_2 profiles with recurrent apnea result in many of the comorbidities seen in recurrent apnea patients. Almendros et al. [11] reported that IH, mimicking the hypoxic profiles encountered in recurrent apnea patients alone, is sufficient to induce tumor growth in mice, whereas sleep deprivation by itself did not have any significant effect on tumor growth.

There have been some studies describing the effects of IH on cancer, although the O_2 profiles in these studies do not represent those encountered with recurrent apnea. Mice bearing KHT tumors exposed to 12 cycles of 10 min of hypoxia per day followed by 10 min of reoxygenation for 8–15 days exhibit increased lung micrometastasis as compared to control mice, whereas no increase in lung micrometastasis was observed in mice exposed to chronic hypoxia [12] suggesting the observed effects were unique to IH. Studies on in vitro cell cultures showed that IH is a key

regulator of interplay between cancer cells and endothelial cells in tumors [13]. Exposure of different tumor cells including B16 melanoma cells, fibrocarcinoma cells, hepatocarcinoma (TLT) cells, and cervix cancer (SiHa) cells to IH exhibits resistance to apoptosis and higher metastatic potential [14].

IH in tumors originates from heterogeneities in RBC flux and influences not only tumor cells but also endothelial cells lining tumor blood vessels. It was shown in vivo that IH (4 min of hypoxia followed by 4 min of reoxygenation for 2 weeks) increased the capillary density in mouse brains indicating a proangiogenic effect. Similarly, in vitro experiments showed that exposure of endothelial cells to IH (three cycles of 1 h hypoxia interrupted by a 30 min reoxygenation) not only rendered them resistant to proapoptotic stresses, including serum deprivation and radiotherapy, but also increased their capacity to participate in angiogenesis [14]. Recent studies by Berger et al. have shown that IH increases the mobilization, proliferative, and angiogenic capacities of endothelial progenitor cells [15]. Together these studies indicate that IH might be a potential contributor to cancer growth.

Signaling Pathways Activated by Intermittent Hypoxia: Relevance to Cancer Development

Several signaling mechanisms have been implicated in progression of cancer depending on its type and tissue. Remarkably, many of the signaling mechanisms activated by IH have been implicated in cancer progression. The following section provides a summary of these studies.

Transcriptional Activators

Hypoxia-Inducible Factors (HIFs): Molecular oxygen (O_2) is essential for the survival of mammalian cells because of its critical role in generating ATP via oxidative phosphorylation. Hypoxia, i.e., low levels of O_2, is a hallmark phenotype of tumors. As early as 1955, it was reported that tumors exhibit regions of severe hypoxia [16]. Oxygen diffuses to a distance of 100–150 μm from blood vessels. Cancer cells located more than 150 μm exhibit necrosis. The uncontrolled cell proliferation causes tumors to outgrow their blood supply, limiting O_2 diffusion resulting in chronic hypoxia. In addition, structural abnormalities in tumor blood vessels result in changes in blood flow leading to cyclic hypoxia [17, 18]. Measurement of blood flow fluctuations in murine and human tumors by different methods have shown that the fluctuations in oxygen levels in tumors vary from several minutes to more than 1 h in duration.

Hypoxia in tumors was shown to be associated with increased metastasis and poor survival in patients suffering from squamous tumors of head and neck,

cervical, or breast cancers [19, 20]. Tumor hypoxia is associated with resistance to radiation therapy and chemotherapy and poor outcome regardless of treatment modality. Cancer cells have adapted a variety of signaling pathways that regulate proliferation, angiogenesis, and death allowing tumors to grow under hypoxic conditions. Cancer cells shift their metabolism from aerobic to anaerobic glycolysis under hypoxia [21] and produce growth factors that induce angiogenesis [22, 23].

How do cancer cells sense hypoxia and what signaling pathways mediate their cellular responses? It is increasingly recognized that hypoxia in cancer cells initiates a transcription program that promotes aggressive tumor phenotype. Hypoxia-inducible factor-1 (HIF-1) is a major activator of transcriptional responses to hypoxia [24]. HIF-1 is comprised of an O_2-regulated HIF-1α subunits and a constitutively expressed aryl hydrocarbon receptor nuclear translocator (ARNT) or HIF-1β subunit (reviewed in [25]). Prolyl hydroxylase (PHD) is a tetrameric enzyme containing two hydroxylase units and two protein disulphide isomerase subunits, which requires O_2, ferrous iron, and 2-oxoglutarate for PHD enzyme activity. In the presence of O_2, PHD covalently modifies the HIFα subunit to a hydroxylated form, which by interacting with Von Hippel-Lindau (VHL) protein, a tumor suppressor, is subjected to ubiquitylation and targeted to proteasome, where it gets degraded [25]. Hypoxia inhibits PHD activity resulting in accumulation of HIF-1α subunit, which dimerizes with HIF-1β subunit. HIF-1 transcriptional activity is also regulated via O_2-dependent asparagine hydroxylation that blocks coactivator recruitment [26]. Once activated, the HIF-1 complex gets translocated to nucleus and initiates transcription by binding to hypoxia-responsive elements on DNA [25].

Overexpression of HIF-1α was reported in 13 out of 19 clinical tumor specimens including colon, breast, gastric, lung, skin, ovarian, pancreatic, prostate, and renal carcinomas [27]. It is now well recognized that HIF-1 activation is a key element in tumor growth and progression. Stabilization of HIF-1 by hypoxia regulates a host of target genes at various stages of tumor growth. For example, HIF-1 activates expression of genes encoding various growth factors involved in cell proliferation, metabolic switch from oxidative to glycolytic metabolism, carbonic anhydrases for pH regulation, cell migration or invasion by induction of matrix metalloproteinases, urokinase plasminogen activator receptor, as well as angiogenesis [28]. Interestingly, HIF-1 is also implicated as a key determinant to induce resistance to chemotherapy.

HIF-2 is another member of HIF family of transcriptional activators. The O_2-regulated HIF-2α subunit, which shares 48 % sequence homology to HIF-1α, also interacts with HIF-1β. Similar to HIF-1, hypoxia leads to HIF-2α accumulation and the resulting transcriptional activation regulates several target genes. HIF-2α expression is also increased in certain cancers including the renal carcinoma and cerebellar hemangioblastomas [23, 29, 30]. The elevated HIF-2α levels appear to be confined to stromal macrophages rather than in the epithelial cancer cells [31]. HIF-2 expression has been associated with increased tumor vascularization and is crucial for the growth of renal cell carcinomas and neuroblastoma tumors [24, 32]. It is becoming increasingly apparent that HIF-1 and HIF-2 contribute to tumorigenesis in a complex, context, and cell-dependent manner. For example, whereas HIF-1α expression positively correlates with decreased patient mortality in many cancers,

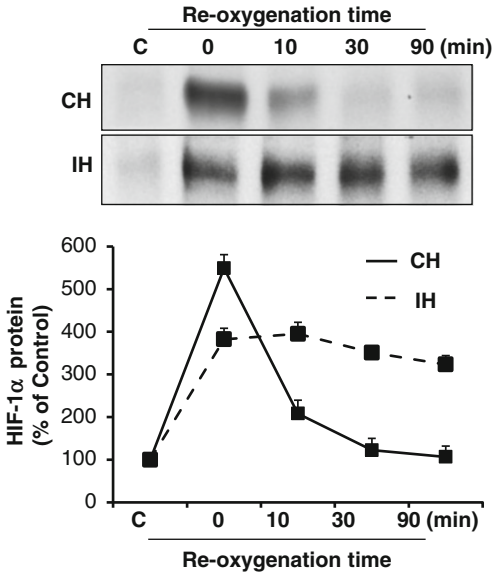

Fig. 5.1 Contrasting effects of intermittent hypoxia (*IH*) and continuous hypoxia (*CH*) on HIF-1α accumulation in rat pheochromocytoma PC12 cells. HIF-1 protein was analyzed by western blot assay. Representative immunoblots in *top panels* and densitometric analysis in *bottom panel* (Data adapted from reference Yuan et al. [38])

HIF-2α expression is a negative prognostic factor in many of these same cancers (reviewed by [33]). Studies on VHL-deficient renal cell carcinoma have shown that HIF-2α promotes tumor growth, whereas HIF-1α inhibits tumor growth. HIF-1α binds to and stabilizes p53 to mediate hypoxia-induced apoptosis, whereas HIF-2 suppresses p53 and promotes chemoresistance [33–35]. Therefore, tumor behavior and drug response can vary significantly according to aberrant expression of HIF-1α and/or HIF-2α in different cancers.

Regulation of HIFs by Intermittent Hypoxia: It is clear from above studies that continuous hypoxia activates HIF-α isoform expression. The duration of hypoxia associated with each episode of recurrent apnea, however, is short and lasts no more than few tens of seconds. Do such brief episodes of IH activate HIF-α isoforms? Yuan et al. [36] established a cell culture system in which rat pheochromocytoma PC12 cells were exposed to IH consisting of alternating cycles of hypoxia (1.5 % O_2 for 30 s) and reoxygenation (20 % O_2 for 4 min), simulating the O_2 profiles associated with recurrent apnea. During each episode of hypoxia, PO_2 near cells decreased by ~20–25 mmHg. Despite the modest hypoxia, HIF-1α protein increased in nuclear extracts in a dose-dependent manner as the duration of IH was increased from 10 to 30 to 60 cycles [36]. In striking contrast, exposing cells to comparable, cumulative duration of continuous hypoxia was ineffective in increasing HIF-1α protein expression. However, extending the hypoxic duration to 4 h did result in a significant increase in HIF-1α protein expression as reported by other investigators [37]. Increased HIF-1 levels caused by continuous hypoxia return to control levels within 10 min of reoxygenation (Fig. 5.1). In striking contrast, HIF-1 levels remained significantly elevated after 90 min of reoxygenation following exposure to 60 cycles of IH (Fig. 5.1). These observations suggest that for a given duration and intensity,

IH is more potent in activating HIF-1 than continuous hypoxia. Unlike continuous hypoxia, IH leads to HIF-1 accumulation that persists during reoxygenation.

A recent study examined signaling pathways underlying HIF-1α accumulation by IH. HIF-1α accumulation by IH was due to reactive oxygen species (ROS)-dependent activation of Ca^{2+} signaling pathways involving phospholipase Cγ (PLCγ) and protein kinase C [38]. More importantly, both increased mTOR-dependent HIF-1α synthesis and decreased hydroxylase-dependent HIF-1α degradation contribute to IH-evoked HIF-1α accumulation. Furthermore, mTOR-dependent protein synthesis is required for the persistent elevation of HIF-1α levels during reoxygenation. Given that continuous hypoxia is ineffective in activating mTOR, these observations suggest IH-mediated HIF-1α accumulation requires recruitment of signaling pathways that are distinct from those described by continuous hypoxia.

Yuan et al. [25] delineated the signaling pathways associated with IH-induced HIF-1-mediated transcription. IH increased HIF-1-dependent reporter gene expression in PC 12 cell cultures. A variety of protein kinases are implicated in transcriptional activation by HIF-1 [25]. Although IH activated ERK1, ERK2, JNK, PKC-α, and PKC-γ, inhibitors of these kinases and inhibitor of phosphatidylinositol 3-kinase (PI-3 kinase) were ineffective in blocking IH-induced HIF-1-mediated reporter gene expression, indicating that signaling via these kinases was not required. In contrast, BAPTA-AM, an intracellular Ca^{2+} chelator, blocked HIF-1 reporter gene activation by IH, suggesting involvement of Ca^{2+} signaling pathways. Calcium-calmodulin (CaM) kinase activity was increased fivefold in cells subjected to IH. KN 93, an inhibitor of CaMK, prevented IH-induced transactivation mediated by HIF-1α and its coactivator p300. CaM kinase II phosphorylated p300 in vitro. These observations suggest that IH induces HIF-1 transcriptional activity via a novel signaling pathway involving CaM kinase. Signaling pathways associated with HIF-1α accumulation and HIF-1 transcriptional activation are summarized in Fig. 5.2.

Complete HIF-1α deficiency results in embryonic lethality at mid-gestation, whereas *hif1a*$^{+/-}$ heterozygous (HET) mice, which are partially deficient in HIF-1α expression, develop normally and are indistinguishable from wild-type (WT) littermates under normoxic conditions [39, 40]. Recent studies examined the importance of HIF-1 activation in IH-induced physiological changes in *Hif1a*$^{+/-}$ heterozygous (HET) mice [41, 42]. In contrast to WT mice, IH was ineffective in increasing HIF-1α protein expression in HET mice. The absence of HIF-1α upregulation was associated with a striking absence of blood pressure elevation, plasma catecholamines, and augmented ventilatory response to hypoxia in HET mice exposed to IH. These studies suggest that activation of HIF-1-mediated transcription is critical for evoking cardiorespiratory responses by IH. Whether HIF-1 is involved in tumor progression by IH, however, remains to be studied.

Although continuous hypoxia increases both HIF-1α and HIF-2α protein [37], IH *increases* HIF-1α but *degrades* HIF-2α protein in cell cultures and in rodents [43]. Thus, continuous and intermittent hypoxia exerts diametrically opposite effects on HIF-1 and HIF-2 protein expression. The IH-induced HIF-2α degradation was due to the activation of calpains, which are Ca^{2+}-activated proteases [43]. Systemic administration of ALLM, a potent inhibitor of calpains, rescues IH-induced

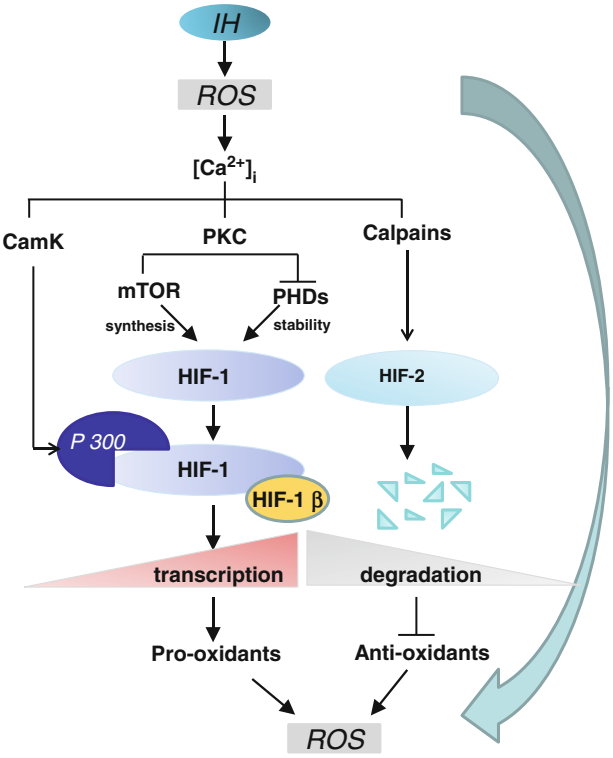

Fig. 5.2 Signaling pathways associated with dysregulation of HIF-1 and HIF-2 by intermittent hypoxia (*IH*) and its consequences on reactive oxygen species (*ROS*) generation. IH leads to ROS-induced ROS (positive feedforward regulation) via dysregulation of HIF-α isoforms. *CamK* calcium-calmodulin-dependent protein kinase, *PKC* protein kinase C, *mTOR* mammalian target of rapamycin, *PHDs* prolyl hydroxylases, *HIF-1* and *HIF-2* hypoxia-inducible factors 1 and 2

HIF-2α degradation in rats. Decreased HIF-2α expression by IH is associated with downregulation of HIF-2-mediated transcriptional response [43]. A recent study demonstrated that *Hif-2α*$^{+/-}$ mice exhibit irregular breathing, apneas, hypertension, and elevated plasma norepinephrine levels similar to that reported in OSA patients or rodents exposed to IH [44]. The role HIF-2 downregulation in IH-induced cancer progression remains to be investigated.

Nuclear Factor Kappa B (NF-κB): The transcriptional activator NF-κB is composed of five family members: RelA (p65), p105/p50 (NF-κB1), p100/p52 (NF-κB2), c-Rel, and RelB. NF-κB functions as an important regulator of the immune and inflammatory responses [45]. NF-κB is induced by a wide variety of inflammatory and immunological stimuli and cell stresses, including cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, bacterial lipopolysaccharide (LPS), low oxygen tension (hypoxia), and DNA damage [45]. NF-κB plays a crucial role in multiple cellular pathways including cell survival, proliferation, adhesion,

and angiogenesis [45]. It was proposed that aberrant activation of NF-κB contributes to most, if not all, of the "hallmarks" of cancer (reviewed by [46, 47]).

Intermittent Hypoxia and NF-κB: In OSA patients, NF-κB activity is increased in monocytes resulting in elevated serum tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8) levels [48] Elevated TNF alpha levels correlated with arterial O_2 desaturation, and treating apnea patients with continuous positive airway pressure (CPAP) normalized TNF-α levels [48]. These observations suggest that IH is a potent activator of NF-κB. Consistent with this possibility, IH has been shown to stimulate NF-κB-mediated transcriptional activation in HeLa cells [49]. Greenberg et al. found elevated NF-κB activity in IH-exposed mice [50] However, the mechanisms by which IH activates NF-κB remain to be investigated.

Immediate Early Genes and Activator Protein (AP-1) Complex: The AP-1 complex exemplifies a network of transcription factors that function in unison under normal circumstances and during the course of tumor development and progression. AP-1 is a dimeric transcription factor that contains members of the JUN, FOS, ATF, and MAF protein families. Two of the components of AP-1—c-Jun and c-Fos—were first identified as viral oncoproteins, and their roles in tumorigenesis are well established. When overexpressed in mice, c-Fos causes osteosarcoma formation by the transformation of chondroblasts and osteoblasts [51]. c-Jun is more important in the development of skin and liver tumors [52]. Recent studies in humans and mice have shown that some JUN and FOS family proteins can suppress tumor formation. The decision as to whether AP-1 is oncogenic or antioncogenic depends on the cell type and its differentiation state, tumor stage, and the genetic background of the tumor. AP-1 can exert its oncogenic or antioncogenic effects by regulating genes involved in cell proliferation, differentiation, apoptosis, angiogenesis, and tumor invasion [53].

Hypoxia is a potent activator of c-Fos [54]. Greenberg et al. reported upregulation of c-Fos protein in the central nervous system of rats exposed to 30 days of IH [55]. IH is a potent activator of *c-Fos* mRNA expression in PC12 cells and the ensuing AP-1-mediated transcriptional activation [56]. Whether activation of AP-1 by IH contributes to cancer progression remain to be studied.

Other Transcription Factors: Little is known on the effects of IH on other transcription factors such as Nrf2 and p53, which are also implicated in cancer progression. Since it is becoming apparent that IH triggers a variety of transcriptional factors, it is likely that cooperation among these transcription factors may be critical for executing tissue specific transcriptional programs relevant to progression of various cancer types in recurrent apnea patients.

Reactive Oxygen Species (ROS)

Tumor cells exhibit higher levels of ROS than normal cells, and aberrant ROS production has been implicated in triggering various tumorigenic pathways [57–60]. Increased generation of ROS and ensuing oxidative stress occurs as a consequence

of imbalance between the production of free radicals (i.e., O_2^-, H_2O_2 or OH^-) by prooxidants and elimination of free radicals by antioxidant enzymes. ROS can be formed by several oxidases. The family of NADPH oxidases (Nox) constitutes one of the major sources of ROS [61]. Both mRNA and protein expression of Nox1, 2, 4, and 5 have been detected at higher levels in various cancer cells and human tumors at early and late stages of tumorigenesis compared with normal controls suggesting that ROS generated by NADPH oxidase is important in both initiation and maintenance phase of tumor development. Nox can affect several hallmarks of cancer including genomic instability, autonomous growth and survival, angiogenesis, invasion, and metastasis [62].

In addition to oxidases, mitochondrial electron transport chain (ETC) constitutes another major source of ROS [63]. A recent study provides evidence for positive feedforward interactions between Nox family and ETC resulting in ROS-induced ROS for sustained oxidative stress under IH [64] (Fig. 5.2). Continuous hypoxia generates ROS by inhibiting complex III of the mitochondrial ETC [65], whereas inhibition at the complex I contribute to ROS generation by IH [56], once again highlighting the differences between two forms of hypoxia. Mitochondrial ROS have been implicated in mediating Myc-induced tumor genesis and oncogene-mediated cell transformation [66].

The antioxidant system includes enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) catalase, and glutathione reductase. Reduced antioxidant defense exacerbates the detrimental effects of increased oxidative stress by prooxidants. Upregulation of antioxidants such as peroxidases (Prx1), Gpx, thioredoxin, and GSH are implicated in chemoresistance of cancer cells [67–69]. Whether ROS promote tumor cell survival or act as antitumorigenic appears to depend on cell and tissue types, the location of ROS production, and the concentration of individual ROS.

Initial studies examining the role of ROS in tumor initiation suggested that oxidative stress acts as DNA-damaging agent. In addition to inducing genomic instability, ROS can contribute to abnormal gene expression, modification of second messenger systems, and blocking of cell-to-cell communications resulting in increased cell proliferation and decreased apoptosis [60]. ROS are reported to be tumorigenic by virtue of their ability to activate multiple intracellular signaling pathways involved in cell proliferation, survival, and cell migration. Proteins and lipids are targets for oxidative stress, and modification of these molecules can increase the risk of tumor growth. The most significant reported effects of ROS have been on protein kinase activation signaling mechanism. ROS might activate protein kinases either directly or indirectly by inhibiting protein phosphatases or a combination of both. For instance, ROS have been shown to activate MAP kinase and phosphoinositide 3-kinase pathways important for cell proliferation and survival [70–72]. Mitochondrial ROS have also been shown to both activate and upregulate the expression of proteins involved in epithelial-to-mesenchymal transition and metastasis, including matrix metalloproteinases (MMPs; [73]). In addition to activating MMP-3, mitochondrial ROS have also been shown to act downstream of MMP-3 to mediate MMP-3-induced cell transformation [74]. Antioxidants exhibit

cancer chemopreventive potential by controlling the onset and progression of tumor by preventing DNA damage as well as by acting on cell cycle checkpoints [75].

Intermittent Hypoxia: A Potent Activator of ROS: IH is interspersed with periods of reoxygenations. It was proposed that IH might generate ROS during the reoxygenation phase [76] analogous to that reported with ischemia-reperfusion [77]. ROS activates specific transcriptional responses and signaling pathways which contribute to the effective translation of the brief hypoxic signals associated with IH to systemic responses elicited by recurrent apnea [78, 79]. Plasma levels of antioxidants such as glutathione peroxidase, folate, vitamin A, E, and B12, and homocysteine have been reported to be significantly lower in OSA patients than in controls of similar age and body mass index (BMI) [80]. Physiological studies have shown that ROS scavengers MnTMPyP as well as N-acetylcysteine (NAC), a precursor of glutathione, prevent IH-induced elevations in blood pressure, plasma catecholamines, and augmented ventilatory response to hypoxia [78]. Recent studies have shown that activation of HIF-1 contributes to Nox 2 upregulation, whereas HIF-2 downregulation to insufficient transcriptional activation of antioxidant enzymes leading to IH-induced oxidative stress [38, 43] (Fig. 5.2). Therefore, it likely that higher incidence of tumors in recurrent apnea patients is due to IH affecting either HIFs directly or indirectly due to regulation of ROS production by HIFs or combination of both.

Inflammatory Cytokines

Chronic inflammation has been linked to various steps involved in carcinogenesis [60]. In a mouse model of lung cancer, it was shown that K-Ras (rat sarcoma viral oncogene) induces tumor genesis [81]. Ras induces the expression of various inflammatory gene products including the proinflammatory cytokines IL-1, IL-6, and IL-11 and the chemokine IL-8. Recent studies show that elevated levels of circulating inflammatory mediators such as C-reactive protein, TNF-α, and IL-6 in OSA patients are in part due to IH [49, 82]. Inflammation of vascular endothelium has been reported in venous endothelial cells harvested from patients with OSA patients [82].

Epigenetic Regulation

Cancer has traditionally been viewed as a set of diseases that are driven by the accumulation of genetic mutations, which are considered major cause of neoplasia [83]. However, this paradigm has now been expanded to incorporate the disruption of epigenetic regulatory mechanisms that are prevalent in cancer [84, 85]. Both genetic and epigenetic mechanisms ultimately lead to abnormal gene expression. The genetic path to cancer is relatively straightforward: mutation of tumor suppressors

and/or oncogenes causes either loss or gain of function and abnormal expression. The epigenetic mechanisms involve changes in chromatin structure including DNA methylation, histone variants and modifications, nucleosome remodeling, as well as small noncoding regulatory RNAs [86]. During tumor initiation and progression, the epigenome goes through multiple alterations, including a genome-wide loss of DNA methylation (hypomethylation), frequent increases in promoter methylation of CpG islands, changes in nucleosome occupancy, and modification profiles. More recently, intriguing evidence has emerged that genetic and epigenetic mechanisms are not separate events in cancer; rather they intertwine and take advantage of each other during tumor genesis [87].

The field of epigenetic regulation in OSA is in its infant stage. Recently, it was reported that adult rats exposed to IH in neonatal period exhibited greater number of apneas, elevated blood pressures, and plasma catecholamines, and these effects were associated with persistent oxidative stress resulting from DNA hypermethylation of antioxidant enzymes including the *Sod2* gene [88]. The autonomic dysfunction, oxidative stress, and DNA hypermethylation of the *Sod2* gene were reversed by treating neonatal rats with decitabine, an inhibitor of DNA methylation [88]. These observations demonstrate that IH is a potent activator of DNA hypermethylation, a major epigenetic mechanism. The levels of DNA methylation of 24 inflammatory-related genes were studied in children with OSA with and without high levels of C-reactive protein, and it was concluded that epigenetic modifications may constitute an important determinant of inflammatory phenotype in OSA, and FOXP3 DNA methylation levels may provide a potential biomarker for end-organ vulnerability [89]. Abnormal eNOS-dependent vascular responses in children with OSA were also reported, and this phenotype was associated with epigenetic modifications in the eNOS gene [90]. DNA hypomethylating agents, such as decitabine, are currently used in the treatment of hematopoietic malignancies [91]. DNA hypomethylating drugs might represent novel therapeutic intervention to prevent cancer progression as well as other morbidities associated with OSA.

Obesity Cancer and Sleep-Disordered Breathing

Obesity is a major comorbidity associated with sleep-disordered breathing with apnea in children and adults. Epidemiological studies have shown that obesity is also associated with increased risk of several cancer types, including colon, breast, endometrium, liver, kidney, esophagus, gastric, pancreatic, gallbladder, and leukemia, and can also lead to poorer treatment and increased cancer-related mortality [92]. The key signaling pathway linking obesity and cancer is the PI3K/Akt/mTOR cascade, which regulates cell proliferation and survival. IH may be the pathological link between OSA, cancer, and obesity, because experimental studies have shown that IH is potent activator of mTOR, which in turn increases HIF-1α. Further studies are needed to delineate signaling pathways linking combined effects of obesity and recurrent apnea with cancer.

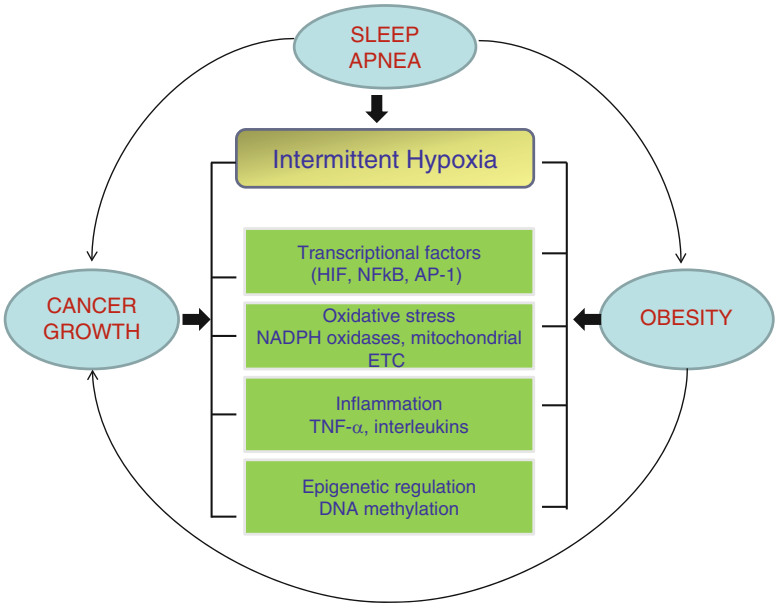

Fig. 5.3 Schematic representation of signaling pathways activated by intermittent hypoxia and their potential contribution to cancer and obesity

Summary and Perspective

It is evident from the above studies that IH mimicking the blood O_2 saturation profiles encountered with recurrent apnea is a potent activator of a variety of signaling pathways. Remarkably, many of the pathways activated by IH have been implicated in cancer initiation and progression as well as obesity (Fig. 5.3). The effects of IH on tumor progression is in the infant stage and much remains to be studied whether these signaling pathways contribute to cancer under the setting of sleep-disordered breathing with apnea.

Acknowledgments The authors' research is supported by the National Institutes of Health Grants HL76537, HL90554, and HL86493.

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Chapter 6
Association of Sleep Apnea and Cancer: From Animal Studies to Human Epidemiologic Data

F. Javier Nieto and Ramon Farré

Abstract This chapter describes results from both animal experiments and human studies that support the hypothesis that sleep apnea might increase the risk of cancer mortality. Following laboratory experiments that demonstrated the pro-oncogenic properties of hypoxia, a melanoma mouse model of sleep apnea showed that tumor growth is greatly enhanced by intermittent hypoxia that mimics the periodicity and intensity of that occurring in sleep apnea patients. This effect appears to be mediated by increased production of vascular endothelial growth factor (VEGF) and tumor vascularization and was stronger in lean than in obese mice. This chapter also describes the results of a 22-year follow-up study among participants in the Wisconsin Sleep Cohort Study showing that presence and severity of sleep apnea (as indicated by the apnea-hypopnea index) is associated with increased risk of total cancer mortality in a dose-response fashion. The association was even stronger when the hypoxemia index (percent sleep time below 90 % O_2 saturation) was used to characterize sleep apnea severity.

This chapter also reviews evidence from recent epidemiologic studies that explore whether or not sleep apnea is also associated with increased cancer incidence. Finally, the strength of the evidence in support of the hypothesis of a causal link between sleep apnea and mortality is discussed, and recommendations for future research in this area are provided.

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_6,

Keywords Melanoma mouse model • Intermittent hypoxia • Obstructive sleep apnea (OSA) • Sleep epidemiology • Hypoxia-inducible factor (HIF) • Sleep arousals • Hypoxia effect on metastasis • OSA relation to cancer mortality • Wisconsin Sleep Cohort • Hypoxemia index

Introduction

This chapter describes how observations stemming from laboratory experiments, combined with descriptive data from an epidemiologic study in humans, led to the design of a melanoma mouse model that demonstrated significantly faster tumor growth in mice subjected to intermittent hypoxia than those breathing normally. These observations, in turn, led to a further interrogation of available data from ongoing epidemiologic studies in human populations that demonstrated that obstructive sleep apnea (OSA) is associated with a clear increase in mortality from cancer. Other recent studies that have explored whether or not OSA is associated with cancer incidence are also reviewed.

The body of investigation described here is a good example of transdisciplinary research, spanning across scientific disciplines that do not traditionally meld together: basic laboratory science, animal experimentation, epidemiology, and clinical research. The results are transformative and translational and push the field of cancer and sleep epidemiology forward.

After briefly describing the laboratory basis, the following paragraphs describe the design and result of the animal models of melanoma growth as well as the human epidemiologic studies that followed. The implications of these findings and suggestions for future research are discussed.

From Cells to Humans and Mice

Hypoxia is a condition commonly found in tumors as the growth rate of their blood vessels is usually lower than that required by the high proliferation rate of tumor cells. The molecular mechanisms and specific pathways determining how hypoxia interacts with cancer cells and modulates tumor progression, metastasis, and resistance to cancer treatments have been studied in detail (see Chap. 5). Specifically, it has been well established that hypoxia increases the transcription of the hypoxia-inducible factor (HIF), thereby increasing both resistance to hypoxia and the expression of vascular endothelial growth factor (VEGF), as well as the formation of new capillaries that facilitate blood supply to the tumor and thus enhance its growth and metastasis [1–3]. Hypoxia in solid tumors is not always continuous, however, because vasomotor phenomena and transients associated with the fast growth of different tumor parts may induce slow intermittent hypoxia events ranging from a few minutes to several hours. Accordingly, the question of whether such a

low-frequency intermittent hypoxia could boost cancer progression—in the same way as continuous hypoxia—has already been investigated by some authors, using hypoxic periods within a range of 4–20 min and hypoxic levels of 5–10 % O_2 concentration [4–6]. Although some data were inconclusive, it seems well established that low-frequency hypoxygenation periods could increase tumor growth and dissemination, mainly via the upregulation of pro-angiogenic and pro-inflammatory factors.

The recurrent upper airway obstructions in OSA result in two significant pathophysiologic challenges: intermittent hypoxia and sleep arousals (sleep disruptions) at the end of each apneic event [7, 8]. Thus, the above observations logically invited the question as to whether or not OSA could accelerate cancer progression in humans. However, no evidence documenting such a relationship existed in the literature until very recently. A hint was provided in a 2008 paper from the Wisconsin Sleep Cohort that documented a strong association between sleep apnea and both total and cardiovascular mortality [9]. This paper did not analyze in detail any cause-specific mortality other than cardiovascular mortality. However, a descriptive table provided in the paper showed that the proportion of cancer deaths among Wisconsin Sleep Cohort participants with severe OSA (8 %) was considerably higher than among those without OSA (2 %). These were unadjusted proportions, did not account for follow-up time or the possibility of confounding by other factors (e.g., age, gender, obesity, smoking), and were based on small numbers (only 37 cancer deaths in total). However, these crude data were consistent with the hypothesis stemming from the laboratory experiments and motivated the design of an animal model to study the potential role of intermittent hypoxia in cancer progression. This was carried out via a mouse model melanoma progression associated with experimentally induced intermittent hypoxemia that specifically mimicked that observed in humans suffering from OSA.

A Mouse Model of Intermittent Hypoxia and Cancer Progression

Animal model research aimed at investigating whether the pathophysiologic challenges associated with OSA could promote cancer progression has started only very recently. Specifically, no data trying to reproduce the high-frequency hypoxia characteristic of OSA (up to one hypoxic event per minute) were available. The first conceptual evidence on this topic was obtained in mice in a melanoma model [10]. Melanoma cancer cells were subcutaneously injected in the flank of identical young male mice distributed in two groups. One group was kept breathing room air as the control group; the animals in the other group were subjected to a pattern of intermittent hypoxia by breathing air of varying oxygen concentration: periodic cycles of 20s of 5 % O_2 followed by 40s of room air (21 % O_2), as shown in Fig. 6.1. This pattern simulated a considerable, but in no way exceptional, rate of 60 apneic events per hour. The level of desaturation actually achieved in the freely moving animals was

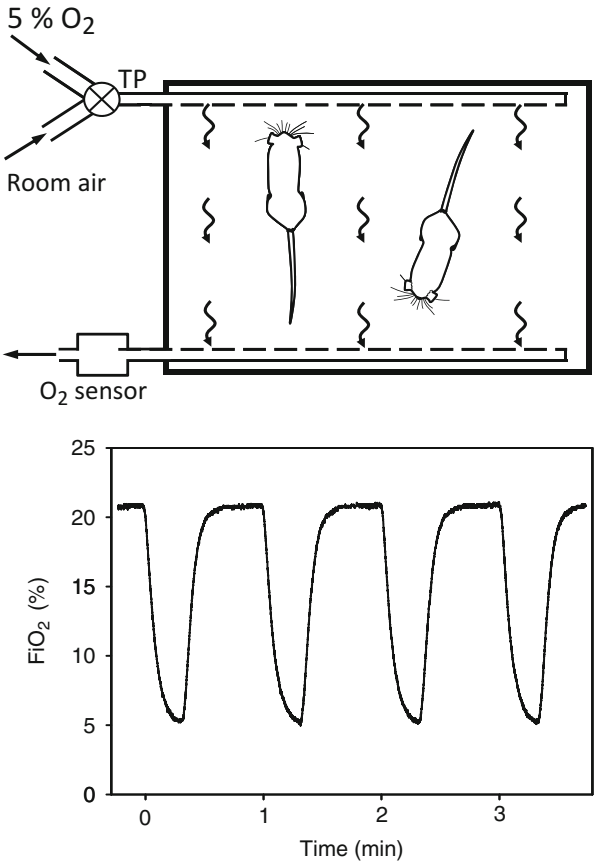

Fig. 6.1 (*Top*) Diagram of the experimental setting subjecting mice to controlled intermittent hypoxia mimicking obstructive sleep apnea. A continuous flow of gas circulated through a box (26 cm long, 18 cm wide, 6 cm high) by means of a distribution system based on several small orifices to achieve a uniform distribution of gas inside the mice cage. A silent pneumatic valve placed near the inlet of the box cyclically switched from the room air entrance (40s) to a gas reservoir of hypoxic air at an oxygen fraction (FiO_2) of 5 % (20s). An oxygen sensor was connected to the gas outlet of the box to continually measure the FiO_2 in the chamber (*bottom*) (Reproduced from Almendros et al. [11] with permission from Sleep Medicine (Elsevier))

not directly measured in the experiment, but on the basis of data previously published [12], the nadir of arterial oxygen saturation was expected to be 80–85 %, which again simulated a condition of severe OSA. The intermittent hypoxic breathing was maintained for 6 h per day during the light cycle. The growth of the melanoma tumor was measured over days to assess whether, as hypothesized, cancer progression was boosted by intermittent hypoxia mimicking OSA. The results showed that over the whole time window of observation (up to 2 weeks after the melanoma cell injection), the size of the tumor was consistently greater in the group of mice

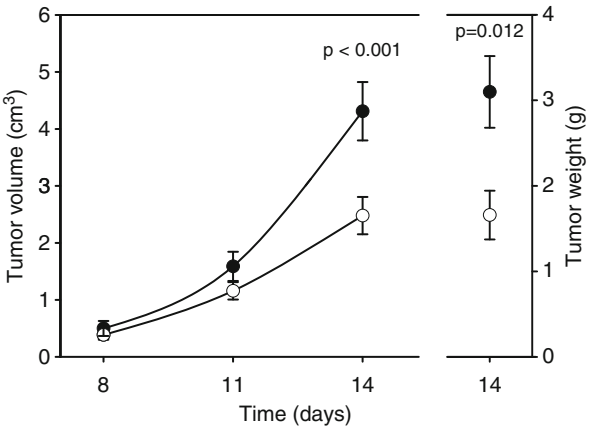

Fig. 6.2 Tumor growth in mice subjected to intermittent hypoxia mimicking obstructive sleep apnea and normoxic controls. At day 14, tumor volume in the animals subjected to intermittent hypoxia was significantly greater than that of the normoxia group. Tumor weight at day 14 was significantly greater in the intermittent hypoxia group than in the normoxia group. Values are mean ± SE (Reproduced from Almendros et al. [10] with permission from European Respiratory Journal)

subjected to intermittent hypoxia, as shown in Fig. 6.2. In fact, the size and weight of the tumor were two times greater than in the control group [10]. Moreover, histological examination of the excised tumor revealed that the tumor was more necrotic in the animals under intermittent hypoxia than in the controls; this indicator has been related to a poor prognosis.

To better understand how intermittent hypoxia heightens tumor progression, a subsequent experiment subjecting both lean and obese animals to intermittent hypoxia was carried out [11]. Because it is well known that obesity enhances tumor progression [13], the aim was to compare the cancer-boosting effects of intermittent hypoxia and obesity alone, along with those of the simultaneous application of these two noxious challenges. The size of the different tumors was measured, and they were also assessed with respect to vascularization and expression of the well-known potent angiogenic agent VEGF. The circulating levels of VEGF in peripheral blood were also measured. On the one hand, the results of this second mouse study confirmed those of the previous one on melanoma under intermittent hypoxia—i.e., a marked enhancement of tumor growth—as well as showing, as expected, that tumors under intermittent hypoxia presented a higher expression of VEGF and greater vascularization. On the other hand, the well-known finding that obesity alone increases tumor growth in mice was again confirmed. Interestingly, the tumor data in the animals subjected to intermittent hypoxia alone or obesity alone were very similar [11]. Remarkably, while a strong effect was observed in lean mice, the application of intermittent hypoxia to the obese animals did not increase tumor progression as compared with obese mice breathing room air. To a certain extent, these results were confusing, since a synergistic effect could be anticipated from the

combination of the two challenges (intermittent hypoxia and obesity). It should be mentioned, however, that the design of this two-hit study was not particularly well suited to any investigation of synergistic effects, since both the intermittent hypoxia and the obesity challenges were of considerable severity: the intermittent hypoxia regime mimicked severe OSA, and the degree of obesity in the animals—a metabolic syndrome mutant strain—was extremely high. It was, therefore, possible that the response triggered by either the intermittent hypoxia applied or the obesity level alone was so strong that the other additional challenge was unable to further increase the magnitude of the response. Experiments with low-magnitude challenges (in terms of both hypoxia and obesity) might be more suitable for assessing how these two factors, which usually coexist in OSA patients, interact to induce cancer progression. However, this study did provide data suggesting that VEGF could be a shared factor that would explain the response of tumor growth to both challenges, since a clear correlation was found between tumor sizes and circulating levels of VEGF in all the animals [11].

In addition to investigating the effect of intermittent hypoxia mimicking OSA on the growth rate of melanoma tumors, this mouse model has recently been used to analyze whether metastasis from the subcutaneous tumor to other organs is also increased by intermittent hypoxia [14]. The animals with the melanoma cells injected in the flank were either subjected to the previously described intermittent hypoxia pattern or to normoxic breathing (control group) for 30 days, then euthanized and subjected to a pathological investigation of melanoma metastasis in different organs. The result was that metastasis was detected only in the lung. Interestingly, significant differences were found when comparing the intermittent hypoxia and the control groups. Indeed, both the percentage of animals with lung metastasis and the size of the metastasis area in the lung were much higher in the intermittent hypoxia group than in the normoxic animals (Fig. 6.3). This model reproduces the whole natural process in metastasis: migration of cancer cells from the tumor stroma to the blood vessels and intravasation, attachment of tumor cells to the lung vessels and extravasation to the parenchyma, homing into the new organ, and, finally, tumor formation [15, 16]. Accordingly, this model of spontaneous metastasis suggests that the intermittent hypoxia experienced by patients with OSA could facilitate cancer dissemination. The observed increase in metastasis could, however, be a result of the enhanced increase in tumor growth induced by intermittent hypoxia, as the latter could promote earlier intravasation of cancer cells, and thus lung metastasis, even if the intravasation and homing in on the target organ were not in themselves enhanced by intermittent hypoxia. To investigate this issue, a second series of experiments was carried out as part of the aforementioned study [14]. Specifically, a model of induced (rather than spontaneous) metastasis was used. The melanoma cells were injected intravenously, reaching the lung directly through the systemic circulation, and then the formation of metastatic nodules in the lung was compared in the animals on normoxia and those on intermittent hypoxia mimicking OSA. This model, which focuses on the final steps of the metastatic cascade (adhesion to the lung vessel walls, intravasation, homing, and tumor formation), with no interference from the potential effects of a primary tumor, showed a tendency to greater metastasis in the animals under intermittent hypoxia [14].

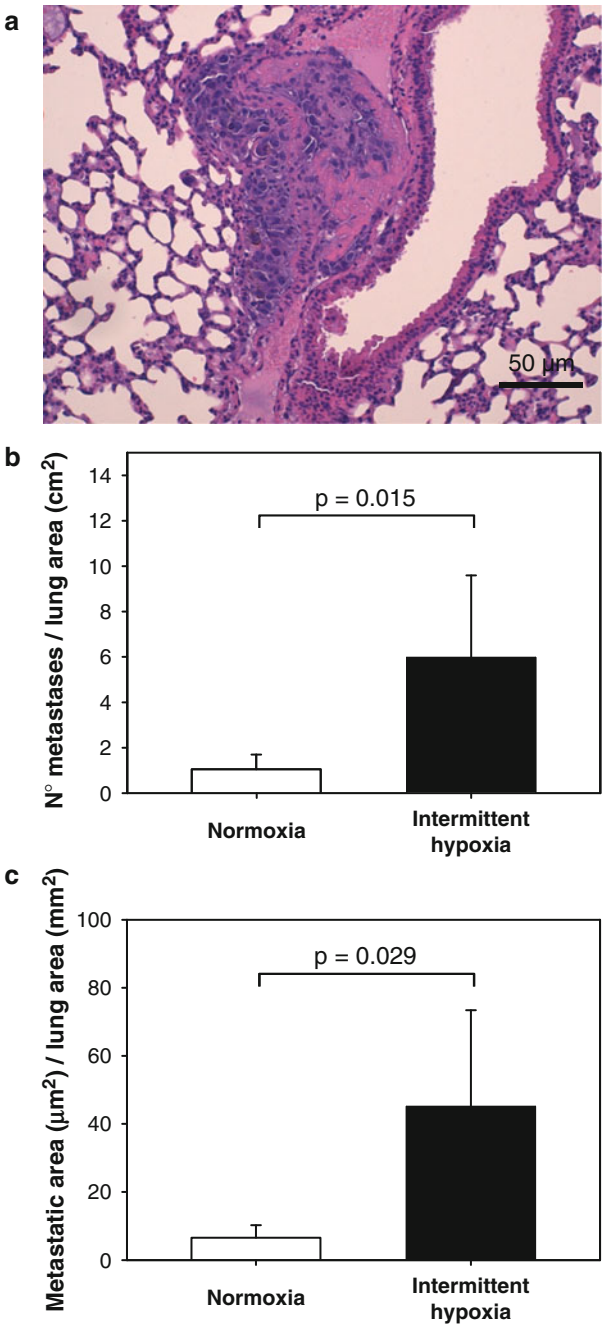

Fig. 6.3 Spontaneous lung melanoma in mice subjected to intermittent hypoxia mimicking obstructive sleep apnea and normoxic controls. (**a**) Example of histological preparation showing lung melanoma cells clearly differentiated from healthy tissue by loss of organization and cell pigmentation. (**b**) Total number of metastases per lung area (cm^2). (**c**): metastatic area (μm^2) per lung area (mm^2) in the normoxia and intermittent hypoxia groups. Values are mean ± SE (Reproduced from Almendros et al. [14] with permission from Respiratory Physiology and Neurobiology (Elsevier))

Back to Humans: OSA and Cancer Mortality

Once the melanoma model results confirmed the working hypothesis, it was time to analyze in further detail the preliminary observation possibly linking OSA with cancer mortality in the Wisconsin Sleep Cohort [9] (see above).

Established in 1989, the Wisconsin Sleep Cohort is the oldest ongoing cohort study of sleep apnea and other sleep disorders in a population-based sample in the world [17]. It is defined as "population based," referring to its sampling frame being the general population rather than patients attending health-care facilities. Specifically, study participants were recruited from rosters of Wisconsin state government employees, ranging from administrative and clerical to educators and managerial professionals. A total of 2,940 people were invited and 1,546 participated in at least one baseline examination that included a full 18-channel polysomnography (PSG) and an extensive evaluation of the participants' sociodemographic characteristics, health history, behaviors, psychosocial, cognitive status, physical exam (including blood pressure and anthropometric measurements), and collection of biological specimens—urine and blood. Follow-up includes both passive methods (e.g., linkage with vital statistics to assess mortality) and active follow-up with repeated contacts that for most participants has included additional exams (with repeated PSG). Detailed descriptions of the methods of this study can be found in the numerous reports that have documented the relation between OSA and hypertension [18], cerebrovascular disease [19], or depression [20], among many other publications.

As mentioned above, a 2008 manuscript from the Wisconsin Sleep Cohort documented a strong association between sleep apnea with both total and cardiovascular mortality [9]. This study involved a prospective analyses of a cohort of 1,522 Wisconsin Sleep Cohort participants followed for up to 18 years (up to March 2008), during which a total of 80 deaths were observed. Relative to those with no OSA and after controlling for possible confounding variables (age, gender, and body mass index), the adjusted relative hazards of total and cardiovascular mortality associated with severe OSA category were 3.0 (95 % confidence interval [CI], 1.4, 6.3) and 2.9 (95 % CI, 0.8, 10.0), respectively. For both outcomes, there was clear evidence of dose-response relationship of cancer mortality with increasing OSA severity, and the associations were stronger when participants who were treated with CPAP in the course of the follow-up were excluded from the analyses.

The original aims of that study did not include examining the associations between OSA and cause-specific mortality other than cardiovascular disease and stroke. In the absence of a previous hypothesis (no epidemiologic or animal studies had explored the possible association between OSA and cancer up to that time), the apparent increase in the crude proportion of cancer deaths among study participants with severe OSA (see above) was attributed to a statistical artifact due to the relatively small number of cancer deaths (Terry Young, 2012, personal communication) and was not analyzed further.

After the results from the melanoma mouse model were presented at an international conference in the spring of 2011 in Barcelona, Spain, the decision was made to update the analyses of the mortality follow-up of the Wisconsin Sleep Cohort and analyze in detail the relation between OSA and cancer-specific mortality [21]. For these

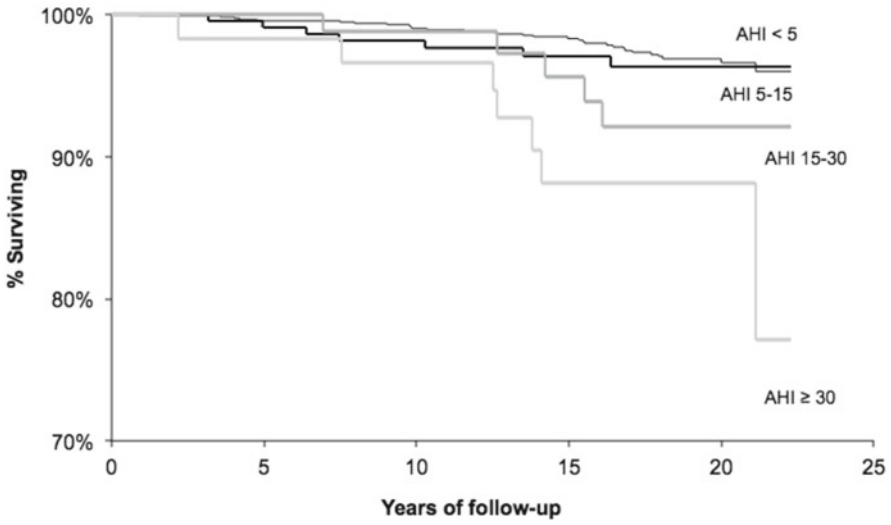

Fig. 6.4 Survival free of cancer mortality according to categories of sleep-disordered breathing, Wisconsin Sleep Cohort, 1989–2011; Kaplan-Meier estimates. *AHI* apnea-hypopnea index (Reproduced from Nieto et al. [21] with permission from the American Journal of Respiratory and Critical Care Medicine (American Thoracic Society))

analyses, available data existed for three more years of follow-up (through the end of 2011) for a total of up to 22 years—median 18 years. The total number of deaths in the cohort was now 112, of which 50 were classified as cancer deaths (instead of 37 as in the original 2008 report). Categories of OSA severity were defined according to widely used criteria [22] as absent (apnea-hypopnea index [AHI] <5), mild ($5 \leq$ AHI <15), moderate ($15 \leq$ AHI <30), and severe (AHI ≥ 30). Of the 50 cancer deaths, 7 occurred among participants without OSA at baseline, 7 among those with mild OSA, 5 in those with moderate, and 7 among those with severe OSA; the corresponding rates of cancer mortality (per 1,000 person-years) were 1.5, 1.9, 3.6, and 7.3, respectively. Figure 6.4 demonstrates how the survival over time progressively decreased with increasing levels of OSA severity. Other features and some of the main results from this study are summarized in the first column of Table 6.1. The main multivariate analyses (controlling for age, gender, body mass index, and smoking) revealed that, compared to subjects without OSA, the adjusted relative hazards of cancer mortality were 1.1 (95 % confidence interval [CI], 0.5–2.7) for mild OSA, 2.0 (95 % CI, 0.7–5.5) for moderate OSA, and 4.8 (95 % CI, 1.7–13.2) for severe OSA (p for trend $=0.0052$). Remarkably, these hazard ratios were stronger than those reported earlier for either total or cardiovascular mortality [9] and remained virtually unchanged after further adjustment for other possible confounders (physical activity, alcohol use, education, diabetes, waist circumference, and sleep duration).

When, instead of the AHI, the hypoxemia index (HI, percent sleep time spent under 90 % oxygen saturation) was used to characterize OSA, the association was even stronger. In the absence of a predefined set of criteria, the cutoff points to define the HI categories for this analysis were based on the same quantile

Table 6.1 Summary of published epidemiologic studies on the association between obstructive sleep apnea (OSA) and cancer risk (mortality or incidence)

	Nieto et al. [21]	Campos-Rodriguez et al. [23]	Christensen et al. [24]
Setting	Wisconsin, USA	Spain, multicenter	Copenhagen, Denmark
Sampling frame (exclusions)	Population based, state employees (excluding those with serious medical conditions)	Clinic based, patients seen in sleep clinics (excluding those with previous diagnosis of cancer)	Population based, random population sample (excluding those with previous diagnosis of cancer)
Number of participants	1,522	4,910	8,783 (snoring analysis), 5,894 (sleepiness analysis)
Length of follow-up (median)	18 years	4.5 years	13 years
OSA assessment	Full PSG	Respiratory polygraphy (68 %) Full PSG (32 %)	Snoring, breathing pauses, sleepiness (self-report)
Outcome	Cancer mortality, n = 50	Cancer incidence, n = 261	Cancer incidence (n = 1,985; 1,097 for sleepiness analysis)
Main results: adjusted hazard ratios (HR) for OSA categories defined as indicated	AHI (<5: ref.) 5–14.9: HR = 1.1 15–29.9: HR = 2.0 ≥30: HR = 4.8[a] HI (<0.8 %: ref.) 0.8–3.5 %: HR = 1.6 3.6–11.2 %: HR = 2.9 >11.2 %: HR = 8.6[a]	AHI tertiles (<18.7: ref.) 18.7–43: HR = 1.1 ≥43: HR = 1.2 HI tertiles (<1.2 %:ref.) 1.2–12 %: HR = 1.6[a] >12 %: HR = 2.3[a]	Snoring (no snoring: ref.) Sometimes: HR = 1.0 Often: HR = 1.0 Don't know: HR = 1.0 Number of sleep symptoms (0: ref.) 1: HR = 1.2 2–3: HR = 1.2
Confounders included in models	Age, sex, BMI, smoking, physical activity, alcohol use, education, diabetes, waist circumference, and sleep duration	Age, sex, BMI, smoking, alcohol, type of study, hospital	Age, sex, BMI, marital status, education, physical activity, alcohol, and smoking
Stratified analyses	Association present in both genders and within categories defined according to age, obesity (slightly stronger among the nonobese), and sleepiness status	Younger: $HR_{HI>12\,\%} = 2.9$[a] Older (≥65): $HR_{HI>12\,\%} = 1.6$ Females: $HR_{HI>12\%} = 1.8$ Males: $HR_{HI>12\,\%} = 2.6$[a] No difference according to obesity status	For sleepiness, association present among young (HR = 4.1 only and 5 cases) but not among old subjects (HR = 0.9)

(continued)

Table 6.1 (continued)

	Nieto et al. [21]	Campos-Rodriguez et al. [23]	Christensen et al. [24]
Cancer subtypes	Same association after exclusion of nonsolid cancers	Not reported	For sleepiness Alcohol-related cancers (HR = 4.9) Virus-related cancers (HR = 2.7) For 2–3 OSA symptoms Smoking-related cancers (HR = 1.7)

PSG polysomnography, *AHI* apnea-hypopnea index, *HI* hypoxemia index, *HR* hazard ratio, *REF* reference category for the hazard ratios
[a]95 % confidence limits for the hazard ratio do not include 1.0

distribution as the AHI cut points defining mild, moderate, and severe OSA. As shown in the summary in Table 6.1, the hazard ratios showed a clearly graded dose-response relationship that was highly statistically significant (p for trend = 0.0008); those with severe OSA according to the HI criterion (HI ≥ 11.2 %) were more than eight times more likely to die of cancer than those without OSA (HI < 0.8 %).

In this study, stratified analysis revealed that the association between OSA and cancer mortality was observed across groups defined by gender, age, and presence of sleepiness. When stratified by obesity status, the association was slightly stronger among the nonobese—an observation that might be interpreted as consistent with the experimental results described above showing that intermittent hypoxemia increases melanoma progression in lean but not in obese mice [11]. Given the small number of events, the study was not able to analyze mortality from specific cancers.

OSA and Cancer Progression, Cancer Incidence, or Both?

The outcome of Nieto et al.'s study was death that had been attributed to cancer, irrespective of the date of cancer incidence and/or date of diagnosis [21]. Consequently, one important limitation of this study is that it was unable to discern whether the observed association was attributable to an increased incidence of cancer or to an accelerated progression (decreased survival) after cancer initiation. The in vitro and animal studies showing a role of intermittent hypoxia in promoting primary tumor growth and metastasis provide a basis in support of the latter. At this time, there are no animal models addressing the question as to whether or not intermittent hypoxia mimicking OSA promotes tumorigenesis. This is a crucial step in cancer pathology since it is the initial phenomenon in the whole cascade: the transformation of a normal or cancer stem cell into a malignant cell capable of triggering a cancerous process. However, there are some indirect data in the literature suggesting that intermittent hypoxia could facilitate cell malignization. One of the most

clearly suggestive data is the fact that OSA patients experience oxidative stress [25, 26]; more particularly, increased markers of DNA oxidation and damage have been detected in patients with this sleep breathing disorder [27, 28]. It is to be expected that an oxidative stress challenge inducing DNA oxidation could result in mutations leading to cell malignization. This process could be facilitated by the inflammatory background of patients with OSA [8, 29–31].

In the absence of animal models documenting a role of intermittent hypoxemia on increased carcinogenesis, two recent epidemiologic studies have explored whether OSA is associated with cancer incidence with mixed results [23, 24]. Campos-Rodriguez et al. analyzed data from a retrospective multicenter cohort study of adult patients referred to sleep laboratories in Spanish hospitals because of suspicion of OSA [23]. The study involved a total sample of 5,320 patients followed for a median of 4.5 years. OSA status was determined by respiratory polygraphy in about two-thirds of the patients; the rest received a full PSG. In this study, OSA was not associated with cancer incidence when assessed using the AHI (either using the same cutoff points to define OSA severity as in the study by Nieto et al. [21] or according to AHI tertiles—see second column of Table 6.1). However, when the HI was used, a statistically significant increase in cancer incidence with increasing levels of OSA (tertiles of HI) was found—the adjusted hazard ratio of cancer incidence associated with a ten-unit increase in the HI was 1.1 (95 % CI, 1.0–1.1). The association between HI and cancer incidence was slightly stronger when patients that were treated over the follow-up were excluded. In stratified analyses, the relative hazards were significantly higher only among younger (<65 years old) and among male patients—the association among older subjects and among women was not statistically significant.

In another population-based study conducted in Denmark, 8,783 participants in the third wave of the Copenhagen City Heart Study were followed for an average of 13 years to assess the relation between OSA symptoms at baseline and incidence of cancer, overall and by cancer subtypes [24]. The main independent variable in this study was the participant's self-report of snoring and breathing cessations—daytime sleepiness (assessed using the Epworth Sleepiness Scale [32]) was available on 5,894 participants in one of the follow-up visits in this study. Overall, this study found no relation between OSA symptoms and cancer incidence (see third column in Table 6.1). However, in subset analyses, a strong association was found between sleepiness and cancer incidence among younger participants (<50 years), although this observation was based on just five cases in the top category of sleepiness (Epworth score > 15). Given the large sample size and long follow-up time (a total of 1,985 incident cases of cancer were observed), analyses according to type of cancer (classified as "alcohol related," "virus related," "hormone related," and "smoking related") were also reported in this study. In this subset analyses, significant associations were found between the number of OSA symptoms and smoking-related cancers and between sleepiness and both alcohol- and virus-related cancers. These results should be interpreted with caution because of the potential multiple comparisons problem. This study is also limited because of the characterization of OSA exclusively based on self-reported symptoms [33].

Overall, the evidence that OSA is associated with increased incidence of cancer is not entirely consistent at this time. If the strong association between OSA and cancer mortality found in the Wisconsin Sleep Cohort [21] is replicated in other studies, particularly when combined with the in vitro evidence and the results from animal models, this would suggest that the main effect is through accelerated cancer progression. The latter could be through accelerated tumor growth, increased likelihood of metastasis, and resistance to treatment. A carcinogenic effect or OSA cannot be ruled out at this point, however, and the suggestive epidemiologic evidence provided by at least one study [23] suggests that this question needs to be further explored in future studies.

Conclusions and Future Directions

The research presented here, ranging from in vitro to animal and human studies, provides strong evidence that OSA might be etiologically implicated in cancer progression. The evidence with regard to cancer incidence (carcinogenesis) is more limited. Nevertheless, the evidence discussed in the preceding paragraphs has evolved only in the last 2–3 years, and it raises at least as many questions as it answers.

The results obtained in the melanoma mouse model under intermittent hypoxia suggest that this challenge could promote cancer growth and dissemination in patients with OSA. However, as with any other initial experimental findings, these data should be interpreted carefully, taking into account the limitations of this animal model. The first point to take into consideration is that melanoma, although simple and well characterized from an experimental viewpoint, is not necessarily representative of other types of cancer. Taking into account that tumor growth and metastasis are dependent on the type of cancer and the specific target organ, the kind of experiment carried out with melanoma must also be performed with a more representative variety of cancer models. A second important subject for debate is the time/amplitude/duration pattern of intermittent hypoxia. This question is not specific to cancer studies but applies to OSA research with animal models in general. In fact, we do not yet know the pattern of intermittent hypoxia that best mimics OSA in rodents, so dose-response studies are needed to investigate how the pattern of intermittent hypoxia modulates cancer. In this respect, the potential effect of the times of the initial application of intermittent hypoxia and injection of cancer cells should also be studied, as the behavior of the tumor cells could depend on the degree of animal preconditioning to the hypoxic regime.

The hypoxic challenge can affect cancer progression, either through direct action on malignant cells or indirectly through systemic pathways. The most well-known systemic influence is the tumor vascularization promoted by VEGF via the bloodstream. However, there is very limited information on the direct effect of intermittent hypoxia on cell proliferation (required for tumor growth) or cell migration/adhesion capacity (involved in metastasis). Some reports suggest that these functions of cancer cells cultured in vitro (i.e., freed from systemic influence) are poorly affected by intermittent hypoxia. Specifically, very recent data suggest that

melanoma cell proliferation in vitro is unaffected by intermittent hypoxia, but that proliferation increases when the melanoma cells are co-cultured with macrophages and more markedly when they were pre-exposed to intermittent hypoxia. These findings clearly suggest that the immune system plays a role in cancer progression in OSA [34]. These data confirm that macrophages can modulate tumor function through local secretion of growth factors, cytokines, and proteases [35]. Therefore, the fact that intermittent hypoxia can indirectly boost cancer progression reinforces the need to establish animal models that seek to mimic OSA as realistically as possible and, more particularly, combine intermittent hypoxia with factors such as obesity and sleep disruption that are able to independently modulate cancer risk and usually coexist in patients with OSA. The value of such an approach is highlighted by very recent data indicating that mice subjected to sleep disruption mimicking OSA presented an increased tumor growth rate compared with control animals with no sleep alteration [36]. Interestingly, as in the case of intermittent hypoxia, it seems that tumor growth enhancement is associated with increased recruitment of macrophages in the tumoral microenvironment [37].

Another issue that should be addressed in future research is the interaction with aging, as cancer appears more frequently in older individuals as a result of the accumulation of mutations over the course of their life. Accordingly, research on old animal models rather than young ones—which are predominant in cancer research—would provide insight into the role played by intermittent hypoxia in carcinogenesis and improve our interpretation of potential increases in cancer incidence and mortality in patients with this sleep breathing disorder.

With respect to the epidemiologic evidence in humans, the evidence published so far is clearly a first step that needs to be replicated and explored in further detail in future studies [33, 38, 39]. Determining whether OSA is associated with increased cancer incidence, accelerated progression, or both, needs to be addressed (see above). This could include longitudinal studies assessing the relation between OSA and survival after cancer diagnosis. Furthermore, most of the epidemiologic evidence up to this point has focused on total cancer rather than on specific cancer types. The hypothesized mechanisms described above and elsewhere (Chap. 5) would suggest a rather generic effect of intermittent hypoxia on a broad range of cancers, at least on solid tumors. Furthermore, as discussed elsewhere [21], this limitation is an unlikely explanation for the strong associations between OSA and mortality found in the Wisconsin Sleep Cohort. If associations are specific for distinct cancer sites but not others, combining all cancer mortality will result in dilution of effects and thus tend to bias the results towards the null.

In any event, the existing epidemiologic evidence linking OSA and cancer progression fits some of the key classic causality criteria [40]: the association is biologically plausible (in view of the existing pathophysiologic knowledge and in vitro evidence); the existing longitudinal evidence supports the existence of temporality in the cause-effect association; the effects are strong; there is evidence of a dose-response relationship; and it is consistent with animal experimental models and other evidence. Lacking is evidence regarding another important criterion: that treatment of OSA will result in a decrease in cancer mortality. Future studies in this area are critical.

If verified in future studies, the implications of the evidence presented here are profound. OSA might be one of the mechanisms by which obesity is a detrimental factor in cancer etiology and natural history. From a clinical standpoint, assessing the presence of OSA (particularly in overweight or obese patients) and treating it if present might have to become a routine part of the clinical management of cancer patients.

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Chapter 7
Shift Work, Obesity, and Cancer

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Abstract Experimental data has consistently demonstrated that disruption of circadian rhythm can promote carcinogenesis in animal models, and epidemiologic data continues to accumulate indicating that disrupting circadian rhythm by shift work increases the risk of cancer in humans. In this chapter, we provide a comprehensive review of epidemiologic studies, both retrospective and prospective, on a worldwide basis, examining the association of shift work with cancer, particularly breast and prostate cancer. We also provide information on the relation of shift work to colorectal, endometrial, lung, skin, and bladder cancer. Also discussed are issues surrounding the relation of shift work to weight gain and obesity and the possibility that obesity may mediate the effect of shift work on cancer.

Keywords Melatonin • Shift work • Obesity • Circadian clock • Night work trades • Breast cancer • Prostate cancer

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_7,

Introduction

Melatonin (5-methoxytryptamine) is an indoleamine produced primarily by the pineal gland, which is secreted exclusively during the dark phase of the light-dark cycle in humans [1]. Several decades ago, reports indicated that melatonin possesses oncostatic properties, leading to novel hypotheses that diminished secretion of melatonin might promote the development of cancer [2–5]. Growing evidence also demonstrates that visible light, including electric light, can acutely suppress melatonin production [4, 5]—a phenomenon often referred to as "circadian disruption" particularly if it occurs at night, as commonly observed in shift workers [6].

In 2007, the International Agency for Research on Cancer classified shift work as a possible carcinogen, based on convincing experimental evidence and supportive, but still limited, epidemiologic data [7]. Indeed, experimental data has consistently demonstrated that circadian disruption can promote carcinogenesis in animals; specifically, exposure to light at night and phase shifts in the light-dark cycle have accelerated tumor development in rodents (reviewed in [7]). In humans, epidemiologic data continues to accumulate, with the majority of existing studies indicating that shift work is related to a modest increase in the risk of breast cancer. A recent systematic review and meta-analysis, published in 2013, found that women with a history of night shift work had a 21 % higher risk of breast cancer compared to women without night work experience (RR = 1.21, 95 % CI = 1.00–1.47) [8]. Initial studies have identified links between shift work and other cancers as well, although this evidence is very limited.

Increasing evidence also suggests that shift workers are more often obese than non-shift workers, which has been attributed, in part, to the negative effects of circadian disruption on glucose and lipid metabolism and reduced thermogenesis related to eating food at night [9]. The direct effects of circadian clock genes have been implicated in metabolism and therefore may contribute to these mechanisms as well [9]. In addition, obesity is an important risk factor for many cancers, including breast cancer, endometrial cancer, colorectal cancer, among others [10]. As a result, obesity is a potential mediator of the observed association between shift work and cancer risk, and it is important to appraise whether previous analyses have evaluated this hypothesis. This chapter will review epidemiologic studies of shift work and cancer risk, with additional emphasis on the role of obesity in this association.

Epidemiologic Studies

To date, 17 epidemiologic studies have examined the association of shift work and breast cancer; 13 of these studies have been conducted using a retrospective study design (i.e., the exposure was measured after the outcome occurred), while four studies have been performed prospectively (i.e., the exposure was measured before the outcome occurred) (Table 7.1). Overall, most studies have found some evidence

Table 7.1 Previous epidemiologic studies of shift work in relation to breast cancer risk among women[a]

Study author and date	Study design	Study base	Exposure	Outcome	Results
Tynes (1996) [14]	Retrospective, nested case-control study	Cohort of all 2,619 female radio and telegraph operators in Norway during 1920–1980	Individual employment histories obtained from Norwegian seamen registries	50 cases occurring between 1961 and 1991, identified through the Norway Cancer Registry; 4–7:1 age-matched controls	Positive association
Schernhammer (2001) [23]	Prospective cohort study	78,562 women participating in the Nurses' Health Study	Self-reported history of rotating night shift work	2,441 cases occurring between 1988 and 1998, identified by self-report and verified by medical records	Positive association
Davis (2001) [19]	Retrospective case-control study	Women, aged 20–74 years, who lived in the Seattle metropolitan area during 1992–1995	Self-reported lifetime occupational history	813 cases occurring between 1992 and 1995, identified by the Cancer Surveillance System of the Fred Hutchinson Cancer Center (Seattle); frequency-matched controls (5-year age strata), identified by random-digit dialing	Positive association
Hansen (2001) [11]	Retrospective case-control study	Women, aged 30–54 years, with a work history in Denmark and born during 1935–1959	Employment histories were reconstructed from national employment records, then combined with survey information about jobs involving primarily night work	7,035 cases having occurred by 1989, identified by the Danish Cancer Registry; 1:1 age-matched controls, identified from the Central Population Registry	Positive association
Schernhammer (2006) [24]	Prospective cohort study	115,022 women participating in the Nurses' Health Study II	Self-reported history of rotating night shift work	1,352 cases occurring between 1989 and 2001, identified by self-report and verified by medical records	Positive association
Lie (2006) [15]	Retrospective, nested case-control study	Cohort of 44,835 nurses educated between 1914 and 1980 in Norway	Individual employment histories obtained from the Norwegian nurse registry, combined with census data in 1960, 1970, and 1980	537 cases occurring between 1960 and 1982, identified by the Norway Cancer Registry; controls were matched 4:1 using incidence density sampling within the Norwegian nurse registry	Positive association

(continued)

Table 7.1 (continued)

Study author and date	Study design	Study base	Exposure	Outcome	Results
O'Leary (2006) [20]	Retrospective case-control study	Women, aged <75 years, who had lived on Long Island at least 15 years in 1996–1997	Self-reported employment histories obtained by interview	576 cases occurring between 1996 and 1997, identified by rapid ascertainment from local hospitals; frequency-matched controls (in 5-year age strata), identified by random-digit dialing and government records	No association
Schwartzbaum (2007) [22]	Retrospective cohort study	1,148,661 female employees working at least half-time in 1970 in Sweden	Census information about employment histories, combined with survey information about jobs involving primarily night work	70 cases occurring between 1971 and 1989 among shift workers, identified by the Swedish Cancer Register; comparison group was all other women in the study base	No association
Pukkala (2009) [25]	Prospective cohort study	7,454,847 women, aged 30–64 years, in the 1960–1990 censuses in Denmark, Finland, Iceland, Norway, and Sweden	Occupations reported on censuses between 1960 and 1990	7,682 cases occurring through 2005 in nurses, identified by national cancer registries; comparison group was all other women in the study	Positive association
Pronk (2010) [26]	Prospective cohort study	73,049 women, aged 40–70 years, cancer-free, living in Shanghai (China), and having been employed outside of the home in 1996–2000	Self-reported employment histories obtained by interview	717 cases occurring between 1996/2000 and 2007, identified by biennial interviews and the Shanghai Cancer Registry and verified by home visits and medical records	No association
Pesch (2010) [21]	Retrospective case-control study	Women, aged ≤80 years, living in Bonn, Germany, during 2000–2004	Self-reported occupational histories obtained by interview	1,143 cases occurring within 6 months of study enrollment, identified from major hospitals in the region; frequency-matched controls (in 5-year age strata) from population registries	No association

Villeneuve (2011) [17]	Retrospective case-control study	Women, aged 25–75 years, living in two specific areas of France	Self-reported occupational histories obtained by interview	1,230 cases occurring between 2005 and 2007, identified from major cancer hospitals; frequency-matched controls (5-year age strata), identified randomly by telephone directory	Positive association
Lie (2011) [16]	Retrospective, nested case-control study	Cohort of 49,402 Norwegian nurses	Lifetime occupational history obtained by interview	699 cases occurring between 1990 and 2007, identified by the Cancer Registry of Norway; 2:1 frequency-matched controls (in 5-year age strata)	Positive association
Menegaux (2012) [18]	Retrospective case-control study	Women, aged 25–75 years, living in two specific areas of France	Lifetime occupational history obtained by interview	1,232 cases occurring between 2005 and 2007, identified from major cancer hospitals; frequency-matched controls (in 10-year age strata), identified randomly by telephone directory	Positive association
Hansen (2012) [12]	Retrospective, nested case-control study	Cohort of 91,140 female members of the Danish Nurses Association	Lifetime occupational history obtained by interview	267 cases occurring between 2001 and 2003, identified by the Danish Cancer Registry; age-matched controls (1 year), identified by incidence density sampling	Positive association
Hansen (2012) [13]	Retrospective, nested case-control study	Cohort of 18,551 women who served in the Danish military between 1964 and 1999	Self-reported occupational history	132 cases occurring between 1990 and 2003, identified by the Danish Cancer Registry; age-matched controls were selected by incidence density sampling	Positive association

[a]Positive association denotes a statistically significantly increased risk; negative association denotes a statistically significantly decreased risk; and no association signifies associations, which did not reach statistical significance

in favor of an association between shift work and breast cancer risk, although few studies have examined shift work exposure in relation to other cancers; still, initial evidence suggests that there may be a link between shift work and prostate cancer.

Retrospective Studies of Shift Work and Breast Cancer Risk

Nine retrospective studies have indicated that shift work might be associated with a higher risk of breast cancer, including three studies in Denmark, three studies in Norway, two studies in France, and one study in the United States. In the first Danish study, a population-based case-control analysis with 7,035 cases was utilized to evaluate breast cancer risk among women in "night work trades" versus "non-night work trades" [11]. This study found that those in "night work trades" had a 50 % higher risk of breast cancer (OR = 1.5, 95 % CI = 1.3–1.7) compared to those in "non-night work trades." "Night work trades" were defined as occupations in which ≥60 % of employees worked at night, based on a national employment survey; "non-night work trades" were defined as those with <40 % of employees working at night. It is notable that exposure status was defined based on thresholds derived from national-level data; in other words, specific information on each participant's night work exposure was not collected. This approach probably led to some exposure misclassification, which implies that the reported association is likely to be underestimated.

Two further studies in Denmark focused specifically on shift worker populations, in which detailed employment histories were obtained from individual participants. One study was a case-control analysis with 267 breast cancer cases, nested within a large cohort of members from the Danish Nurses Association. In this study, women with a history of rotating night shift work—after midnight—had an 80 % increased risk of breast cancer compared to women with a history of permanent day work (OR = 1.8, 95 % CI = 1.2–2.8); indeed, women with a history of both rotating shift work and permanent night work had an even higher risk compared to permanent day workers (OR = 2.9, 95 % CI = 1.1–8.0) [12]. A second case-control study (n = 132 breast cancer cases), nested within a cohort of female military employees in Denmark, also found that long-term night shift work was related to a higher risk of breast cancer (e.g., p-trend = 0.03, OR = 2.1, 95 % CI = 1.0–4.5 for ≥15 years of night shift work vs. none) [13]. Although these studies of shift worker populations had much smaller case numbers—and therefore lower power—compared to the initial study on night work trades in Denmark, the greater accuracy of exposure measurements based on individual employment histories probably enabled the detection of significant associations. In total, all three Danish studies provide evidence in support of an association between night shift work and breast cancer risk.

In Norway, a study of 2,619 radio and telegraph operators reported that the standardized incidence ratio for breast cancer over 30 years was significantly higher for women in this occupation compared to those in the general population (SIR adjusted for duration of employment = 1.5, 95 % CI = 1.1–2.0) [14]. Moreover, in a subset of this cohort with detailed work histories, there was possible evidence to suggest that

cumulative exposure to shift work was related to breast cancer risk in women aged <50 years (p-trend = 0.31; OR = 1.9, 95 % CI = 0.5–7.0 comparing high levels of shift work vs. none) and women aged ≥50 years (p-trend = 0.13; OR = 4.3, 95 % CI = 0.7–26.0). However, a limitation of this study was the small number of breast cancer cases (n = 50) included in the case-control study, which led to wide confidence intervals; thus, the interpretation of these data is limited, particularly in the stratified analyses.

Two additional studies evaluated associations between shift work and breast cancer within a cohort of more than 40,000 nurses in Norway. One of these studies reported that longer duration of night work was associated with an increased risk of breast cancer (n = 537 cases; p-trend = 0.01, OR = 2.21, 95 % 1.10–4.45 comparing nurses with 30+ years vs. none) [15]. Although this finding was significant, participants' exposure status was determined based on assumptions about which clinical positions tended to involve night work rather than individual information about exposure status; thus, exposure misclassification probably limited the ability to detect stronger associations in this study. A second study in this cohort found that women working 5+ years, with schedules involving 5+ consecutive night shifts, had a higher breast cancer risk compared to those who never worked night shifts (OR = 1.6, 95 % CI = 1.0–2.4) [16]. Unlike the first study of Norwegian nurses, this study involved an extensive telephone interview to ascertain each individual's employment history, which likely provided more accurate exposure classification regarding night work. Overall, both of these Norwegian studies support the notion that night shift work and breast cancer are related.

In addition, two case-control studies were conducted in France, involving 2,500 women (1,200 of whom had breast cancer) with extensive employment histories. One study reported that working as a nurse for ≥10 years might be associated with a higher risk of breast cancer compared to working in other occupations (OR = 1.4, 95 % CI = 0.9–2.1), although this association did not reach statistical significance [17]. However, in a second analysis using this study population, women with any history of night work had an elevated breast cancer risk when they were compared to women who never worked at night (OR = 1.35, 95 % CI = 1.01–1.80) [18]. Importantly, additional exposure metrics related to frequency and duration of night work indicated that longer-term exposure was related to an increased risk of breast cancer as well (e.g., OR = 1.40, 95 % CI = 1.01–1.92 for women with ≥4.5 years of night work experience vs. none). As noted for other studies, the availability of detailed information on employment history from each participant was an important strength of this study design, which enabled better detection of the associations of interest. In general, then, results from these French studies suggest that an association might exist between shift work and breast cancer risk in women.

Finally, in a US-based case-control study, extensive employment histories were used to identify relations between night shift work and breast cancer in the Seattle, Washington area [19]. In particular, women with a history of overnight shift work had greater odds of breast cancer than women who had never worked such shifts (n = 813 cases; OR = 1.6, 95 % CI = 1.0–2.5), and there was evidence of a linear trend toward greater risk of breast cancer with increasing time spent on overnight shifts (p-trend = 0.04,

OR = 2.3, 95 % CI = 1.0–5.3 comparing women with ≥5.7 h per week vs. none). Although these associations were borderline significant, the elevated risk was apparent in analyses that dichotomized the shift work exposure (i.e., ever vs. never categorization) and evaluated a dose-response relation; therefore, this study lends further support for a potential relation between shift work and breast cancer risk.

Four studies with retrospective designs identified no association between shift work and breast cancer risk. One case-control study, nested within the Long Island Cohort, found no association between shift work and risk of developing breast cancer (e.g., OR = 1.04, 95 % CI = 0.79–1.38 comparing women with evening or overnight shift work vs. none). However, the authors limited exposure recall to the past 15 years of work experience, which may have biased the study toward a null result if shift work exposure prior to that time period is etiologically relevant for breast cancer [20]. Another potential limitation of this study is the unusually high incidence of breast cancer in the Long Island area, which possibly could have masked the effect of shift work on breast cancer. As a result, these findings may not provide insight into the association between shift work and breast cancer in the general population.

Another nested case-control study, conducted in Germany, found that women with a history of shift work had a similar breast cancer risk compared to women with no history of shift work (OR = 0.96, 95 % CI = 0.67–1.38), and results were similar when analyses focused on night shift work specifically (OR = 0.91, 95 % CI = 0.55–1.49 comparing night shift workers vs. non-shift workers) [21]. Other shift work metrics, such as greater cumulative number of lifetime night shifts and greater duration of night shift work, were associated with nonsignificantly elevated risks of breast cancer (e.g., OR = 1.73, 95 % CI = 0.71–4.22 comparing women with ≥807 cumulative lifetime nights shifts vs. none and OR = 2.48, 95 % CI = 0.62–9.99 comparing women with ≥20 years of night shift work vs. none). However, the number of breast cancer cases was relatively small for analyses of night shift work, cumulative shift work, and shift work duration given the low prevalence of shift work (13 %) in this population; as a result, wide confidence intervals made interpretation difficult.

Finally, a retrospective cohort study among >1 million female employees in Sweden found that shift work (defined as occupations that have ≥40 % of employees in shift work) was not associated with breast cancer incidence compared to other types of work (defined as occupations with <30 % of employees in shift work) (standardized incidence ratio = 0.94, 95 % CI = 0.74–1.18 after adjustment for age, socioeconomic status, occupational position, and place of residence) [22]. As previously noted, the use of national-level data to establish thresholds defining exposure status is likely to cause considerable misclassification, and thus underestimation, of the association of interest. This may be of particular concern here, given the crude exposure and reference group definitions.

Prospective Studies of Shift Work and Breast Cancer Risk

Three of four prospective studies have provided evidence in favor of an association between shift work and breast cancer. In the Nurses' Health Studies, Schernhammer

et al. [23, 24] reported that women with the most extensive histories of rotating shift work had a modestly increased risk of breast cancer compared to those reporting no rotating shift work [23, 24]. Specifically, in premenopausal women, those with ≥20 years of shift work experience had a 79 % higher risk of breast cancer (95 % CI = 1.06–3.01) than their counterparts; in postmenopausal women, breast cancer risk was elevated by 36 % (95 % CI = 1.04–1.78) among those with ≥30 years versus no history of rotating shift work. One limitation of these studies is that women were asked to report durations of "rotating night work" defined as at least three nights per month in addition to days or evenings in that month; however, participants were not specifically asked about permanent night shift work, and therefore women with such work histories may have provided the same response as women without any shift work history. To the extent this occurred, women with permanent night shift experience were included in the reference group with non-shift workers, which may have biased the observed associations toward the null because permanent night workers are hypothesized to have intermediate circadian disruptions (and therefore, possibly intermediate breast cancer risk) compared to non-shift workers and rotating night shift workers. Thus, the true association between shift work and breast cancer risk might be stronger than it appears in these studies.

Another prospective cohort study, conducted among 7.5 million women in five Nordic countries during 1961–2005, identified those in the nursing occupation as being at moderately greater risk of breast cancer compared to women working in other occupations (crude standardized incidence ratio = 1.18, 95 % CI = 1.15–1.20), although the possibility remains that other occupational exposures might explain this association [25]. This analysis included a very large study population, but the lack of control for potential confounding factors is a major limitation; therefore, this study provides only weak evidence in favor of the association between shift work and breast cancer risk.

Finally, in a prospective cohort study in Shanghai, China, a history of working night shifts was not associated with breast cancer (HR = 1.0, 95 % CI = 0.9–1.2 comparing women with any night shift work vs. none), and neither were additional shift work metrics that incorporated frequency, duration, and cumulative exposure [26]. Limitations of this study, however, were the lack of information to distinguish fixed versus rotating shift work and a low prevalence of extreme durations of shift work (e.g., ≥20 years). Either or both of these issues may have contributed to these null findings and could explain why shift work was not associated with breast cancer risk in this study. Thus, these findings stand in contrast with the other three prospective studies, which reported at least modest relations between shift work or the nursing profession and increased risk of breast cancer.

Previous Studies of Shift Work and Prostate Cancer Risk

Four studies—two retrospective studies and two prospective studies—have examined the association between shift work and prostate cancer risk (Table 7.2). The first retrospective case-control study, involving 400 prostate cancer cases and 512

Table 7.2 Previous epidemiologic studies of shift work in relation to risks of prostate and other cancers

Study author and date	Cancer type	Study design	Study base	Exposure assessment	Outcome assessment	Results
Schernhammer (2003) [31]	Colorectal	Prospective cohort study	78,586 women in the Nurses' Health Study	Self-reported history of rotating night shift work	602 cases occurring between 1988 and 1998, identified by self-report and verified by medical records	Positive association
Kubo (2006) [29]	Prostate	Prospective cohort study	14,052 working men, aged 40–65 years, in Japan	Self-reported work schedule via questionnaire	31 cases, identified by area cancer registries	Positive association
Conlon (2007) [28]	Prostate	Retrospective case-control study	2,392 men, aged 45–84 years, living in Northeastern Ontario	Self-reported lifetime employment history via questionnaire	760 prostate cancer cases, occurring during 1995–1998	Positive association
Viswanathan (2007) [32]	Endometrial	Prospective cohort study	53,487 women participating in the Nurses' Health Study	Self-reported history of rotating night shift work	515 cases occurring between 1988 and 2004, identified by self-report and verified by medical records	Positive association
Lahti (2008) [35]	Non-Hodgkin lymphoma	Prospective cohort study	1,669,272 men and women, aged 25–64 years, working in Finland	Census information about employment histories, combined with survey information about jobs involving primarily night work	6,307 cases, occurring during 1971–1995, and identified by the Finnish Cancer Registry	Positive association in men only
Kubo (2011) [30]	Prostate	Prospective cohort study	4,995 men, aged 49–65 years, working in a Japanese manufacturing corporation	Long-term work schedule obtained from corporation records	17 cases, identified from health insurance records	No association
Poole (2011) [33]	Ovarian	Prospective cohort study	181,548 women participating in the Nurses' Health Study and Nurses' Health Study II	Self-reported history of rotating night shift work	718 cases, occurring between 1988 and 2007 in the Nurses' Health Study and 1989–2008 in the Nurses' Health Study II, and identified by self-report and verified by medical records	No association

Schernhammer (2011) [34]	Skin	Prospective cohort study	68,336 women participating in the Nurses' Health Study	Self-reported history of rotating night shift work	10,799 cases, occurring during 1988–2006, and identified by self-report and verified by medical records	Negative association
Parent (2012) [27]	Prostate	Retrospective case-control study	3,649 men, aged 35–70 years, living in the greater Montreal area	Lifetime occupational history obtained by interview	400 cases, occurring during 1979–1985	Positive association
	Non-Hodgkin lymphoma				197 cases, occurring during 1979–1985	Positive association
	Lung				761 cases, occurring during 1979–1985	Positive association
	Colon				439 cases, occurring during 1979–1985	Positive association
	Bladder				439 cases, occurring during 1979–1985	Positive association
	Rectum				236 cases, occurring during 1979–1985	Positive association
	Stomach				228 cases, occurring during 1979–1985	No association
	Kidney				158 cases, occurring during 1979–1985	No association
	Melanoma				94 cases, occurring during 1979–1985	No association
	Pancreas				94 cases, occurring during 1979–1985	Positive association
	Esophagus				91 cases, occurring during 1979–1985	No association

Positive association denotes a statistically significantly increased risk; negative association denotes a statistically significantly decreased risk; and no association signifies associations, which did not reach statistical significance

controls from Montreal, identified an association between ever having performed night shift work (defined as work that included time between 1 am to 2 am) and higher odds of prostate cancer (OR = 2.77, 95 % CI = 1.96, 3.92) [27]. However, additional analyses based on cumulative duration of night work exposure and recency of night work did not find associations with prostate cancer, which would have strengthened the evidence for a causal association in this study. A potential limitation of this work is that participants were not asked detailed questions about the frequency of their night shift work or whether their night work involved rotating shifts, which are thought to produce more circadian disruptions than permanent night work; thus, it is possible that lacking this information prohibited the observation of a more convincing dose-response relationship.

The second retrospective study, a case-control design based on 760 prostate cancer cases and 1,632 frequency-matched controls, found that men who normally worked full-time rotating shifts had higher odds of prostate cancer compared to men who did not normally work such shifts (OR = 1.19, 95 % CI = 1.00–1.42); however, this result should be interpreted with caution, as it is modest in magnitude and only borderline significant [28]. There was also a suggestion that men with the longest duration of rotating shifts might have greater odds of prostate cancer compared to those who did not work rotating shifts (OR = 1.30, 95 % CI = 0.97–1.74), although no dose-response relation was observed across five categories of shift work duration (p-trend = 0.4), and other shift work metrics were not related to prostate cancer risk. One limitation of this research was the crude exposure assessment, which asked participants to report their "usual" work time as day, evening/night, or rotating; thus, exposure misclassification may have caused some underestimation of the associations of interest, as men who engaged in rotating shift work occasionally, but not predominantly, would not have contributed to risk in the rotating shift work group.

A prospective cohort study in Japan reported that men who worked rotating shifts had a significantly higher risk of prostate cancer compared to those working daytime shifts (RR = 3.0, 95 % CI = 1.2–7.7), and men working fixed night shifts had a nonsignificantly increased risk compared to the same reference group (RR = 2.3, 95 % CI = 0.6–9.2) [29]. Due to the small number of cases (n = 31), these estimates have wide confidence intervals and therefore should be interpreted with caution. However, this study also had a crude exposure measurement based on a single report of a participant's most common work schedule. Thus, associations might be underestimated due to exposure misclassification for the same reason cited above, namely, that men with occasional rotating shifts would be likely to contribute to risk in the unexposed group.

An additional study, also prospectively conducted in Japan, found a nonsignificantly increased risk of prostate cancer related to the performance of shift work compared to daytime work (OR = 1.79, 95 % CI = 0.57–5.68). However, there were only 17 prostate cancer cases identified in this cohort, which produced very wide confidence intervals and therefore prohibits meaningful interpretation of these results in the context of other studies [30].

In sum, overall, evidence for a relation between shift work and prostate cancer is very limited, both by the small number of studies and by major limitations involved in those studies that have been conducted.

Previous Studies of Shift Work and Risk of Other Cancers

Several studies have examined associations between shift work and other cancers as well (Table 7.2). In prospective analyses of the Nurses' Health Study, women with the longest durations of rotating shift work had modestly increased risks of colorectal cancer (n = 602 cases; RR = 1.35, 95 % CI = 1.03–1.77 for ≥15 years vs. none) [31] and endometrial cancer (n = 515 cases; RR = 1.47, 95 % CI = 1.03–2.10 for ≥20 years vs. none) [32]; however, there was no association between rotating shift work and ovarian cancer in an analysis combining the Nurses' Health Study and Nurses' Health Study II (n = 718 cases; RR = 0.80, 95 % CI = 0.51–1.23 comparing women with ≥20 vs. no years of shift work) [33]. In addition, women with longer durations of shift work had a decreased risk of skin cancer in the Nurses' Health Study cohort (n = 10,799 cases; RR = 0.86, 95 % CI = 0.81–0.92 for ≥10 years vs. none), although this association was modified by hair color and therefore might be explained by genetic factors that determine hair color and increase genetic susceptibility to skin cancer risk [34].

Likewise, a retrospective case-control study in Montreal found increased risks of colon cancer (OR = 2.03, 95 % CI = 1.43–2.89) and rectal cancer (OR = 2.09, 95 % CI = 1.40–3.14) among men who had ever worked night shifts compared to those who had never worked night shifts; however, no association was observed between night shift work and melanoma (OR = 1.04, 95 % CI = 0.49–2.22), contrary to the skin cancer finding in the Nurses' Health Study [27]. Additionally, these results indicated that night work was related to higher odds of lung cancer (OR = 1.76, 95 % CI = 1.25–2.47), bladder cancer (OR = 1.74, 95 % CI = 1.22–2.49), non-Hodgkin lymphoma (OR = 2.31, 95 % CI = 1.48–3.61), and pancreatic cancer (OR = 2.27, 95 % CI = 1.24–4.15), but not stomach cancer (OR = 1.34, 95 % CI = 0.85–2.10), kidney cancer (OR = 1.42, 95 % CI = 0.86–2.35), or esophageal cancer (OR = 1.51, 95 % CI = 0.80, 2.84).

A final prospective study, involving a cohort of >1.6 million Finnish employees, found a slightly higher risk of non-Hodgkin lymphoma among men with exposure to night shift work (n = 3,813 cases; RR = 1.10, 95 % CI = 1.03–1.19)—consistent with the Montreal study findings in men [35]. However, this association was not apparent for women (n = 2,494 cases; RR = 1.02, 95 % CI = 0.94–1.12).

Consideration of Obesity in Previous Epidemiologic Studies

Numerous epidemiologic studies have examined the association between shift work and obesity in various different countries. Most of these studies have utilized existing data from employment records in particular companies, which provide convenient but typically limited information on shift work and health-related variables because this information was not originally collected for research purposes. As a result, many of these studies have methodological issues that potentially limit the interpretation of their results. Still, 22 of 23 currently published studies found some

evidence that obesity is significantly more common among individuals with shift work experience compared to those without such experience [36–57]; only one study did not identify a possible link [58]. Nineteen of the 23 studies were either cross-sectional or retrospective in design [36–55, 58]; for example, in a large, cross-sectional study of 27,485 working adults in Sweden, the risk of obesity was approximately 40 % greater comparing shift workers versus day workers (after adjustment for age and socioeconomic status, OR = 1.39, 95 % CI = 1.25–1.55 for women and OR = 1.44, 95 % CI = 1.27–1.64 for men) [37]. However, as in this study, many analyses of shift work and obesity lack adjustment for potentially important confounding variables (e.g., other health and lifestyle factors), and therefore prospective studies with more extensive information on these variables have provided critical insight.

Four such prospective studies have been conducted, all of which indicate that individuals who perform shift work tend to experience significant weight gain over time—including two studies in Japan, one study in Australia, and one study in the United States. The first Japanese study, conducted among 1,529 male factory workers, reported that participants who changed from day to shift work (at some point over the 10-year study period) had more significant increases in body mass index than those who worked a day schedule throughout the study period (after adjusting for age, body mass index at baseline, smoking, alcohol intake, and physical activity, mean increases = 1.08 kg/m vs. 0.62 kg/m^2 comparing these two groups; $p < 0.05$); the same was true for individuals who maintained a shift work schedule over the study period (adjusted mean increases = 0.89 kg/m vs. 0.62 kg/m^2 for this group comparison; $p < 0.05$) [54]. A second study in Japan, including 7,254 male steel workers, found that rotating shift work was associated with a modestly increased risk of weight gain (≥5 % of initial body mass index) over a 14-year period (OR = 1.14, 95 % CI = 1.06–1.23 comparing rotating shift vs. day workers, adjusting for age, alcohol intake, smoking, and physical activity) [55]. Likewise, in an Australian study of 2,078 female nurses and midwives, women who changed from day to shift work, or who maintained shift work, over a 2-year period experienced an increase in body mass index that was greater than for women who only performed day work (mean changes in body mass index = 0.13 kg/m^2 for day-shift workers and 0.56 kg/m^2 for shift-shift workers vs. −0.02 kg/m^2 day-day workers, controlling for age, smoking, and full-time vs. part-time work; $p = 0.01$ and 0.04 for these comparisons, respectively). In contrast, those who switched from shift to day work had a greater decrease in their body mass index compared to day work maintainers during the same period (adjusted mean changes in body mass index = −3.02 kg/m vs. −0.02 kg/m^2; $p < 0.001$) [56]. Finally, in the largest and most detailed analysis to date, each 5-year increase in rotating shift work experience was associated with a gain of 0.17 kg/m^2 in body mass index (95 % CI = 0.14–0.19) or 0.45 kg in weight (95 % CI = 0.38–0.53), among 107,663 women who were followed over 18 years in the US Nurses' Health Study 2 [57]. Statistical models were adjusted extensively for age, baseline body mass index, alcohol intake, smoking, physical activity, and other health and lifestyle indicators. Thus, findings from this study—which was designed to ascertain specific information on important health

and lifestyle factors, including shift work and obesity—are consistent with previous analyses that have reported shift work exposure being associated with greater weight gain based on historical employment records. In summary, existing literature on shift work and obesity supports the negative effects of shift work on weight over time, even after accounting for key confounding factors that might influence this association.

The clear link between shift work and obesity has motivated the inclusion of body mass index as a variable in previous analyses of shift work and cancer risk; in most studies, body mass index has been considered a possible confounding factor, resulting in analyses that adjust for this variable in statistical models. Although it is possible that obesity predicts both shift work and cancer risk—as would be required for obesity to be a potential confounding factor of this relation—it is probably more likely that shift work predicts obesity, in addition to obesity being a risk factor for many types of cancer. This scenario is suggested by the prospective studies of shift work and obesity described above; that is, obesity is a stronger candidate for effect modification than confounding of the association between shift work and cancer, as shift work appears to influence the risk of obesity over time. Yet, only three prior studies have conducted stratified analyses based on obesity status to evaluate the possibility of effect modification. Two of these studies focused on shift work and breast cancer, but they found no evidence of effect modification by obesity [24, 26]; a third study of shift work and endometrial cancer did identify obesity as an effect modifier [32]. Specifically, rotating shift work was primarily related to endometrial cancer among obese women (RR = 2.09, 95 % CI = 1.24–3.52), but not among nonobese women (RR = 1.07, 95 % CI = 0.60–1.92), in the Nurses' Health Study. Clearly, additional studies need to carefully consider the role of body mass index—a possible confounding factor, but more likely effect modifying factor—in the association between shift work and obesity.

Summary

Consistent with biologic evidence, the epidemiologic literature suggests that shift work is probably associated with a modestly increased risk of breast cancer. There may also be such an association with prostate cancer, although research on this and other cancers is still limited. A key distinguishing feature of prior studies is the method of exposure assessment: retrospective studies have relied heavily on either company records of shift work or the coupling of brief employment histories and job matrices (which make broad assumptions about the amount of shift work involved in specific occupations or occupational settings); in contrast, prospective studies have tended to ascertain more detailed shift work information from participants. Because exposure misclassification is much more likely when shift work history is derived from employment records and job matrices, studies that have used this approach tend to be more limited in their ability to detect associations with shift work. This limitation may also explain why some studies have reported either no

association or a weak association between shift work and cancer. In addition, previous studies indicate that individuals who are exposed to shift work are more likely to be obese, and obesity is a risk factor for several major cancers; thus, obesity is a good candidate for modifying the association between shift work and cancer risk, although few studies have explored this possibility. Thus, future research should focus on (1) prospective collection of detailed information on shift work exposure, (2) investigation of shift work in relation to risk of cancers other than breast cancer, and (3) evaluation of obesity as a possible effect modifier of associations between shift work and cancer risk.

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Chapter 8
Sleep Disorders and Cancer Risk

Cheryl L. Thompson and Li Li

Abstract Sleep disturbance is emerging as a novel risk factor for cancer and a number of other chronic diseases. Disruption of circadian rhythm with resultant perturbed homeostasis is believed to drive sleep disturbance-associated tumorigenesis. Much of the supporting evidence comes from studies of shift work and, more recently, short duration of sleep with risks of various types of cancer and precancerous lesions. Less is known about the relationship of other sleep disorders, which encompass a number of conditions that broadly affect sleep health, with cancer. This chapter reviews current knowledge of the association between common sleep disorders and cancer and briefly discusses the molecular mechanisms underlying the link between sleep disturbance and cancer. Effective intervention on sleep health can potentially be a new avenue for reducing cancer risk and enhancing survival.

Keywords Sleep duration • Sleep disorders • Cancer

Introduction

Sufficient and quality sleep on a daily basis is an important part of healthy living. Sleep deprivation has been associated with all-cause mortality and a number of chronic diseases such as coronary heart disease, diabetes, metabolic syndrome, and obesity [1–4]. Increasing data have also associated sleep disturbance with risks of various types of cancer. Much of the evidence supporting a cancer link comes from epidemiological studies of shift work and short duration of sleep [5–10].

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_8,

The relationship of other sleep disorders and cancer has not been well studied. The overarching category of sleep disorders encompasses a large number of conditions that broadly affect the quality and/or duration of sleep. Aside from a single large registry-based study conducted in Taiwan showed that an earlier diagnosis of a sleep disorder (excluding sleep apneas) is associated with a slight increase (about 12 %) in risk of subsequent cancer [11], little work has been done looking at overall diagnosis of sleep disorders and risk of cancer. This may be in part due to the underdiagnosis of many sleep disorders in the general population. Nevertheless, increasing evidence supports that disruption of circadian rhythm, likely prevailing in individuals with specific sleep disorders, lack of sufficient sleep, and being engaged in shift work, is causally linked to carcinogenesis.

Insomnias

About 30 % of the worldwide adult population experience some degree of insomnia, a disorder of falling asleep or staying asleep [12]. Associated with subsequent daytime dysfunction, the high prevalence of insomnia is a known public health issue. Emerging evidence is also showing that insomnia has a role in cancer development (see more details in Chap. 9). A new study based on the large Women's Health Initiative cohort of over 100,000 postmenopausal women found women with worse insomnia scores (based on symptoms of insomnia) were about 44 % more likely to develop thyroid cancer [13].

Sleep Apnea

Sleep apnea is a sleep disorder in which breathing temporarily halts resulting in a hypoxic environment. The most common type of sleep apnea is obstructive sleep apnea (OSA), where the cause of the pause in breathing is due to physical obstruction. Prevalence rates of OSA are challenging to measure due to the high rate of undiagnosed cases, but it has been estimated that up to about 5 % of adults in the United States (USA) and other western countries may have undiagnosed OSA (reviewed in [14]).

There has been evidence that OSA also increases ones risk of developing cancer. A study using a melanoma mouse model has shown that mice subjected to intermittent hypoxia have increased tumor growth compared to those who were not [15]. Their data suggests that this effect is similar to and independent from the effect of obesity on tumor growth and is at least partially mediated by circulating vascular endothelial growth factor (VEGF) [15]. Interestingly, other research by this group has shown that hypoxia also increases tumor progression rates [16].

Although it is challenging to measure sleep apnea in large population studies, largely due to the high undiagnosed rates as well as reliance on self-report, there has

been some success in quantifying apnea in a couple large cohort studies utilizing polysomnography, a sleep study used diagnostically in sleep medicine. In a large cohort of cancer patients on whom a polysomnography was obtained as part of the Wisconsin Sleep Cohort Study, both total and cancer-related mortality increased with apnea-hypopnea index (AHI) [17]. However, another large population cohort in Spain has shown that these associations were limited to men or younger patients [18].

More details on the relationship between sleep apnea and cancer risk, as well as the potential underlying mechanisms, are provided in Chap. 6.

Circadian Rhythm Sleep Disorders

Disruptions in the circadian rhythm are well known to cause a number of conditions, such as jet lag and fatigue. Our endogenous circadian rhythm is regulated by the suprachiasmatic nuclei (SCN), and our body depends on this rhythm for a number of normal biological processes. In fact, mouse studies have shown a large portion of our genome to be regulated by our circadian rhythm [19], thus suggesting the widespread effect of circadian rhythm disruptions. For a more detailed review, see Chap. 4.

A number of epidemiological studies have demonstrated an association between working night shifts with increased risk of a number of cancers, including breast and prostate cancer [5–9, 20]. However, results have not been consistent, and differences in study design have made them difficult to compare. More detail on the association of shift work in cancer risk can be found in Chap. 7.

In addition, having light on at night, which is known to disrupt the natural circadian rhythm and decrease melatonin production, has been associated with increased risk of breast cancer [21, 22]. This hypothesis came from the observed associations of shift work with cancer but also early epidemiological studies suggesting that blind women had substantially lower risks of breast cancer compared to other women [23–26]. In a breast cancer xenograft mouse model, having a light at night accelerated tumor growth, at least in part through activation of insulin-like growth factor 1 receptor (IGF-1R) and the Akt stimulatory kinase phosphoinositide-dependent protein kinase 1 (PDK1) [27]. Others have used an ecologic study of 164 countries to suggest that light at night may increase risk of prostate cancer [28]. Their data did not suggest that increased prevalence of light at night was associated with increased incidence of lung or colorectal cancer. However, more work needs to be done to evaluate the association of light at night at risk of these cancers.

Interestingly, dysregulations of a large number of circadian rhythm genes have been identified in a number of cancers. For example, Period 1 (PER1) has been shown to be downregulated in prostate cancer tissues, compared to normal prostate [29], and also downregulated in colorectal cancer [30], endometrial cancer [31], and oral squamous cell carcinoma [32]. Reduced expression of the Period 3 (PER3) gene in colon tissue has been associated with risk of developing colon cancer [33]. A recent study of circadian rhythm genes in head and neck cancers showed a

downregulation of many key circadian rhythm genes, including PER1, PER2, PER3, CRY1, CRY2, and BMAL1 [34]. These are just a few examples of the well-established deregulation of circadian rhythm genes in tumors.

To further study the role of circadian rhythm genes in risk of cancer, a number of epidemiological studies have investigated the role of individual inherited variation in these genes with risk of cancer. Single nucleotide polymorphisms (SNPs) in the CLOCK gene [35], the NPAS2 gene [36], as well as the CRY2 gene [37] have been associated with risk of developing breast cancer. Interestingly, a meta-analysis of three large genome-wide association studies by pathways found excess variants of circadian rhythm genes associated with breast cancer, suggesting the importance of variants in these pathways in determining breast cancer risk [38]. SNPs in CRY2 were also associated with risk of non-Hodgkin's lymphoma [39]. A large study of 41 SNPs in 10 circadian rhythm genes identified 12 SNPs in 9 genes associated with risk of prostate cancer [40].

Hypersomnia

Traditionally, hypersomnia, or excessive sleeping, has been, along with fatigue, well documented as a symptom of cancer, a result of cancer development and treatment, and has been established as one of the common complaints among patients of a number of different cancers [41–43], including childhood cancers [44]. To date, studies of diagnosed hypersomnia with risk of cancer are still lacking.

Sleep Quality and Duration and Risk of Cancer

Sleep Quality

Poor quality of sleep is a known problem in cancer patients. The effects of chemotherapy and anxiety on sleep quality in these patients have been well studied, and interventions to improve sleep quality and/or duration among cancer patients have shown widespread improvements in cancer mortality and outcomes, as well as mental health, and overall quality of life (reviewed in [45]). However, there are very few reports on the association of sleep quality as a risk factor for cancer. The biological plausibility of a correlation of sleep quality and risk of cancer is strong – indeed poor sleep quality is a disruption of one's circadian rhythm and may also explain the increased risk among shift workers. However, the only reports to date have found no association with sleep quality and risk of colorectal adenomas [10] and breast cancer [46, 47].

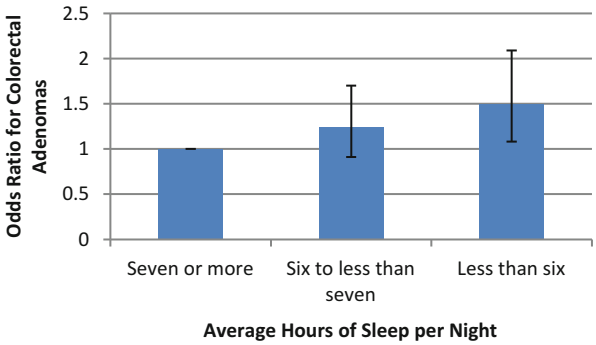

Fig. 8.1 Odds ratio for colorectal adenomas by hours of sleep per night (From [10])

Short Duration of Sleep

Duration of sleep is another component of sleep studied with respect to cancer risk. Short duration of sleep may represent a number of factors related to sleep. Indeed, lack of sufficient sleep duration can disrupt circadian rhythm. Furthermore, there is a high correlation of sleep duration with insomnia and sleep quality. Although not independent of the conditions previously described, it has been studied independently with respect to a number of different cancers.

We have previously demonstrated an inverse association of self-reported typical hours of sleep per night with likelihood of incident colorectal adenomas in a prospective screening colonoscopy-based study of colorectal adenomas [10]. Compared to individuals reporting at least 7 h of sleep per night, those individuals reporting fewer than 6 h of sleep per night had an estimated 50 % increase risk in colorectal adenomas (Fig. 8.1). A recent study as part of the Women's Health Initiative (WHI) has shown similar results with regard to risk of colorectal cancer [48].

Probably, the cancer for which sleep duration has been studied most with regard to risk is breast cancer. There are also a number of epidemiological studies that have investigated the association of sleep duration and risk of breast cancer. In these studies, the association of short sleep duration and incidence of breast cancer has been mixed, with one prospective cohort suggesting a decreased risk of breast cancer in women who slept longer [47] and a retrospective case-control study suggesting the same [49]. However, two other studies provided data showing an inverse association between sleep duration and risk of breast cancer, where women with less sleep were at increased risk of breast cancer, which is in line with the hypothesis of short sleep duration increasing risk [50, 51]. Two others did not find evidence of an association in either direction [46, 52]. However, lack of consistency among study designs and cutoffs for determining "short sleep," and confounders, as well as differences in

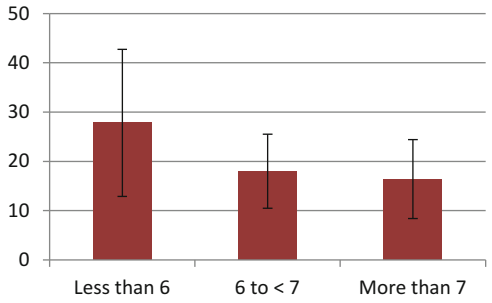

Fig. 8.2 Average Oncotype DX score by sleep duration (From [54])

populations may account for the disparities in findings. Thus, rigorous studies, using both epidemiological data and animal models, are needed to help clarify this association.

In a large, prospective cohort of over 20,000 men, Kakizaki et al. found that sleeping 6 or fewer hours was associated with an approximately 38 % increased risk of prostate cancer, compared with those reporting 7–8 h of sleep. Another study noted a non-statistically significant trend toward reduced incidence of endometrial cancer over the, on average, 7.5 years of follow-up with more sleep reported at baseline in the WHI sample population [53].

Although their number of cancer cases was small, another study found no evidence of an association between sleep duration and risk of thyroid cancer in a large cohort of postmenopausal women [13]. More epidemiological and basic research must be done to understand the role of sleep duration and sleep deprivation on risk of developing these and other cancers for which this association has not been evaluated, such as lung cancer.

New evidence is also emerging on the role of sleep duration in cancer phenotype. OncotypeDX is a clinical test used to measure likelihood of recurrence. We have recently shown that short sleep prior to diagnosis was associated with a higher OncotypeDX recurrence score among breast cancer patients [54] (Fig. 8.2). Breast cancer patients who reported less than 6 h of sleep per night prior to diagnosis were about twice as likely to fall into the "high-risk" recurrence category compared to women who reported at least 7 h of sleep per night before diagnosis. This suggests that short sleep may lead to a more aggressive breast cancer phenotype. Furthermore, new data from our group in a larger sample of a breast cancer patients, including patients with all molecular subtypes of breast cancer, found that women newly diagnosed with higher-grade tumors reported regularly getting fewer hours of sleep per night in the 2 years prior to diagnosis, and, again, this association was limited to postmenopausal breast cancer patients (Table 8.1, unpublished).

Mechanisms of Sleep Disorders and Cancer Risk

Although the exact mechanisms by which various sleep disorders may affect the initiation and progression of cancer are largely unknown, disruption of circadian rhythm, pervasive in individuals with sleep disorders, is thought to be the

Table 8.1 Mean average hours of sleep per night by tumor grade

	All patients			Premenopausal			Postmenopausal		
	Hours of sleep per night, mean (SD)	p*	p**	Hours of sleep per night, mean (SD)	p*	p**	Hours of sleep per night, mean (SD)	p*	p**
All	7.03 (1.20)	–	–	7.08 (1.24)	–	–	7.02 (1.20)	–	–
Grade		0.032	0.052		0.022	0.89		0.018	0.049
1	7.23 (1.20)			7.63 (1.34)			7.16 (1.17)		
2	7.05 (1.24)			6.75 (1.27)			7.11 (1.23)		
3	6.89 (1.18)			7.27 (1.38)			6.82 (1.13)		

*p-value of ANOVA (univariate); **p-value of sleep duration in ordinal or standard logistic regression adjusted for age, race, hormone replacement therapy (*HRT*), family history of breast cancer, body mass index (*BMI*), current smoking, current alcohol consumption, and physical activity

underlying denominator linking sleep disorders, as well as shift work and sleep deprivation, to cancer. The circadian system synchronizes the host's daily cyclical physiology from gene expression to behavior [55]. Disruption of circadian rhythm may influence tumorigenesis through a number of mechanisms, including disturbed homeostasis and metabolism (details provided in Chap. 2), suppression of melatonin secretion (details provided in Chap. 3), intermittent hypoxia and oxidative stress (details provided in Chap. 5), reduced capacity in DNA repair, and energy imbalance. In this chapter, we focus our review on the latter two.

DNA Repair

Circadian rhythms are genetically determined and generated by the circadian machinery comprised of a set of clock genes regulating cell cycle and proliferation [56]. Increasing evidence supports the notion that circadian clock control of the cell cycle functions as a protective mechanism against DNA damage to maintain genome integrity [57]. PER1 (PERIOD1) and TIM (TIMELESS), two core circadian proteins, directly interact with ataxia telangiectasia mutated (ATM)-checkpoint kinase 2 (Chk2) and ataxia telangiectasia and Rad3-related (ATR)-Chk1, two key components of the cell cycle checkpoint system [58]. ATM is critical for the activation of the cell cycle checkpoints in response to DNA double-strand breaks and phosphorylation of downstream substrates involved in cell cycle rest and DNA damage repair [59]. Cryptochrome 2 (CRY2), a key component of the circadian feedback loop, has also been shown to play an important role in the regulation of DNA strand break repair [60–62]. In breast cancer cell lines (MCF-7), CRY2 silenced (CRY2-) cells accumulated significantly more unrepaired DNA damage than CRY2+ cells [63]. A seminal study has shown that DNA excision repair capacity in mouse brain is regulated by circadian rhythm with maximum activity in the afternoon/evening hours and minimum activity in the midnight/morning hours [64]. The researchers further showed that circadian clock control of nucleotide excision repair occurs through transcriptional control of the DNA damage recognition factor xeroderma

pigmentosum A (XPA) protein expression. Daily oscillation of XPA orchestrates daily oscillation of the entire nucleotide excision repair system. Thus, disruption of circadian rhythm comprises the host's DNA repair capacity leading to genome instability and the development of cancer. Disruption of circadian rhythm can also compromise DNA repair indirectly through suppression of melatonin production (details provided in Chap. 3).

Energy Imbalance

Accumulating evidence suggests that sleep disturbance plays an etiological role in the pathogenesis of obesity, metabolic syndrome, and cancer. Epidemiological data supporting an inverse association between short duration of sleep and obesity are particularly strong [65]. Obesity is well established as a "probable" cause for cancer, and we have shown that sleep disturbance is an integral part of the syndrome of insulin resistance or metabolic syndrome [66]. Energy imbalance, excess energy intake in comparison to energy expenditure, is believed to be an important mediator underlying these connections. While data on how specific sleep disorders may impact energy balance are limited, an increasing number of intervention trials have shown that sleep restriction or disruption of regular sleep patterns results in positive energy balance and weight gain [65, 67]. Sleep deprivation may disrupt hormonal regulation of hunger and satiety, specifically by increasing ghrelin and decreasing leptin [68–71]. Sleep deprivation may also disrupt hormonal circadian rhythms and hormonal regulation of energy substrate utilization. Elevated cortisol level promotes fat storage and, in the presence of an energy deficit, promotes greater proportional loss of lean body mass and preservation of fat mass [72, 73]. A recent 2-week-long sleep restriction trial has gained new insight of how sleep loss influences energy expenditure and intake [74]. Contrary to the common belief that insufficient sleep reduces energy expenditure, sleep loss increases total daily energy expenditure by approximately ~5 % (~111 kcal/day). Increased total daily energy expenditure during sleep loss was predominantly driven by the energy cost of additional wakefulness. However, sleep loss significantly delays circadian melatonin phase and leads to an earlier circadian phase of wake time. Increased wakefulness promotes dysregulated eating behavior, especially excessive food intake of fat and carbohydrates beyond that necessary to offset the increased energy expenditure of sleep loss and, thereby, lead to energy imbalance and weight gain. Adipose tissue dysfunction resulting from energy imbalance leads to chronic inflammation, oxidative stress, and insulin resistance, all of which promote tumorigenesis.

Future Directions

Overall, there is promising new evidence of the role of sleep disorders in increasing the risk of a number of cancers. This evidence comes from a wide range of measures – including sleep duration, sleep quality, or the diagnosis of specific sleep disorders.

There have also been some good mouse models that have established the link between sleep and cancer development. For example, a mouse model of oxidative DNA damage from carcinogens showed the effect of melatonin in reducing the DNA damage to a similar level as the mice not exposed to the carcinogen [75]. However, overall there have been very few non-epidemiological studies that have investigated the link between sleep and cancer. These studies should be done to further understand the role of sleep in cancer development, aggressiveness, and progressions as well as to help identify the mechanisms underlying these associations.

One of the challenges in understanding the role of sleep disorders, sleep duration, sleep quality, or other markers of sleep is the lack of reliable measures of long-term sleep habits. Most studies to date use self-report of typical sleep habits. However, self-report is subjective, and the further in the past an individual is queried regarding their sleep habits, the less accurate they are. Prospective cohorts may capture sleep habits at a fixed time in the study (e.g., at baseline recruitment, or a certain age), whereas retrospective studies may ask about the recent past. Furthermore, sleep habits can change significantly over time, and the time frame most important with regard to cancer risk is an unanswered question. It has been proposed that researchers investigate a sort of "sleep-years" measure for sleep duration analogous to "pack-years" in smoking research [76]. While this could be a measure more strongly associated with cancer risk, it still does not solve the issues with sleep quality changes over time or recall necessary for retrospective studies. Therefore, null results may be a fact that these measures of sleep cannot be captured accurately enough in a large enough scale.

Another challenge of investigating the role of sleep and cancer risk is untangling the other confounders associated with poor sleep. Sleep duration is well known to be lower, and sleep quality poorer, in obese individuals, and, in parallel, obesity is associated with increased risk of developing poorer sleep and sleep disorders [77]. Further, obesity, or high BMI, is associated with increased risk of a number of cancers [78]. Other lifestyle factors are highly correlated with sleeping as well, such as smoking and physical activity, and which there is evidence for the association of these factors with increased cancer risk as well [79, 80]. Therefore, it is important to account for these potential confounders in all epidemiological research of sleep and cancer risk.

Evidence accumulated to date supports sleep as a modifiable risk factor for cancer development and survival. Behavioral and therapeutic interventions targeting sleep may represent new avenues for the cancer prevention.

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Chapter 9
Contribution of Sleep Disturbance to Cancer Fatigue

Christine Miaskowski and Bradley E. Aouizerat

Abstract Oncology patients are at high risk for developing sleep disturbance and fatigue due a number of physiological and psychological factors associated with cancer, its treatment, and the burden of living with a chronic condition. Progress in our understanding of sleep disturbance and fatigue in oncology patients has been stymied by varying definitions for each symptom, as well as different instruments to measure each symptom. In addition, the co-occurrence of these and other common symptoms suggests that analytic methodologies that are currently available should be considered to model the relationships between these and among other common symptoms. The purpose of the chapter is to describe the prevalence, risk factors, measurement considerations, proposed mechanisms for and novel approaches to the study of these two common symptoms in oncology patients. Interventions to improve sleep and reduce fatigue are also described.

Keywords Fatigue • Sleep disturbance • Symptom clusters • Interventions

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_9,

Prevalence of Sleep Disturbance and Fatigue in Oncology Patients

Prevalence of Sleep Disturbance. Oncology patients are at high risk for developing sleep disturbance due to a number of physiological and psychological factors associated with cancer, its treatment, and the burden of living with a chronic condition. Prevalence rates for sleep disturbance among oncology patients range from 30 % to 55 %, which is approximately twice the rate found in the general population [1–3]. Despite the high prevalence of sleep disturbance in oncology patients, detailed descriptions of the specific types of sleep disturbance (i.e., nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters) remain limited. A detailed description of the prevalence of sleep disturbance in oncology patients can be found in Chap. 10.

Prevalence of Fatigue. The management of many common symptoms (e.g., depression, nausea, vomiting) associated with cancer and its treatment has improved. In contrast, a common and persistent problem for these patients [4] and survivors [5] is fatigue. While the term cancer-related fatigue is commonly used to describe this symptom, the occurrence of fatigue prior to treatment [6–8], in cancer survivors [6, 9, 10] and in a variety of chronic illnesses [11–13], suggests that this term may be misleading. The term ignores the possibility that predisposition (i.e., genetic risk), environmental factors (e.g., social support), demographic characteristics (e.g., younger age, lower income), or acquired susceptibility for fatigue (e.g., chronic viral infection, epigenetic risk) may be exacerbated by cancer and/or its treatment. In order to accommodate non-cancer-related determinants of fatigue that influence the occurrence, severity, and duration of fatigue in oncology patients, the term fatigue will be used throughout this chapter.

Fatigue is defined as a persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or its treatment that is not proportional to activity and which interferes with daily functioning [14, 15]. The severity of fatigue in oncology patients is greater than that experienced by the general population [16]. Fatigue in oncology patients can range from mild to severe, is distressing, and is typically unrelieved by rest [17]. What is most perplexing about this symptom is that while fatigue is a normal and expected side effect of cancer treatments (i.e., surgery, chemotherapy, radiation therapy, biotherapy) [18], it can persist long after the termination of therapy [19]. In fact, approximately one-third of cancer survivors continue to experience fatigue [19–21], and for approximately 15 % of cancer survivors, the fatigue is severe [19, 22].

Fatigue is the most prevalent and distressing symptom reported by patients undergoing treatment for cancer [23]. Importantly, the severity of fatigue can lead to treatment discontinuation [4]. Fatigue occurs in 14–96 % of people with cancer. The wide range in prevalence rates is due not only to different prevalence estimates among different cancer diagnoses and cancer treatments but to the lack of uniform diagnostic criteria for fatigue [24, 25]. Importantly, chronic fatigue occurs in 20–35 % of cancer survivors. Numerous studies have documented the deleterious effects of

fatigue on oncology patients' function and quality of life [25, 26]. Fatigue disrupts common daily activities, which contributes to the strong correlation between levels of fatigue and poorer quality of life [26]. Twenty to forty percent of patients with cancer find common daily activities (e.g., running errands, general household chores, taking care of family, preparing food, social activities) to be considerably more difficult than before their cancer diagnosis [26]. Approximately 60 % of patients with cancer find these activities somewhat more difficult than before their cancer diagnosis [26]. The impact of fatigue on oncology patients and survivors is enormous in terms of inability to tolerate treatments, lost productivity, and lost days from work.

A number of organizations have identified that fatigue is an important clinical problem. The National Comprehensive Cancer Network developed evidence-based guidelines for fatigue with virtually no evidence to support its recommendations because clinicians needed some guidance about how to manage this devastating symptom. In addition, the Oncology Nursing Society has identified fatigue as one if its top research priorities for over two decades. Finally, in 2005 and 2010, the US National Institutes of Health National Cancer Institute convened conferences on cancer-associated fatigue. At both meetings, studies on the mechanisms that underlie the development of fatigue were identified as high-priority areas for research. However, no definitive mechanisms for fatigue have been identified.

Co-occurrence of Sleep Disturbance and Fatigue. The co-occurrence of sleep disturbance (i.e., altered circadian rhythms) and fatigue in oncology patients is well recognized [27–29]. Sleep disturbance and fatigue are consistently among the most common symptoms reported by oncology patients. Although each symptom has been studied in a variety of cancer populations, relatively few studies have measured both symptoms using valid and reliable measures of each symptom.

The first in-depth description of circadian rhythm parameters (i.e., nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters) and how these values correlated with fatigue severity was reported by Berger and colleagues [30]. Although both objective and subjective estimates of sleep disturbance were positively correlated with fatigue severity, subjective measures of sleep disturbance were associated with a greater number of parameters as compared to objective sleep measures. Studies that examined for the co-occurrence of sleep disturbance and fatigue in oncology patients found similar relationships [29, 31, 32], regardless of cancer diagnosis or type of treatment [32–34].

A detailed review on the co-occurrence of sleep disturbance and fatigue in oncology patients was published by Roscoe and colleagues [35]. Studies included in the review evaluated patients with a variety of cancer diagnoses (e.g., brain tumor, bone metastases, breast cancer, colorectal cancer, lung cancer, prostate cancer) who were undergoing treatment. Seven studies measured both symptoms by recall over a range of time frames [35]. Among the 25 studies evaluated, fatigue and sleep disturbance were positively correlated. Only two studies [36, 37] failed to observe the co-occurrence of sleep disturbance and fatigue. The correlation between sleep disturbance and fatigue was observed using not only subjective but objective measures of sleep disturbance (e.g., actigraphy). In five studies, a positive correlation was found between objective sleep disturbance and fatigue [1, 38–41], while one

study did not find this association [42]. The poor correlation between objective measures of sleep disturbance and fatigue has been observed by others [29, 30].

A persistent challenge in the study of fatigue and sleep disturbance is the elucidation of the sequence of symptom occurrence. Although sleep disturbance predicts fatigue [7, 22, 43], evidence suggests that fatigue can predict sleep disturbance [44]. Understanding the relationship between sleep disturbance and fatigue will require the continuous measurement of both symptoms. Studies are needed, which use ecological momentary assessment [36], to provide more definitive analyses of the relationship between how these two symptoms change over time.

The Impact of Fatigue on Society. It is estimated that in 2008, the economic impact from indirect morbidity in the USA exceeded 18.2 billion dollars (www.cancer.org). Although the total economic impact of fatigue is unknown, the large number of individuals affected by this problem suggests that it has a considerable economic impact on the individual as well as on society. This hypothesis is supported by a study by Curt and colleagues who interviewed 419 oncology patients about their experience with fatigue [45]. While 59 % of the patients were working when diagnosed with cancer, fatigue had a profound effect on their ability to work. On average, patients missed 4.2 days of work per month, 11 % took unpaid family or medical leave, 28 % stopped working altogether, and 23 % went on disability because of fatigue. Moreover, their family caregivers missed 4.5 days of work per month and 5 % stopped working altogether or went on disability. Clearly, the economic impact of fatigue on society is staggering.

Measurement of Fatigue in Oncology Patients

Individuals describe fatigue using different words, including tired, lack of energy, weak, lethargic, exhausted, bored, cannot sleep, or having sleep disturbances. However, the diagnosis of fatigue is not standardized, which contributes to underdiagnosis [25]. Currently, consensus on a definition of fatigue is lacking. However, general agreement exists that fatigue is a subjective and multidimensional phenomenon whose assessment requires the use of self-report measures. In fact, numerous scales exist for the measurement of fatigue [46] that have well-established validity and reliability. However, a limitation of several of these scales is that they have not demonstrated sensitivity to change. This consideration is significant because the experience of fatigue varies not only diurnally but over long periods of time [7, 8, 47]. Although fatigue measures continue to emerge, a common set of instruments are available to measure fatigue in oncology patients (Table 9.1). Several detailed reviews of fatigue measures are available [46, 48, 49]. Only those instruments that are multidimensional and that were used in studies of more than one cancer are described in Table 9.1.

A number of important considerations need to be evaluated when one selects a fatigue measure, including the psychometrics of the instrument, the time frame for recall, and the instrument's sensitivity to change. While a number of psychometric

Table 9.1 Summary of fatigue measures

Instrument	Number of items	Scale type	Dimensions of fatigue	Responsive to change	Internal consistency	Types of cancer patients	Reference
Fatigue Functional Impact Scale	8	Likert	Physical, mental	Yes, but modest	0.90–0.91	Heterogeneous cancer (non-hematologic malignancies, non-small cell lung cancer, chemotherapy	[147]
Fatigue Questionnaire	11	Likert	Physical, mental	Untested	0.88–0.90	Hodgkin's disease, Hodgkin's disease survivors, lymphoma patients	[148]
Fatigue Scale-Adolescent	14	Likert	Physical, mental, emotional, social	Untested	0.67–0.95	Acute lymphoblastic leukemia, acute myelogenous leukemia, Hodgkin's disease, solid tumors, brain tumor	[149]
Fatigue Severity Inventory	13	Numeric rating	Physical, mental	Yes	0.94	Breast cancer, heterogeneous cancer	[150]
Lee Fatigue Scale	18	Numeric rating	Physical, mental	Yes	0.91–0.96	Breast cancer, prostate cancer, chemotherapy, radiotherapy	[151]
Multidimensional Fatigue Inventory	20	Likert	Cognitive, physical, emotional	Untested	0.84	Breast cancer, urogenital cancers	[152]
Piper Fatigue Scale-Revised	22	Likert	Affective, cognitive, sensory, severity	Untested	0.97	Breast cancer, lung cancer	[153]

properties can be used to evaluate the validity and reliability of a fatigue instrument [50], only the most commonly used index of reliability (Cronbach's alpha, α) is provided in Table 9.1. An important consideration is the time frame for recalling the fatigue experience (i.e., experience of fatigue in the past month, experience of fatigue in the past week, experience of fatigue in the past 24 h, experience of fatigue right now). The specific time frame chosen will depend on the research question. When other concurrent symptoms (e.g., sleep disturbance, depressive symptoms, anxiety, pain) are evaluated, all of the various self-report measures should have similar recall periods [51]. The selection of the time frame for recall is particularly important when longitudinal measurement of fatigue is of interest. This approach requires that the fatigue measure is sensitive to change (Table 9.1).

Measurement of Sleep Disturbance in Oncology Patients

Like fatigue, sleep is a multidimensional phenomenon. Although the number of instruments that are available to measure sleep is more modest than those for the measurement of fatigue, the measurement of sleep is more complex in that it can be measured both objectively and subjectively. Polysomnography is considered the gold standard for the objective measurement of sleep. However, it is cumbersome, resource intensive, and impractical for use outside of laboratory settings and for longitudinal studies of sleep. Actigraphy, which measures global movement during rest and activity, is currently the most widely accepted tool to measure objective sleep patterns [52].

The agreement between subjective and objective measures of sleep disturbance is generally poor [53–56]. An important observation is that subjective sleep disturbance tends to be more strongly correlated with other symptoms (e.g., fatigue [22, 57]), quality of life, and patient-reported outcomes [58, 59]. Several detailed reviews of instruments for the measurement sleep disturbance are available [52, 60–64]. Similar to the measurement of fatigue, a limitation of several of the sleep disturbance measures is that they have not demonstrated sensitivity to change. The most commonly used valid and reliable subjective measures of sleep disturbance that were used in studies of oncology patients are listed in Table 9.2.

Similar to the measurement of fatigue, a number of important considerations need to be evaluated when one selects a measure of sleep disturbance, including the psychometrics of the instrument, the time frame of recall, and if the instrument is sensitive to change. The most commonly used index of reliability (Cronbach's alpha, α) is provided in Table 9.3. The selection of an instrument to measure sleep disturbance requires consideration of the time frame for recalling the sleep experience (i.e., experience of sleep in the past month, experience of sleep in the past week, experience of sleep in the past 24 h), the time frame for recall of other symptoms measured in the same individual, and if the instrument is sensitive to change.

Table 9.2 Summary of measures of subjective sleep disturbance

Instrument	Number of items	Scale type	Dimensions of sleep	Responsive to change	Internal consistency	Types of cancer patients	Reference
General Sleep Disturbance Scale	21	Numeric rating	Quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness	Yes	0.84	Breast cancer, prostate cancer, acute lymphoblastic leukemia, non-Hodgkin's lymphoma	[154]
Pittsburgh Sleep Quality Index	19	Likert	Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep Disturbances, use of sleeping medications, daytime dysfunction	Yes	0.83	Breast cancer, lymphoma	[155]
Medical Outcomes Study Sleep Scale	12	Likert	Awakening short of breath or with a headache, quantity of sleep, sleep adequacy, sleep disturbance, somnolence, snoring	Yes	0.73–0.82	Breast cancer, lung cancer	[50]
Insomnia Severity Index	7	Likert	Degree of distress caused by sleep problem Difficulty with sleep maintenance, difficulty with sleep onset, noticeability of sleep problem to others, problem with early awakening, satisfaction with sleep pattern, interference with daily functioning as a result of sleep problems	Yes	0.76–0.90	Breast cancer, ovarian cancer, heterogeneous cancers	[54]

Mechanism(s) That Underlie Fatigue in Oncology Patients

Difficulties in the diagnosis and treatment of fatigue are both a cause and a result of our lack of understanding of the fundamental mechanisms that underlie this debilitating symptom. Multiple etiologies for fatigue are described including anemia [65], nutritional deficits [66], cytokine-induced sickness behavior [67], and the co-occurrence and influence of other symptoms (e.g., sleep disturbance [39, 68]). In a recent review [69], Xin Wang summarized several new hypotheses regarding the pathophysiology of fatigue. These hypotheses, which are summarized in Table 9.3, include cytokine dysregulation, circadian rhythm modulation, serotonin dysregulation, hypothalamic-pituitary-adrenal (HPA) axis disruption, vagal afferent activation, and adenosine triphosphate depletion. Fatigue may originate from two physiological compartments: central and peripheral. Central fatigue originates within the brain and spinal cord, while peripheral fatigue occurs in the neuromuscular junctions and muscle tissues. Fatigue in oncology patients most likely occurs through central as well as peripheral mechanisms. Although the cancer itself is associated with fatigue [70] and is often a symptom that leads patients to seek medical care that results in a cancer diagnosis, the persistence of fatigue, regardless of disease severity, indicates that fatigue associated with the cancer itself is not the only determinant of fatigue.

Table 9.3 Proposed mechanisms for fatigue associated with cancer

Mechanism	Theoretical underpinning	Potential influence on sleep disturbance
Adenosine triphosphate (ATP) depletion	Lack of energy is a common complaint of cancer patients who have a decreased ability to perform mechanical work. Cancer and its treatments have been hypothesized to impair ATP regeneration and lead to the accumulation of by-products in the neuromuscular junctions and skeletal muscle. This mechanism may best explain peripheral fatigue as a contributing factor in cancer-related fatigue	ATP depletion and increased adenosine production are observed in the presence of sleep apnea [156]. Animal models revealed that altered ATP metabolism is associated with differences in wake/sleep patterns [81, 82]
Circadian rhythm modulation	Circadian rhythm is influenced by numerous signaling molecules (e.g., the stress hormone—cortisol) that result in decreased amplitude, which are associated with fatigue. Whereas the assumption is that circadian dysfunction results in fatigue via sleep disruption, this has not been causally proven	Most cancer patients undergo considerable disruption in their sleep/wake patterns, which may be due in part to stress-mediated alterations in circadian rhythm. One's innate ability to tolerate or adjust to disruptions in sleep/wake patterns will impact severity of cancer-related fatigue

(continued)

Table 9.3 (continued)

Mechanism	Theoretical underpinning	Potential influence on sleep disturbance
Cytokine dysregulation	Based on animal and human models of sickness behavior induced by pro-inflammatory molecules culminate in a constellation of symptoms that include fatigue and sleep disturbance [67, 106]. This mechanism accommodates preexisting susceptibility for, as well as treatment-induced changes in cancer-related fatigue [77, 78]	Based on animal and human models of sickness behavior induced by pro-inflammatory molecules culminate in a constellation of symptoms that include fatigue and sleep disturbance [67, 106]. This mechanism accommodates preexisting susceptibility for, as well as treatment-induced changes in cancer-related fatigue [77, 78]
Hypothalamic-pituitary-adrenal (HPA) axis disruption	The HPA axis regulates the release of the stress hormone cortisol. Fatigue is associated with reduced HPA function, such as dysregulation of corticotropin homeostasis in response to chronic stress [157]. Cancer and its treatment [158] and both innate (i.e., genetic) and acquired (e.g., psychosocial, epigenetic) factors can impact HPA axis function and increase the risk for cancer-related fatigue	HPA hyperactivity has been associated with sleep disturbance [159] and insomnia [96]
Serotonin dysregulation	Increased evidence supports a role for serotonin metabolism and neurotransmission in fatigue, which has been demonstrated in animal models [95]. Increases in both serotonin and specific serotonin receptors in localized regions of the brain result in decreases in drive for body movement, modified HPA axis function, and a sensation of decreased capacity for physical activities [160]	Serotonin and serotonin receptors display a series of complex interactions that influence sleep and wakefulness [161]. Serotonin reuptake inhibitors can lead to sleep disruption by altering serotonin/receptor interactions [161]
Vagal afferent activation	Based on animal studies, cancer and its treatment cause the release of neuroactive molecules (e.g., serotonin) into the periphery. These agents can activate vagal afferents, decreasing somatic motor output, and are associated with changes in specific regions of the brain also seen with induced fatigue [162, 163]	Sleep disruption is mediated in part by signaling via vagal afferents [163]. Stimulation of vagal afferents by neuroactive molecules provides a connection between peripheral and central mechanisms to effect sleep and fatigue [164]

Adapted from Wang [69]

In addition to fatigue caused by cancer, the treatments for cancer (i.e., surgery [71], radiation therapy [72], chemotherapy [73], and hormonal therapy [74]) can induce fatigue. Finally, the observation that one of the most consistent predictors of fatigue after a cancer diagnosis and its treatment is preexisting fatigue [6–8] suggests that innate factors (e.g., genetic [75]) may contribute to fatigue.

To date, genetic association studies of fatigue in patients with cancer have focused on genes that participate in immune activation which results in cytokine-induced sickness behavior. The first study of genomic markers of fatigue was conducted in a small number of fatigued (n = 33) and non-fatigued (n = 14) breast cancer survivors [76]. Single nucleotide polymorphisms (SNPs, a common form of DNA variation) in interleukin 1 beta and interleukin 6 were examined. Variations in both genes were associated with fatigue status. In another study of a heterogeneous sample of oncology patients and their family caregivers, variation in an SNP in tumor necrosis factor alpha was associated with increased levels of fatigue. Similar to tumor necrosis factor alpha, an SNP in interleukin 6 was associated with fatigue and sleep disturbance prior to radiation therapy and with the trajectories of both symptoms in the 6 months following radiation therapy [77, 78].

The associations between gene variations in interleukin 1 beta, interleukin 6, and tumor necrosis factor alpha and fatigue and sleep disturbance were replicated in an independent sample of women diagnosed with early-stage breast cancer (n = 171). Variation in tumor necrosis factor alpha and interleukin 6 was independently associated with fatigue. In addition, using a liability index that was created by counting the number of rare alleles each patient carried across all three genes, patients with a higher liability index had more fatigue [79]. Taken together, these data suggest that cytokines play an important role in the susceptibility for and severity of fatigue and demonstrate that risk for fatigue occurs independent of the contributions of the cancer itself or its treatment. Future studies of the central and peripheral mechanisms of fatigue will undoubtedly focus on genes that underlie the pathways described in Table 9.3.

Mechanism(s) for the Contribution of Sleep Disturbance to Fatigue. The strong and potentially reciprocal relationship between fatigue and sleep disturbance suggests a shared physiological pathway(s) (Table 9.3). A challenge to progress in understanding the mechanisms that underlie sleep disturbance and fatigue in oncology patients is that the proposed mechanisms for fatigue are equally plausible for sleep disruption and vice versa. A persistent problem that limits a synthesis of the literature is that most of published research that examined the relationship between sleep disturbance and fatigue varied in their study designs, samples, and timing of measures [80]. A synthesis of the literature and potential causal relationships between sleep disturbance and fatigue for each mechanism is described below.

Adenosine Triphosphate (ATP) Depletion. Depletion of adenosine triphosphate (ATP) in the forebrain of rats induces sleep [81]. Similar studies in mice revealed that disruption of ATP homeostasis can occur following sleep deprivation [82]. In patients with sleep apnea, severe hypoxemia was associated with increased plasma adenosine levels, the production of which occurs in response to ATP

depletion [82]. Analogous studies of the association between ATP homeostasis and fatigue are not available. Therefore, it is unclear if the fatigue experienced by oncology patients is associated with ATP depletion or if sleep mediates the relationship between ATP depletion and fatigue.

Circadian Rhythm Modulation. Sleep disturbance is pervasive during cancer treatment and in survivors [60]. Circadian rhythms are approximately 24-h cycles of physiological processes that influence behavior. These rhythms are generated by molecular "pacemakers" or "clocks" that are entrained by external queues such as light [83]. In a recent study of women with breast cancer as compared to healthy controls [84], increased fatigue was associated with disruptions in circadian rhythms. Of note, the occurrence of fatigue and altered circadian rhythms, as well as their associations, preceded chemotherapy treatment [84]. Similar relationships were observed in other studies of oncology patients, both prior to [29, 42, 44] and after [22, 44, 85] cancer treatment.

The association between sleep disturbance and fatigue prior to treatment, as well as in the general population, suggests that innate variability in various components of the molecular circadian clocks may contribute to the occurrence and severity of both symptoms. The various components of the molecular clocks are encoded by a group of genes referred to circadian genes [86]. Although no studies have examined the relationship between variations in circadian genes and either sleep disturbance or fatigue in oncology patients, a number of studies were done in non-oncology samples. Variations in the gene TIMELESS were associated not only with fatigue in the setting of depression but with fatigue that co-occurred with early awakenings in a population-based Finnish sample [87]. In addition, in one study, an association was made between cytokine dysfunction and circadian dysregulation [88]. Of note, tumor necrosis factor alpha and interleukin 1 beta inhibited molecular clock gene functions and were associated with disrupted sleep rhythms in mice [88].

Cytokine Dysregulation. Cytokine dysregulation is associated with both sleep disturbance and fatigue. Inflammation appears to disrupt sleep in part by altering sleep architecture [89]. In population-based studies, elevations in markers of inflammation are associated with increased levels of fatigue [90]. In addition, sleep disturbance mediates the relationship between elevated levels of interleukin 6 and increased fatigue [89]. Antagonism of tumor necrosis factor alpha is associated with improved sleep [91], which suggests that the relationship between inflammatory cytokines and sleep disturbance is reciprocal. Taken together with the genetic associations observed between cytokines (i.e., interleukin 6, tumor necrosis factor alpha) and sleep disturbance and fatigue in oncology patients [76–79], cytokine disruption appears to play a central role in the development of fatigue through the disruption of sleep.

Hypothalamic-Pituitary-Adrenal Axis Disruption. A growing body of evidence suggests that abnormalities in the circadian rhythms of stress-related hormones are associated with fatigue and sleep disturbances [92, 93]. Perturbations to the hypothalamic-pituitary-adrenal axis, the primary neuroendocrine interface that responds to

stress, induce important biologic and behavioral consequences. Deep sleep has an inhibitory effect on the hypothalamic-pituitary-adrenal axis. Conversely, activation of the hypothalamic-pituitary-adrenal axis, with the administration of glucocorticoids (i.e., a biochemical mediator of stress), leads to increased arousal and sleep disruption. Cancer-associated stressors may alter the circadian functions of hypothalamic-pituitary-adrenal axis-associated neuroendocrine activities, which result in the symptoms of fatigue and disrupted sleep-wake patterns in patients with cancer.

Serotonin Dysregulation and Vagal Afferent Activation. The involvement of serotoninergic neurons in sleep is well established [94]. Neuroactive molecules (e.g., serotonin) activate vagal afferents and induce fatigue [95, 96]. Serotonin N-acetyltransferase is the rate-limiting enzyme in the synthesis of melatonin from serotonin [97]. In a recent study of oncology patients who were and were not depressed [98], the effect of the selective serotonin reuptake inhibitor paroxetine as compared to placebo on sleep disturbance was examined. Although sleep disturbance remained prevalent in both groups, paroxetine treatment was associated with improved sleep in both depressed and non-depressed cancer patients [98]. However, improvements in fatigue were not observed [99]. It is not clear why improvements in fatigue did not parallel decreases in sleep disturbance in these oncology patients.

Co-occurrence of Sleep Disturbance, Fatigue, and Other Common Symptoms

While sleep and fatigue are prevalent in oncology patients, many other symptoms can co-occur. Depressive symptoms, anxiety, pain, nausea, and cognitive impairment are but a few of the symptoms that occur in oncology patients [10, 43, 100, 101]. All of these symptoms can have negative effects on patient outcomes [100–102]. The occurrence of these symptoms can be caused or exacerbated by the cancer itself or its treatment [103]. In addition, multiple co-occurring symptoms are associated with decreased quality of life [10]. These observations beg the question of whether the study of fatigue and sleep disturbance without consideration of the occurrence and impact of other common symptoms may limit progress in our understanding of the mechanisms that underlie these commonly co-occurring symptoms [104]. Emerging evidence supports the hypothesis [67, 105–107] that shared mechanisms exist for the co-occurrence of common symptoms [108, 109]. Moreover, an increased understanding of the mechanisms that underlie the co-occurrence of multiple symptoms may prove crucial to the development of successful interventions to reduce the severity of said symptoms and to improve the quality of life of oncology patients [107].

The study of multiple co-occurring symptoms in cancer patients has led to the emergence of “symptom cluster” research. Importantly, these co-occurring symptoms form groups termed symptom clusters [110]. Symptom clusters are associated with decreased quality of life [104, 111, 112] as well as with decreased function

and decreased survival [113]. Importantly, symptom clusters can occur prior to treatment [109, 114, 115]. Although the study of symptom clusters is nascent, research of specific symptom clusters is occurring.

To date, the majority of the studies of symptom clusters in oncology patients are cross-sectional. However, because symptoms fluctuate over time, longitudinal studies of how symptom clusters change over time are needed to provide a better understanding of the mechanism(s) that underlie the development and maintenance of symptom clusters. The importance of studying symptoms over time is supported by a recent work that examined the co-occurrence of symptoms at different time points in the same sample and found that similar symptom clusters occurred at each time point [116].

Although awareness of the co-occurrence of symptoms has existed for over two decades [101, 117], the study of symptom clusters is considerably more recent [118]. An enduring challenge in the study of symptom clusters remains the lack of consistency in the methods used to cluster symptoms [119]. Currently, the analytic methods used to cluster co-occurring symptoms include correlation, regression modeling [120, 121], factor analysis [122], principal component analysis [121, 123], cluster analysis [104, 111], and latent variable modeling [109]. While the decisions that dictate the use of a specific approach are beyond the scope of this chapter, they can be found in several reviews of analytic methods for clustering symptoms [124–126]. Symptom cluster research can be grouped into two categories: de novo identification of symptom clusters (i.e., clustering *symptoms*) and the identification of subgroups of patients based on a specific symptom cluster (i.e., clustering *patients*) [110].

De Novo Identification of Symptom Clusters. De novo identification of symptom clusters is the most common type of symptom cluster research that occurs with oncology patients. Cluster analysis has been used to identify symptom clusters primarily in heterogeneous [127–129] samples, as well as in homogeneous (i.e., lung [130, 131], breast [132]) samples of oncology patients. The specific symptoms identified in each cluster differed across the studies, presumably due to the use of different instruments to measure symptoms and differing analytic approaches (i.e., factor analysis [128–131], hierarchical cluster analysis [127, 132]). Nevertheless, the identification of symptom clusters represents an important starting point from which to move on to the clustering of patients based on an a priori defined symptom cluster.

Identification of Subgroups of Patients Based on a Specific Symptom Cluster. While the study of how symptoms cluster (i.e., co-occur) is evolving, research that focuses on the identification of distinct subgroups of patients based on their experience with a specific symptom cluster is nascent. Few groups attempted to identify specific subgroups of patients based on their experience with a specific symptom cluster (e.g., pain, fatigue, sleep disturbance, depression [104, 109, 111]). The most common symptom clusters studied to date are the pain-fatigue-sleep disturbance-depression symptom cluster [104, 109, 111] and the pain-fatigue-sleep disturbance symptom cluster [57, 120, 133].

The pain-fatigue-sleep disturbance symptom cluster occurs in both homogeneous [133] and heterogeneous [57, 120] samples of oncology patients. The most common demographic and clinical characteristics evaluated included age, gender, number of comorbid conditions, stage of disease, and cancer treatment. However, the associations between these characteristics and the pain-fatigue-sleep disturbance symptom cluster varied among the three studies, which suggests that these characteristics are not the primary determinants of this cluster.

The impact of the pain-fatigue-sleep disturbance-depression symptom cluster was evaluated in several heterogeneous samples of oncology patients [104, 109, 111]. The subgroups of oncology patients identified with similar levels of the pain-fatigue-sleep disturbance-depression symptom cluster occur in strikingly similar proportions across the three samples. One subgroup of patients, which constituted approximately 5–20 % of the samples, reported low levels of all four symptoms [103, 108, 109]. In contrast, approximately 10–20 % of participants reported high levels of all four symptoms [103, 108, 109]. Similar to the pain-fatigue-sleep disturbance symptom cluster, the association of clinical and demographic characteristics varied among the studies, with lower functional status being the most consistently observed characteristic associated with pain-fatigue-sleep disturbance-depression cluster membership (i.e., lower functional status was associated with the "all high" pain-fatigue-sleep disturbance-depression subgroup) [103, 108, 109].

The impact of the pain-fatigue-sleep disturbance-depression symptom cluster was documented in two independent samples of oncology patients [104, 111]. In both studies, subgroups of patients with higher levels of all four symptoms were younger and had poorer functional status and worse quality of life. In addition, in a recent study, a genetic predisposition was documented for this symptom cluster [109]. The identification of genetic markers associated with subgroup membership may provide insights into the molecular mechanism(s) that underlie this symptom cluster.

Novel Methods to Study Sleep Disturbance and Fatigue in Cancer. A key consideration in the study of symptoms and symptom clusters is the analytic approach to model these symptoms. The emergence of novel methods for modeling change, the identification of latent variables, and the availability of computational resources required for such complex modeling have set the stage for a more sophisticated examination of symptoms. Another important consideration is the particular instrument(s) used to assess symptoms. Instruments can be unidimensional or multidimensional and can measure different dimensions of the symptom experience (e.g., occurrence, severity, frequency, distress) [134]. The majority of studies of fatigue, sleep disturbance, and symptom clusters that include sleep disturbance and/or fatigue have focused on a single time point (i.e., cross-sectional) or a small number of repeated measures. More sophisticated approaches to modeling changes in the symptom experience over time are available that include the identification of subgroups of individuals who are more similar in their experience of a symptom(s) than other individuals (i.e., latent variable modeling). And finally, the study of changes in symptoms over time necessitates the use of instruments that are sensitive to change, a feature which has not been examined for many of the measures that evaluate fatigue and sleep disturbance (see Tables 9.1 and 9.2).

Interventions for Sleep Disturbance and Fatigue

Currently, an efficacious treatment to reduce fatigue associated with cancer and its treatment is not available. Interventions to ameliorate fatigue were designed based on the understanding that fatigue is influenced by both behavioral and cognitive factors. While pharmacologic [135] and non-pharmacologic [136] interventions to reduce fatigue severity were evaluated, only modest improvements in fatigue severity occurred across numerous studies. Most of these studies were done during the period of active cancer treatment, and most of the studies evaluated patients with breast cancer. Additional intervention research is warranted in patients with other types of cancer, patients with metastatic disease, and in cancer survivors with persistent fatigue.

Pharmacologic interventions that were evaluated for the treatment of fatigue include antidepressants, hemopoietic growth factors, progestational steroids, and psychostimulants [137]. Although the hemopoietic growth factors, erythropoietin and darbepoetin, induced a small reduction in fatigue in oncology patients [135], safety concerns for this class of drugs have resulted in the discontinuation of their use for the treatment of fatigue. The only drug currently showing promise in the treatment of fatigue in oncology patients is the psychostimulant methylphenidate. However, improvements in fatigue were small [137].

Non-pharmacologic interventions have focused on psychosocial interventions or exercise-based interventions [136]. Exercise-based interventions of modest intensity were associated with modest decreases in fatigue in oncology patients [138–141]. Generally, interventions were limited to oncology patients with breast or prostate cancer. However, the type of exercise and dose are still the subject of debate and research [138–141]. In comparison, evidence to support the use of psychosocial interventions for the treatment of fatigue is less consistent [142]. However, a small reduction in the severity of fatigue in oncology patients has been observed with the use of group psychotherapy or cognitive-behavioral interventions [143].

Although interventions to treat fatigue alone have shown modest success, the impact of interventions to improve sleep and fatigue in oncology patients remains a topic of importance. The behavioral therapies tested thus far were unsuccessful in improving sleep and fatigue [144, 145]. However, research studies that evaluated the efficacy of interventions to improve both sleep and fatigue are extremely limited. The increased focus on symptom cluster research may lead to interventions to treat not only sleep and fatigue but other co-occurring symptoms.

Summary

Overall, the picture for oncology patients with fatigue remains bleak. Even though the occurrence of fatigue in oncology patients was described over three decades ago [146], research on fatigue has lagged behind research on other symptoms (e.g., pain, nausea) associated with cancer or its treatment. Severity of fatigue is not predictable by tumor type, treatment, or stage of disease. No clear precipitating factors, no clear

mechanisms, and no targeted therapies are available for fatigue in oncology patients. Although recognized as a serious clinical symptom, fatigue is frequently underreported by oncology patients because they do not want to distract clinicians from treating their cancer. In addition, it is underrecognized and undertreated by oncology clinicians because of lack of effective treatments. However, both basic and clinical research on the etiology of fatigue and co-occurring symptoms, including sleep disturbance, continues to provide additional opportunities for the development of novel interventions to treat these common problems.

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Chapter 10
Sleep Disturbances in Cancer Survivors

Lavinia Fiorentino and Sonia Ancoli-Israel

Abstract A diagnosis of cancer and the subsequent cancer treatments are often associated with sleep disturbances. These sleep disturbances can last for years after the end of the cancer treatment. In cancer patients and survivors, sleep disturbances are associated with anxiety, depression, cognitive impairment, increased sensitivity to physical pain, impaired immune system functioning, lowered quality of life, and increased mortality. Given these associations and the high prevalence of sleep disturbance in cancer patients, it is paramount that clinicians assess sleep disturbances and treat sleep disorders in cancer patients and survivors. Improving the quality of sleep in cancer patients may have critical effects on the lives of cancer patients, effects that range from higher quality of life to length of survivorship.

Keywords Insomnia • Cancer • Fatigue • Cognitive behavioral therapy • Survivors • Breast cancer

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_10,

Why Is It Important to Study Sleep in Cancer Patients and Survivors?

A diagnosis of cancer and the subsequent cancer treatments (chemotherapy, radiation, surgery) are often associated with sleep disturbances, which, in many cases, last long into the cancer survivorship years. Sleep disturbance is associated with a variety of medical and psychological complaints; among the ones most pertinent to cancer patients are anxiety, depression, cognitive impairment, increased sensitivity to physical pain, impaired immune system functioning, lowered quality of life, and increased mortality. Given these associations and the high prevalence of sleep disturbance in cancer patients, it should become paramount for clinicians to assess for sleep disturbance and treat sleep disorders in cancer patients and survivors. Improving the quality of sleep in cancer patients may have critical effects on the lives of cancer patients, effects that range from higher quality of life to length of survivorship.

While a few studies have explored the prevalence of sleep-disordered breathing (SDB) in head and neck cancer patients [1, 2], and a few examined periodic limb movements in sleep (PLMS) among breast cancer patients [3], the majority of sleep studies conducted in cancer patients have examined insomnia. This chapter will focus primarily on insomnia.

Epidemiology

Patients with cancer report difficulty falling asleep, difficulty staying asleep, and non-restorative sleep, before, during, and for years after treatment [4]. While there have been no large-scale epidemiological studies of sleep disturbance in patients with cancer, there have been many smaller studies, mostly cross-sectional in nature, using convenient samples, different methodologies, and heterogeneous definitions and measures of sleep disturbances. Because of this large variability in methods, the estimates of sleep disturbance in cancer patients range from 30 to 75 % [5, 6], double that of the general population.

Insomnia in cancer patients has been reported through subjective (self-report) measurement studies as well as objective (polysomnography and actigraphy) measurement studies.

Subjective Sleep Measures

Studies that examined subjective sleep reports in cancer patients found significant complaints of difficulty sleeping [7], with the severity of the complaints being comparable to the insomnia complaints in other medical conditions [8]. Anderson and colleagues compared 354 cancer patients, 72 psychiatric patients, and 290

non-patient volunteers and found that 62 % of the cancer patients reported moderate to severe sleep disturbance, while only 30 % of the volunteers and 53 % of the depressed patients reported the same complaint [9]. Patients with different types of cancer reported different kinds and different rates of sleep problems.

In a survey of more than 1000 patients with different types of cancer and at different treatment phases, 31 % reported insomnia symptoms, 28 % complained of excessive sleepiness, and 41 % reported restless legs [10]. Lung cancer patients had the highest or second-highest prevalence of sleep problems in general, while breast cancer patients had a high prevalence of insomnia and fatigue. In another survey, Savard et al. studied the prevalence of insomnia in 300 women with breast cancer and found that 19 % met the diagnostic criteria for insomnia and that in 95 % the insomnia was chronic [3]. Furthermore, they found that in more than 50 % the onset of insomnia preceded the breast cancer diagnosis and that in 58 % of the cases the patients reported that cancer aggravated their sleep problems.

Engstrom et al. administered an extensive sleep-specific telephone survey to 150 patients with lung or breast cancer that were undergoing a variety of treatments [11]. Of patients interviewed, 44 % reported a sleep problem in the previous month; however, only about 17 % communicated the problem to their doctors. In a second phase of the survey study, another group of cancer patients (n = 20) was interviewed, 45 % of whom reported a sleep problem in the prior month, half of whom rated the sleep problem as moderate, severe, or intolerable. The most frequent type of sleep complaint was awakening during the night, which was reported by more than 90 % of the patients. About 85 % reported sleeping fewer hours than normal, 75 % complained of difficulty getting back to sleep, and 39 % reported daytime napping. These results help identify the type of sleep complaints cancer patients suffer from.

Another way to obtain information about the prevalence of insomnia and sleep disturbances in cancer patients is by looking at sedative/hypnotic use. Derogatis and colleagues reported that the most frequently prescribed psychotropic medications in cancer patients were hypnotics, accounting for 48 % of total prescriptions [12]. Furthermore, out of 814 total prescriptions for hypnotics, "sleep" was the physician's stated reason for the prescription in 85 % of cases compared to 14 % for "medical procedure," 1 % for "nausea/vomiting," 1 % for "psychological distress," none for "pain," and none for "other." The same results were replicated in a more recent study that showed that 44 % of approximately 400 prescriptions over 200 consecutive cancer clinic patients were for hypnotic medications [13]. The patient sample in this study was broad and ranged in cancer diagnoses, severity, and time since diagnosis (1 to 204 months, mean 23 months).

Objective Sleep Measures

The gold standard for recording sleep is polysomnography (PSG), which consists of an overnight sleep measurement that records brain waves, eye movement, muscle tension, and often respiration, heart rate, and leg movements. While not invasive,

PSG recordings can be burdensome and time consuming, particularly for cancer patients who are often overwhelmed with medical appointments and are fatigued and/or in pain. Therefore, only a few studies have used PSG to study sleep in cancer.

Silberfarb et al. compared lung cancer patients, breast cancer patients, insomnia patients, and normal volunteers with PSG findings and showed that, as predictable, patients with insomnia had the shortest total sleep time of all the groups [14]. While the lung cancer patients spent more time in bed, they did not sleep more than the breast cancer patients or than the normal controls and therefore had lower sleep efficiency (the percent of the time in bed actually spent asleep) as well as longer sleep onset latency (time it takes to fall asleep) and spent more time awake during the night than those with breast cancer or the normal sleepers. Our laboratory collected PSG data immediately post cycle 4 of chemotherapy in 33 breast cancer patients and found that patients experienced disturbed sleep; they spent more time in the lighter stages of sleep (stages N1 and N2) and less time spent in deeper stages (stages N3 and REM sleep). The women in this study also spent more time awake with lower sleep efficiency than the general population, even after the completion of their chemotherapy [15].

Some studies have used PSG to examine the prevalence of other specific sleep disorders. In the Silberfarb et al. [16] study described above, none of the cancer patients were found to have SDB, but there was a higher prevalence of PLMS in the cancer patients compared to the controls or the insomnia patients. In our own data, we reported that 36 % of breast cancer patients had PLMS [15]. PLMS is treatable; therefore, it is important to rule out PLMS as a cause of sleep disturbance in patients with cancer.

A couple of small-scale studies (from 17 to 33 patients) found elevated prevalence of obstructive sleep apnea (OSA) in patients with head and neck cancers (from 12 % to 91.7 %) [1, 2]. Findings from our laboratory found that 48 % of our breast cancer patients had at least five respiratory events per hour of sleep [17], a substantially higher prevalence than that reported in age-comparable non-cancer women.

Actigraphy is another way to measure sleep objectively. An actigraph consists of a small device about the size of a wristwatch, which is worn on the wrist of the nondominant hand, and records movement via motion-sensitive accelerometers. Algorithms have been developed to estimate sleep and wake time from the movement, and correlation studies with PSG suggest high reliability [18]. Actigraphy is easy to use and is ecologically friendly; patients wear it during the day and night while attending their lives as they would if they were not wearing it. Therefore, it is particularly suitable to study sleep in cancer patients.

Miaskowski and Lee studied wrist actigraphy over a 48-h period in 24 patients at various time points during radiation therapy for bone metastases [19]. They found that as radiation therapy progressed, the subjective sleep complaints increased and sleep efficiency declined. Interestingly, frequent urination, rather than pain intensity, was reported to be the main cause of awakening in the night. In a recent pilot study, Payne et al. reported that, compared to healthy controls, breast cancer patients had significantly shorter total sleep time as estimated from actigraphy [20].

In our laboratory, actigraphic sleep measures and patient reports of sleep quality were measured in 82 women before and during chemotherapy for breast cancer. We found that breast cancer patients were already complaining of sleep problems before the start of chemotherapy and actigraphic recordings confirmed that the women were asleep on average for only 77 % of the night [21]. During treatment, the percent sleep dropped to 74 %.

There is evidence of objective sleep being disrupted by hot flashes in women with breast cancer. Savard and colleagues reported that nights with hot flashes were associated with more percentage wake time, lower percentage stage two, and less efficient sleep compared to nights with no hot flashes [22]. Hot flashes are also common in men undergoing androgen-suppressive therapy for prostate cancer. Hence, recording and measuring hot flashes in future studies investigating sleep in these cancer populations is advisable.

Insomnia in Cancer Patients

Insomnia is the most prevalent and most studied sleep disorder in cancer patients. In order to be diagnosed with insomnia, a patient must have difficulty initiating or maintaining sleep or a non-restorative sleep which lasts for at least 1 month and which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Furthermore, chronic insomnia is defined by the duration of the insomnia episode ranging from 30 days to 6 months depending on the study [23]. Factors that make people more vulnerable to insomnia, particularly complaints of initiating and maintaining sleep, include previous complaints of insomnia (odds ratio, 3.5), female gender (odds ratio, 1.5), advancing age (odds ratio, 1.3), snoring (odds ratio, 1.3), and multiple concomitant health problems (odds ratios, 1.1 to 1.7) [24]. Cancer patients tend to have two of these risk factors for insomnia (i.e., advancing age and concomitant health problems).

The etiology of insomnia is largely unknown, but the main theoretical framework explaining the occurrence of insomnia is Spielman's three-factor (3-P) model of insomnia [25]. This model postulates three factors which are necessary for the development of chronic insomnia: predisposing factors that make a person prone or vulnerable towards insomnia, precipitating factors that trigger the insomnia, and perpetuating factors that maintain the insomnia (see Table 10.1).

Etiology, Consequences, and Correlates of Insomnia in Cancer Patients

Most studies on sleep problems in cancer have been conducted in women with breast cancer. The population of women with breast cancer is possibly more prone to insomnia for various reasons, including disruption of sleep due to increased

Table 10.1 Example of the 3-P model applied to a cancer patient

A. Predisposing factors	1. Genetic predisposition towards hyperarousability
	2. History of anxiety or depression
B. Precipitating factors	1. Diagnosis of breast cancer
	2. Increased stress related to diagnosis
	3. Increased stress related to forced reduced employment and financial consequences
	4. Surgical pain
	5. Chemotherapy-related circadian disruption
C. Perpetuating factors	1. Napping or spending increased time in bed to make up for lost sleep at night
	2. Increased caffeine intake to combat tiredness
	3. Reduced social contact because of daytime sleepiness and fatigue
	4. Increased stress due to fear of sleep deprivation leading to poorer health and cancer prognosis

frequency and severity of the hot flashes associated with sudden menopause secondary to the breast cancer treatment. Other possible factors include increased depression, and anxiety and fatigue levels following the breast cancer diagnosis.

Several studies have confirmed these risk factors. Savard et al. studied the prevalence, clinical characteristics, and risk factors for insomnia in 300 breast cancer patients [3]. Their study showed that factors associated with high risk of insomnia were sick leave, unemployment, widowhood, lumpectomy, chemotherapy, and a less severe stage of cancer at diagnosis. Furthermore, lower performance status, anxiety, depression, and confusion were reported to be associated with sleep disturbance in advanced cancer patients. A large survey of 982 different types of cancer patients found that insomnia-related risk factors included fatigue, age, restless legs, sedative/hypnotic use, low or variable mood, dreams, and recent cancer surgery [10]. In palliative care patients, the study of participants with complaints of pain and symptom management revealed that difficulty falling asleep was mostly associated with fatigue and anxiety, while early awakening was more importantly associated with fatigue [26]. A prospective study in terminally ill patients with cancer, being younger, having diarrhea, and living alone was significantly associated with sleep disturbance. Interestingly, an increase in psychological distress was the only significant predictive factor for the development of sleep disturbances between registration and admission to a palliative care unit [27].

Radiation and chemotherapy are both reported to be associated with sleep disturbances. However, as mentioned above, studies have shown that sleep disturbances may already exist before the start of treatment [21]. Cimprich et al. administered self-report items relating to sleep quality, fatigue, and distress to breast cancer patients who had not yet undergone cancer treatment. They found that insomnia was the most frequent symptom, with 88 % of the sample reporting difficulty sleeping, and that it was correlated with high levels of distress [28]. Other findings were that self-reported distress and anxiety symptoms were correlated with insomnia even before treatment had begun and that self-ratings of fatigue and sleep difficulty were high.

In patients whose self-ratings of anxiety and anger were lower, the levels of insomnia and fatigue were still high. Data from our laboratory showed that disturbed sleep pretreatment was correlated with fatigue, depressive symptoms, and functional outcome in breast cancer patients [21] and sleep quality during chemotherapy was associated with the presence and severity of pretreatment symptoms [29].

Studies have shown that pain and psychiatric disorders (e.g., depression and anxiety) have also been reported as possible contributors to poor sleep in cancer, as these factors may work together to induce sleep difficulties. As Engstrom et al. [11] posited, pain may be the cause of nocturnal awakenings and that the usual return to sleep is prevented by psychological distress. Lewin and Dahl pointed out that in a variety of medical conditions, the management of pain interrelates with sleep quality in many ways [30]. They theorized that since sleep leads to recovery and repair of tissue and may offer a temporary cessation of the psychological awareness of pain, poor sleep can lead to difficulty managing pain, creating a self-perpetuating cycle of pain and poor sleep. Surprisingly, though, there are few studies supporting the notion that pain leads to disrupted sleep. On the contrary, Silberfarb and colleagues compared 32 cancer patients (15 breast cancers, 17 lung cancers), 32 age- and sex-matched normal volunteers, and 32 patients with insomnia and found that only breast cancer patients complained of pain prior to bedtime even though their sleep quality was not significantly affected [16].

Pain in cancer patients is most often treated with opioids, and sedation is a common side effect of opioids. However, the relationship between opioid use and sleep has not been well studied. Limited PSG data show that opioids decrease REM sleep and slow-wave sleep [31], suggesting that rather than improving sleep by being sedated, opioids may actually contribute to the sleep disturbances in cancer patients with chronic pain. In addition, the most serious adverse effect of opioids is respiratory depression which may exacerbate the hypoxemia in those individuals with SDB and thus lead to more interrupted sleep.

The relationship between sleep disturbances and depressive symptoms has not been thoroughly studied in cancer patients. It is known that insomnia is often comorbid with depression and that sleep disturbance is a risk factor of depressive symptoms. It is also known that the amount of insomnia in cancer patients has been shown to be as high as the amount of insomnia found in depressed patients and that depression and sleep disturbances already exist before the start of cancer treatment [21, 28]. This suggests that sleep problems may be independent of depressive symptoms.

Insomnia may also exacerbate cancer-related fatigue (CRF), one of the most widely known complaints in cancer patients. Different dimensions of fatigue (physical, cognitive, emotional, behavioral, etc.) are likely to be associated with disrupted sleep and desynchronized sleep/wake rhythms. Our laboratory used actigraphy to measure circadian activity rhythms, fatigue, and sleep/wake patterns in breast cancer patients. We found that circadian rhythms were robust at baseline, but became desynchronized during chemotherapy, and this desynchronization was correlated with fatigue, low daytime light exposure, and decreased quality of life [21, 32].

Treatment

The treatments for insomnia in cancer patients are the same treatments that are available to the general population, primarily cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy. The NIH State-of-the-Science Conference on insomnia concluded that CBT-I is as effective as prescription medications for brief treatment of chronic insomnia and that there are indications that the beneficial effects of CBT, in contrast to those produced by medications, may last well beyond termination of treatment [23]. CBT-I can be delivered individually or in group. It usually involves meeting for 5–8 weekly sessions of approximately 1 h each. CBT-I aims at eliminating the perpetuating factors of insomnia (3-P model explained above). It includes sleep education as well as a variety of techniques: sleep restriction (restricting time in bed to time asleep), stimulus control (using bed for sleep only), relaxation, setting aside a worry time, and cognitive restructuring (restructuring maladaptive thoughts into more adaptive ones).

There are data suggesting that CBT-I is effective for the treatment of insomnia in cancer. Savard et al. conducted a randomized wait-list-controlled study on the effects of CBT-I on insomnia in women with breast cancer [33]. Results suggested that CBT-I was effective in decreasing sleep complaints as well as decreasing levels of depression and anxiety and increasing quality of life. Therapeutic effects were maintained at follow-up. Fiorentino et al. performed a randomized controlled crossover pilot study using CBT-I among breast cancer survivors with insomnia and found that CBT-I improved sleep measured with both subjective (sleep diary and questionnaire) and objective (actigraphy) measurements (see Figs. 10.1 and 10.2) [34].

Although efficacious, the compliance to the behavioral prescriptions of CBT-I for cancer patients can be a problem. Commitment, time, fatigue, and cognitive difficulties can all affect the willingness and ability to commit to and maintain the behavioral changes that CBT-I promotes. Another issue in the delivery and implementation of CBT-I in cancer patients is the current scarcity of therapists trained in CBT-I.

Pharmacologic interventions are the most common treatment for sleep in the general population as well as in cancer patients. The NIH State-of-the-Science Conference on insomnia concluded that the newer, shorter-acting benzodiazepine receptor agonists are efficacious in the management of insomnia and the frequency and severity of adverse effects associated with these agents are much lower than those seen with the older, longer-acting benzodiazepines [23]. It has also been concluded that all antidepressants, antihistamines (H1 receptor antagonists), and antipsychotics have potentially significant adverse effects which raises concerns about the risk–benefit ratio; thus, their use in the treatment of chronic insomnia was not recommended.

Although pharmacotherapy is the most prescribed therapy for cancer patients with sleep disturbances [10, 35], there is a paucity of studies related to pharmacologic interventions in cancer patients. A recent review concluded that evidence is not sufficient to recommend specific pharmacologic interventions for sleep

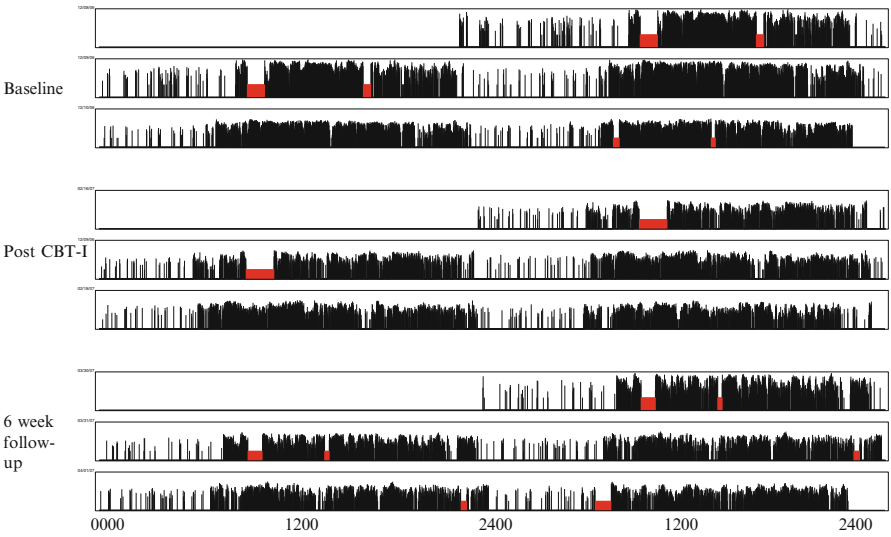

Fig. 10.1 Actigraphy plot of breast cancer participant assigned to the condition receiving CBT-I immediately after baseline assessment. *Black lines* represent activity, while the *white space* is sleep. *Red* represents the times the patient took off the actigraph (e.g., for showering). The graph is double plotted to better see circadian rhythms. It is noticeable that sleep is of better quality during the three nights after CBT-I and continues to improve after the 6-week follow-up

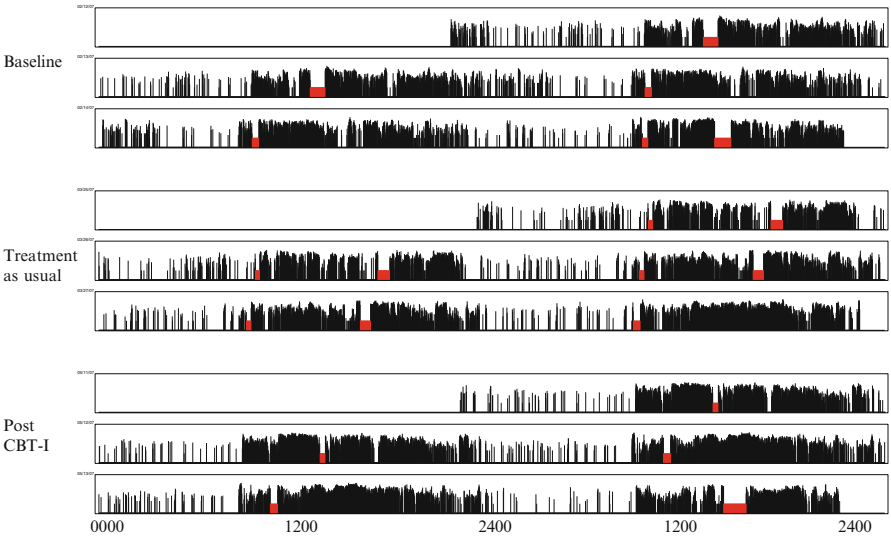

Fig. 10.2 Actigraphy plot of breast cancer participant assigned to the condition receiving 6 weeks of treatment as usual after the baseline assessment and then CBT-I. *Black lines* represent activity, while the *white space* is sleep. *Red* represents the times the patient took off the actigraph (e.g., for showering). The graph is double plotted to better see circadian rhythms. It is noticeable that sleep is equally poor during the first two assessments and improves during the three nights after CBT-I

disturbances in cancer patients [6]. Clinicians need to evaluate the relative effectiveness and side-effect profiles of pharmacologic agents, and researchers need to be challenged to evaluate the impact of pharmacologic treatment on sleep disturbances among cancer patients [6].

Bright light therapy is another non-pharmacologic treatment option that appears promising. Data from our laboratory suggest that increased bright light exposure improves fatigue, sleep (increases total sleep time, decreases wake time during the night, and decreases daytime napping), circadian rhythms, and quality of life during chemotherapy for patients with breast cancer [36–38].

Conclusion and Future Directions

Sleep disturbances, particularly insomnia, are common in cancer survivors. Their etiology can be multifactorial and can have deleterious consequences on the patient's quality of life. The emotional impact of a cancer diagnosis, the family and social repercussions, the cancer itself, the cancer-related symptoms, and the cancer treatments all may start or exacerbate sleep problems. However, despite their prevalence and severity, complaints of poor sleep are often overlooked in cancer patients and are rarely treated, aside from occasional use of sedative/hypnotics or sedating antidepressants. As several studies have now confirmed the beneficial effects of cognitive behavioral therapy for insomnia (CBT-I) in cancer patients (mostly breast cancer) and survivors, CBT-I needs to be considered as the first-line treatment.

Hypnotics are commonly prescribed to cancer patients. Despite this common use, little to nothing is known about the safety of these drugs in cancer patients. Given the possible interaction effects of the hypnotic/sedatives with cancer treatment agents, the side effects, and potential tolerance and addiction issues, the common use of these drugs in cancer patients is concerning.

More basic research is needed to improve the knowledge of the underlying mechanisms relating poor sleep and cancer. Translational research is needed to increase the dissemination of the efficacious treatments to cancer clinics and hospitals and therefore increase accessibility of the treatment to cancer patients and survivors. The long-term goal of research on sleep disturbances in cancer patients should be to illuminate approaches that might improve the quality of life of cancer patients during diagnosis, treatment, and survivorship.

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Chapter 11
Sleep-Focused Interventions: Investigating the Effects of Sleep Restriction on Energy Balance

Marie-Pierre St-Onge and Ari Shechter

Abstract Obesity has reached epidemic proportions, and excess body weight and adiposity have been linked to many adverse health conditions including various cancers. Rising obesity rates over the last few decades have been paralleled by concomitant reductions in nocturnal sleep duration, and epidemiological evidence has demonstrated a relationship between short sleep and increased weight gain and obesity. Causality cannot be inferred from these studies however, so laboratory-based interventions are essential to determine the nature of the short sleep-obesity link. The aim of this chapter is to summarize and evaluate the clinical intervention studies which altered sleep either by partially restricting sleep episode length or by completely eliminating the sleep episode to investigate the resulting effects on energy balance. Specific energy balance parameters considered include energy expenditure, subjective hunger/appetite ratings, appetite-regulating hormones, and food intake. Most studies support a role of short sleep in increasing food intake, but the results on energy expenditure, hunger, and hormonal regulation of food intake are less consistent. This chapter critically evaluates how methodological differences may contribute to discrepancies and inconsistencies between study results, with an emphasis on the roles of sex, the state of energy balance of study participants, and the timing of manipulated sleep schedules within the intervention studies.

Keywords Sleep • Sleep deprivation • Sleep duration • Energy balance • Energy expenditure • Hunger • Appetite hormones • Food intake • Obesity

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7_11,

Introduction

Obesity has reached epidemic proportions worldwide, and a recent estimate indicates that almost a third of the adult population in the United States is obese (body mass index [BMI] ≥30 kg/m^2) [1]. Obesity is a problem that has been linked to adverse health outcomes, including cardiovascular disease, diabetes, and overall reductions in life expectancy. Moreover, epidemiological evidence has demonstrated an association between obesity and increased risk of developing a variety of cancer types, including cancers of the esophagus, colon, breast, endometrium, kidney, liver, and pancreas [2]. Clearly understanding the various factors which contribute to the increased prevalence of obesity will therefore have widespread ramifications for many aspects of public health, including cancer.

One such potential contributor is sleep, which researchers increasingly point to as having a functional role in maintaining proper metabolism in addition to its more well-established roles in cognition and brain function. Over the past few decades, the drastic increase in the prevalence of obesity has been reflected by substantial decreases in the amount of sleep being obtained. For example, whereas in 1960 modal sleep duration was observed to be 8–8.9 h/night, by 2004 more than 30 % of adults aged 30–64 years reported sleeping <6 h/night [3]. More recently, the results of a large, cross-sectional population-based study of adults in the United States showed that 7.8 % report sleeping <5 h/night, 28.3 % report sleeping ≤6 h/night, and 59.1 % of those surveyed report sleeping ≤7 h/night [4].

These decreases in nocturnal sleep duration are likely due to modern technological advances, including widespread use of television and computers at night, and other light-emitting and alerting electronic appliances. Indeed, striking data from the 2011 Sleep in America Poll conducted by the National Sleep Foundation indicate that 95 % of those surveyed use some type of light-emitting electronic device, such as television, computer, cell phone, or tablet in the hour before going to sleep [5]. Exposure to bright, artificial light during the hours preceding bedtime can significantly suppress the release of the sleep-promoting hormone melatonin, which can delay sleep initiation and shorten sleep duration [6]. Related to this is the case of shift workers, who are exposed to high levels of ambient lighting during nighttime hours and frequently experience curtailment of sleep length by 1–4 h/night [7]. These workers show increased BMI and obesity prevalence compared to day workers [8, 9]. Additionally, a disproportionately high incidence of breast cancer was found in shift-working women [10]. One hypothesized mechanism underlying this association was exposure to light at night and subsequent melatonin suppression which can promote breast cancer development [11]. However, the contributions of chronic sleep restriction and obesity in individuals with atypical work schedules have not been established. Interestingly, it was recently observed that exposure to light at night is associated with higher odds of obesity and dyslipidemia [12], which further suggests an interaction between short sleep, obesity, and cancer.

Mounting epidemiological evidence supports the association between short sleep duration and the development of obesity, with increased odds of obesity observed in

individuals habitually sleeping <7 h/night [13, 14]. Despite the associations, observational studies alone cannot establish a direct link between reduced sleep duration and increased obesity. Indeed, some authors have questioned the clinical relevance of the epidemiological studies and remain skeptical of the proposed causal links between short sleep and obesity [15]. It becomes apparent, therefore, that sleep-focused intervention studies are necessary to clearly determine the role of short sleep as a contributor to the development of obesity. An understanding of the mechanisms underlying this relationship will help determine if short sleep is a modifiable risk factor that affects obesity risk [16] and could potentially lead to targeted lifestyle treatment options for body weight management efforts.

This chapter will focus on laboratory-based clinical intervention studies which manipulated the duration of sleep to determine the resulting effects on energy balance-related parameters. We will consider studies that altered sleep either by partially restricting sleep episode length or by completely eliminating the sleep episode. The specific energy balance parameters included are energy expenditure (EE), hunger/appetite, appetite-regulating hormones, and food intake. A particular focus of this chapter will be on the specific methodological differences that characterize the various intervention studies and how these methodological differences may contribute to discrepancies and inconsistencies in the literature. Our aim, therefore, is to critically review the literature of laboratory-based sleep-focused intervention studies to more fully examine the functional implications of sleep restriction on energy balance while considering the confounding effects of differences in methods used in the various trials.

Energy Balance and Obesity

In practical terms, body weight gain and obesity are thought to develop as a consequence of excessive food intake and/or reduced physical activity [17]. Body weight stability is achieved when energy intake is equal to the energy output. Thus, energy balance is the quantifiable relationship between the intake and output of energy from the body. A major goal of the laboratory-based clinical intervention studies described in this chapter is to mechanistically support or disprove the epidemiological evidence in determining if sleep restriction is a causal factor in the pathway to obesity. If so, sleep restriction is expected to result in an energy imbalance such that energy intake is increased relative to EE (i.e., energy intake > energy output).

Total EE (TEE) is the summation of several components, including resting metabolic rate (RMR; the amount of energy fueling the body at rest), the thermic effect of food (TEF; energy associated with absorption and metabolism of food), and physical activity (PA; voluntary activity like exercise and non-exercise activity) [17]. The amount of food and composition of meals consumed under ad libitum conditions, either via totally free access or during a test meal, is a method of quantifying energy intake. Related to food intake is the hormonal and cognitive control of hunger and appetite. Thus, while measures of circulating appetite-regulating

hormones, as well as current levels of subjective hunger and appetite, do not assess energy intake, per se, they represent an important aspect of the controls of food intake. It should be pointed out that while some have determined how sleep restriction conditions affect a calculated value of energy balance [18, 19], most researchers have rather investigated how sleep can influence the various components of energy balance (e.g., RMR, TEF, food intake) or energy balance-regulating factors (e.g., hunger, hormones).

Methodological Issues: Factors Which Can Influence Energy Balance Parameters or Their Assessment

A variety of issues arise when attempting to compare the results across various intervention studies which have used different methodological approaches to address the question of how sleep restriction affects energy balance. The following sections will systematically address the various methods used for experimental manipulation and data collection and their potential effects on the expression of the outcome variables, including EE, hunger, appetite-regulating hormones, and food intake.

Sleep Duration and Timing Effects

One of the most important aspects to consider when comparing across sleep-focused interventions is the nature of the manipulation, i.e., the duration of the sleep episode that is allowed. The most extreme case of sleep restriction is total sleep deprivation wherein sleep is completely eliminated for ≥24 h [20–24]. Partial sleep restriction, a model of sleep curtailment that is a closer approximation of what is experienced in daily life, allows for sleep episodes that are less than the "typical" sleep episode length (7–8 h/night) and ranges from an allowance of 3 h/night to 5.5 h/night in the studies included in this chapter [18, 19, 25–33]. Though not discussed here, it should be noted that some intervention studies have utilized manipulations which were designed to disturb sleep quality or the relative expression of specific sleep stages without affecting total sleep duration [34–36].

Hormone secretion within the hypothalamic-pituitary axis (HPA), which can affect metabolism and energy balance, is affected by the presence or absence of sleep, per se. Growth hormone and prolactin are observed to increase during sleep, whereas secretion of thyroid-stimulating hormone is inhibited by sleep [3]. Cortisol secretion is increased following total sleep deprivation [3], although the results are less consistent for partial sleep restriction [37]. Distinct sleep stages, as illustrated by cortical electroencephalographic activity, also play a role in the peripheral and central regulation of hormones and physiology, as slow-wave sleep (SWS) increases

GH release and decreases sympathetic nerve activity [3], whereas rapid eye movement (REM) sleep appears to be associated with orexin (hypocretin) release [38]. A sleep stage-specific alteration in EE has also been reported [39]. The effects of total sleep deprivation may therefore be quite distinct from more moderate, partial sleep deprivation in which some sleep is allowed.

Related to the duration of the sleep episode is the length of the exposure to the sleep manipulation. Most studies of acute total sleep deprivation are 1 day [20–23], which may be similar to real-life circumstances in which it is rare to have total sleep elimination for longer than 24 h. Within the clinical laboratory setting, an even more realistic approximation of common real-life circumstances may be a chronic exposure to a milder partial sleep curtailment. Nonetheless, experimental designs have not been uniform, and sleep curtailment manipulations have lasted for as little 1 day to as long as 14 days [18, 19, 25–33]. Short-term sleep restriction may have different metabolic effects than longer-term periods where the body has time to habituate to a new sleep regimen and achieve a new equilibrium. This has not been studied thus far.

Although it may be less apparent than sleep episode length, the timing or scheduling of in-lab sleep opportunities may influence the expression of energy balance-related parameters. One common practice is to center the timing of the restricted sleep episode at the same or a similar clock time as the habitual/baseline sleep episode. For example, researchers may compare a short sleep episode scheduled from 0200 to 0600 h with a normal length episode scheduled from 0000 to 0800 h [25] or compare sleep episodes occurring at 0100–0500 h with those occurring at 2200–0800 h [29]. Alternatively, sleep duration may be restricted by eliminating the early portion of the sleep episode and anchoring sleep time to the wake time of the habitual sleep condition. An example of this would be comparing a short sleep episode scheduled from 0400 to 0800 h to a habitual sleep episode occurring from 2200 to 0800 h [30, 32]. A third option, used by at least one study, is to anchor the sleep episode to bedtime, such as from 2230 to 0400 h for short sleep and from 2230 to 0600 h for habitual sleep [22].

Sleep episode timing is important to consider since sleep is not a uniform process, and the amount and presence of specific sleep stages throughout the night are not constant. A sleep-regulatory interaction between circadian and homeostatic mechanisms [40] dictates that SWS, under a homeostatic regulation, is highest at the start of the sleep episode (regardless of clock time), whereas REM sleep expression, under a circadian regulation, is highest during the early morning hours [41]. Depending on the specifics of the experimental sleep manipulation, the amount of REM sleep may be disproportionately reduced compared to SWS which is expected to be conserved, as may be the case when short sleep episodes are anchored at the start or middle of habitual sleep. These nuances in the timing of the sleep episode are important since a growing body of literature is revealing that sleep architecture plays a role in energy balance regulation [42, 43]. Specifically, REM sleep expression has been demonstrated to be inversely related to hunger ratings and intake of fat and carbohydrate [42]. Moreover, recent epidemiological studies have described an effect of sleep episode timing on food intake and BMI [44, 45].

Methodology of Measurements

Measures of Energy Expenditure

In considering the effects of sleep restriction on energy output, researchers have typically focused on TEE and two of its main components, RMR and postprandial EE, or the TEF. TEE can be measured with the use of doubly labeled water (DLW) [18, 19] and also via whole-room indirect calorimetry (metabolic chamber) [21]. Whereas both can be used to estimate EE over a 24-h period, important differences between the two methods exist. DLW is best suited for measures of long-term free-living EE, whereas indirect calorimetry may be more suited for use within the controlled laboratory environment. However, most researchers may not have access to metabolic chambers at their facilities, and metabolic carts are used to measure RMR by indirect calorimetry over short periods (up to several hours). Caution should be used when making comparisons of TEE measured by each method, since it was observed that free-living EE estimated with DLW was 15 % greater than TEE measured in a metabolic chamber [46]. This is likely due to restricted movements within the confines of a small room. Participants' PA levels are greatly reduced when they are restricted to the small room for 24-h metabolic recordings, compared to free-living conditions. To assess free-living PA, researchers have typically employed either wrist- [27] or waist-worn [18, 25] actigraphy. Of course, the site of attachment of actigraphic recording devices may influence recorded activity levels. Calmly sitting and reading or using the computer may manifest as high activity for wrist-placed recordings but minimal for waist-based recordings, though one study found that wrist actigraphy is a slightly more accurate estimate of calorimetry-based EE than waist placement [47]. Moreover, translation of activity counts to actual caloric expenditure relies on algorithms that have their own inherent errors. RMR [18–20, 26] and TEF [19, 20] are almost uniformly measured via indirect calorimetry using a ventilated hood metabolic cart.

Measures of Hunger/Appetite

In the laboratory setting, subjective ratings of hunger and appetite in response to sleep restriction have been made using either visual analogue scales (VAS) or Likert scales. A VAS typically consists of a bipolar horizontal 10-cm line, with one side expressing minimal extreme and the other side maximal extreme, on which participants rate their current level of hunger (or appetite) along the continuum. A Likert scale is a numeric rating scale on which participants select their current level of hunger (or appetite) by selecting a number between two extreme values. Both the VAS and Likert scales have been established as valid and reliable measurement tools and are thought to yield comparable results [48].

The timing of hunger/appetite assessments may influence the reported results. Indeed, a circadian rhythm of leptin secretion has been described [49] which is

likely to drive a variation of hunger/satiety across the 24-h day. Moreover, food intake has an effect on subjective hunger. It may therefore be difficult to compare the results from ratings taken at one time point, e.g., in the morning in a fasted state [20, 22, 31], with those taken in the evening before dinner [28], 15–30 min before each meal [23], or throughout the day [18, 25, 27, 30].

Measures of Appetite-Regulating Hormones

As was described for appetite ratings, the timing and frequency of the sampling of appetite-regulating hormones is an important experimental detail to consider. This is particularly true for leptin, a satiety hormone, which, as described, circulates with an endogenous circadian rhythmicity [49]. Accordingly, a number of researchers have sampled plasma leptin in response to sleep restriction continuously over a ≥24-h span [18–20, 23, 24, 33] or repeatedly across the daytime and evening but not throughout the night [27, 29, 30]. Some studies discussed here included several leptin measurements selectively taken during the morning [22, 31, 32] or single morning and evening measurements to approximate the diurnal variation [28].

Similar considerations should be made for ghrelin, the other appetite-regulating hormone whose secretion has been most extensively studied in response to sleep restriction. Plasma ghrelin has been sampled in the context of sleep restriction across the 24-h day [18–20] or repeatedly across the daytime and evening but not throughout the night [27, 29]. Importantly, ghrelin, an appetite-stimulating hormone, is affected by food intake, showing a preprandial rise and a postprandial fall in its levels [50]. This should be considered when comparing the results of the study which sampled ghrelin selectively in the morning under fasting conditions [22] with the aforementioned studies with continuous sampling. It should also be noted that whereas most studies measured total ghrelin, only two have reported on active ghrelin levels in response to sleep restriction and these show different results [51, 52].

Availability of food and presentation of meals during the intervention period also makes the comparison of appetite-regulating hormones between studies difficult, since many of these hormones respond to energy intake. As stated, ghrelin levels decrease after a meal [50], whereas leptin levels are stimulated by food intake [53]. Most of the studies investigating the leptin or ghrelin response to sleep restriction presented food in fixed, standardized meals [18, 20, 28, 30, 31, 33], although others allowed for ad libitum food intake [19, 27, 32] and one sampled hormones under conditions of constant intravenous glucose infusion [29]. Unrestricted access to energy intake will often lead to a relative positive energy balance between restricted and habitual sleep, since sleep restriction leads to overeating relative to habitual sleep duration (see below) [18, 19, 25]. This can explain discordant hormonal responses to sleep restriction between studies and would also be expected to explain differences in hunger and appetite ratings, as discussed above. On the other hand, at least one sleep restriction study was conducted under a state of mild negative energy balance [51], which can also affect hormone levels and appetite regulation. In that case, however, food intake was matched during both sleep phases, and the degree of

energy imbalance was equivalent under restricted and habitual sleep. In general, however, most studies did not determine and report energy balance state. Additionally, utilizing controlled feeding in sleep restriction experiments does not necessarily guarantee stable energy balance between sleep phase conditions. Specifically, participants can be over- or underfed, even on a controlled diet, due to slight inaccuracies in energy requirement estimation equations [54].

Measures of Food Intake

The effects of sleep restriction on food intake are assessed by allowing participants to eat freely while measuring total energy consumed and the macronutrient composition of what is eaten. Typically, food is weighed by the investigator before and after meals to determine consumption, and the nutritional content is determined with computer software [18–20, 25, 27]. Differences in the method of food presentation, however, may account for slight discrepancies in the literature. In the studies to date, food intake was measured with buffet/constant availability of food [27], food served in excess at fixed meal times [19, 20, 25], or under conditions of complete participant control over food selection and eating time [18].

Sex Effects

Sex-based differences can contribute to interindividual variability when exploring the interaction between sleep and energy balance. Important changes in physiology, hormone secretion, and behavior across the menstrual cycle in premenopausal women can also affect this relationship.

Whereas sleep macrostructure appears not to be affected by sex [55], sleep complaints are more prevalent in women who are 1.5–2 times more likely to report insomnia symptoms than men [56]. Alterations in sleep across the menstrual cycle have been reported, with reduced REM sleep observed during the postovulatory luteal phase compared to the preovulatory follicular phase [57]. Body temperature and thermoregulation are also significantly modulated by both sex [55] and menstrual phase [55, 58].

Sex-based differences in EE are not widespread [59], although decreased RMR has been observed in women compared to men [60]. In terms of menstrual cycle, some have demonstrated increases in 24-h EE [61, 62] and TEF [62] during the luteal phase compared to the follicular phase. Women have higher fasting serum leptin levels compared to men at similar total body fat mass [63], and they have a higher 24-h leptin profile [64]. Leptin levels appear to have a menstrual phase variation, with increased levels observed during the luteal phase compared to the follicular phase [65, 66]. Sex-based differences in ghrelin levels, however, have been inconsistently observed [67, 68], and ghrelin appears to be stable across the menstrual cycle [69]. Daily energy requirements are higher for men than women, and

this is reflected in the significantly increased daily energy intake observed in men compared to women after controlling for age, height, and weight [70]. Food intake is often observed to have a menstrual cycle variation, with increased intake during the luteal phase compared to the follicular phase, though inconsistencies also exist [71]. Taken together, it is therefore important to be aware of the sex distribution within each study as well as phase of the menstrual cycle when measurements are taken when ovulating women were included. Although it is acceptable for studies to make assessments within subjects at the same phase of the menstrual cycle, this does not discriminate whether there are menstrual cycle phase effects on the impact of sleep duration on energy balance parameters. For example, it is possible that sleep restriction could have a greater impact on food intake in women studied in the luteal phase compared to those studied in the follicular since the luteal phase is a phase of relative hyperphagia. Such menstrual phase effects have not been studied to date. Furthermore, enrolling and testing women regardless of the phase of the menstrual cycle could attenuate the effects observed.

Sleep and Energy Balance

Sleep Restriction and Energy Expenditure

Methodological details and findings of studies which have focused on the effects of sleep restriction on EE are summarized in Table 11.1.

Four investigations included measures of RMR [18–20, 26]. St-Onge and colleagues exposed male and female participants to a time in bed (TIB) of either 9 h (2200–0700 h) or 4 h (0100–0500 h) for 4 days before measuring RMR in the morning via indirect calorimetry [18]. No significant differences were observed between conditions. A study by Buxton and colleagues compared RMR measured via indirect calorimetry at ~0820 h after either 10-h or 5-h TIB (sleep episodes centered at 0300 h) for 7 days and also observed no between-condition differences [26]. Similarly, Nedeltcheva and colleagues also observed no difference in RMR after awakening when comparing between 8.5-h and 5.5-h TIB (sleep episodes centered at habitual sleep midpoint) for 14 days [19]. The only instance of an effect on RMR was reported by Benedict and colleagues [20]. In that study, RMR recorded in the morning from 0745 to 0815 h was significantly reduced after one night of total sleep elimination compared to an 8-h (2300–0700 h) sleep opportunity. This indicates that RMR is not likely to be a factor which influences energy balance under conditions of chronic partial sleep restriction, although a complete elimination of sleep does seem to affect next-morning metabolism.

The results of the latter two studies by Nedeltcheva et al. [19] and Benedict et al. [20] demonstrate that, similar to the effects observed in RMR, an effect of sleep on TEF was only observed after a night of total sleep deprivation as opposed to a milder partial sleep curtailment. Specifically, TEF was unchanged after sleeping 5.5 h/night

Table 11.1 Methodological details and findings of studies of the effects of sleep restriction on EE

Author (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Meal presentation conditions during study	Duration of sleep restriction preceding measure	Measure	Measurement method	Significant effect of restricted sleep
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	4 days	RMR	IC in morning	None
Buxton et al. [26]	n = 20 men	Baseline = 10 h Short = 5 h	Centered at 0300	Fixed, standardized meals	7 days	RMR	IC at ~820 h	None
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	Ad libitum energy available during fixed meal times; in lab	14 days	RMR	IC after awakening	None
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	Fixed, standardized meals	1 day	RMR	IC from 745 to 0815 h	Reduced in elimination vs. habitual
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	Ad libitum energy available during fixed meal times; in lab	14 days	TEF	IC for 4 h after breakfast	None
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	Fixed, standardized meals	1 day	TEF	IC for 4 h after morning test meal	Reduced in elimination vs. habitual
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	4 days	TEE	DLW	None
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	Ad libitum energy available during fixed meal times; in lab	14 days	TEE	DLW	None

Jung et al. [21]	n = 5 men n = 2 women	Habitual = 8 h Elimination = 0 h	Based on individuals habitual schedule	Fixed, standardized meals	1 day	TEE	Metabolic chamber	24-h EE increased in elimination vs. habitual
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–700 Short = 0245–0700	Ad libitum energy available; in lab	2 days	PA	Wrist actigraphy	Lower daytime, increased low-intensity and decreased high-intensity activity in short vs. habitual
Brondel et al. [25]	n = 12 men	Habitual = 8 h Short = 4 h	Habitual = 0000–0800 Short = 0200–0600	Ad libitum energy available during fixed meal times; matched	2 days	PA	Waist actigraphy	Increased afternoon (1215–2015 h) activity in short vs. habitual
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	4 days	PA	Waist actigraphy	Less percentage of time spent in heavy and very heavy activity in short vs. habitual

EE energy expenditure, *RMR* resting metabolic rate, *TEF* thermic effect of food, *TEE* total energy expenditure, *PA* physical activity, *IC* indirect calorimetry, *DLW* doubly labeled water

or 8.5 h/night for 14 days [19] but was significantly decreased after a night of sleep elimination compared to after an 8-h sleep opportunity [20].

Two of the studies described above [18, 19] utilized DLW to assess daily TEE. No significant changes in TEE were observed either after 4 days of restricting sleep to 4 h/night [18] or after 14 days of restricting sleep to 5.5 h/night [19]. A study conducted by Jung and colleagues in a metabolic chamber [21] compared TEE throughout 24 h when an 8-h sleep episode was allowed (sleep timing based on participants' habitual sleep schedule) and when sleep was eliminated. TEE was significantly increased during sleep elimination compared to sleep allowance conditions. Increases were mainly observed during the habitual night, which supports a role of sleep in energy conservation [21]. Critical differences between these studies include the use of DLW or metabolic chamber for EE measures and the use of partial or total sleep deprivation.

Free-living PA under sleep-restricted conditions has been measured with the use of actigraphy. Two of these studies with somewhat similar experimental designs report contradictory results [25, 27]. Both studies included men exclusively. Schmid et al. found lower daytime PA after 2 days of 4.25-h TIB compared to 8.25-h TIB [27]. This study utilized wrist-worn actigraphy, and short sleep timing was anchored to habitual wake-up time (habitual, 2245–0700 h; short, 0245–0700 h) [27]. Conversely, Brondel et al. found increased afternoon-to-evening (1215–2015 h) PA after 2 days of 4-h TIB compared to 8-h TIB [25]. The Brondel et al. [25] study, on the other hand, utilized waist-worn actigraphy, and short sleep timing was anchored to the midpoint of habitual sleep (habitual, 0000–0800 h; short, 0200–0600 h). St-Onge et al. observed that less percentage of time was spent in heavy and very heavy activity after short (4-h TIB, 0100–0500 h) vs. habitual (9-h TIB, 2200–0700 h) sleep, when PA was assessed in men and women with waist-worn actigraphy [18].

Taken together, the findings of the studies described above suggest that a few nights of moderate partial sleep restriction do not have a large effect on energy metabolism. In contrast, a single night of total sleep elimination results in a wakefulness-associated increase in nocturnal EE. A speculative extension of this finding is that it may lead to compensatory decreases in next-day RMR [16]. Though contradictory results are present, partial sleep restriction may reduce the intensity and amount of PA, which could be a contributor in the pathway to obesity.

Sleep Restriction and Hunger/Appetite

Methodological details and findings of studies which have focused on the effects of sleep restriction on ratings of hunger/appetite are summarized in Table 11.2.

As described above, subjective hunger is commonly assessed in response to sleep curtailment, as a preliminary means of determining the effects of sleep restriction on energy intake. Omisade and colleagues exposed 15 women to 3-h TIB (0500–0800 h) or 10-h TIB (2200–0800 h) for 1 day and observed that hunger was not altered when assessed once at 1830 h [28]. Spiegel and colleagues reported

Table 11.2 Methodological details and findings of studies of the effects of sleep restriction on hunger/appetite ratings

Author (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Meal presentation conditions during study	Duration of sleep restriction preceding measure	Measure	Measurement method	Significant effect of restricted sleep
Omisade et al. [28]	n = 15 women	Baseline = 10 h Short = 3 h	Baseline = 2200–0800 Short = 0500–0800	Fixed, standardized meals; matched	1 day	Hunger	10-cm VAS at 1830 h (predinner)	None
Spiegel et al. [29]	n = 12 men	Extended = 10 h Short = 4 h	Extended = 2200–800 Short = 0100–0500	Intravenous glucose infusion at constant rate of 5 g/kg of body weight	2 days	Hunger	10-cm VAS 1×/h from 0900 to 2100 h	Increased in short vs. extended
Brondel et al. [25]	n = 12 men	Habitual = 8 h Short = 4 h	Habitual = 0000–0800 Short = 0200–0600	Ad libitum energy available during fixed meal times; matched	2 days	Hunger	Hunger: 10-cm VAS at 0900, 1030, 1200, 1530, 1700, 1830 h	Preprandial values increased before breakfast and dinner in short vs. habitual
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–700 Short = 0245–0700	Ad libitum energy available; in lab	2 days	Hunger	0–9 Likert scale 1×/h from 0800 to 2300 h	None
St-Onge et al. [18]	n = 14 men n = 13 men	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	3 days	Hunger	0–10 Likert scale 1×/h from 0700 to 2200	None
Reynolds et al. [30]	n = 14 men	Baseline = 10 h Short = 4 h	Baseline = 2200–0800 Short = 0400–0800	Fixed, standardized meals; 2000 kcal/day	5 days	Hunger	VAS at 1100, 1230, 1630, and 1930 h	None
van Leeuwen et al. [31]	n = 15 men	Habitual = 8 h Short = 4 h	Habitual = 2300–700 Short = 0300–0700	Fixed, standardized meals	5 days	Hunger	1–5 Likert scale at 0730 h in fasted state	None

(continued)

Table 11.2 (continued)

Author (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Meal presentation conditions during study	Duration of sleep restriction preceding measure	Measure	Measurement method	Significant effect of restricted sleep
Schmid et al. [22]	n = 9 men	Habitual = 7.5 h Short = 5 h Elimination = 0 h	Habitual = 2230–600 Short = 2230–0330	Intake not monitored during free living/ eating outside lab	1 day	Hunger	0–9 Likert scale at 0730 h in fasted state	Increased after elimination vs. baseline and short
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	Fixed, standardized meals	1 day	Hunger	VAS at 0700 h	Increased in elimination vs. habitual
Pejovic et al. [23]	n = 10 men n = 11 women	Habitual = 8 h Elimination = 0 h	Habitual = 2230–0630	Chose hospital cafeteria meals at fixed times in lab	1 day	Hunger	0–10 Likert scale at 0700, 1200, 1800 h (preprandial)	None
Spiegel et al. [29]	n = 12 men	Extended = 10 h Short = 4 h	Extended = 2200–800 Short = 0100–0500	Intravenous glucose infusion at constant rate of 5 g/kg of body weight	2 days	Appetite	10-cm VAS 1×/h from 0900 to 2100 h	Increased ratings for sweets, salty, and starchy foods in short vs. extended
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–700 Short = 0245–0700	Ad libitum energy available; in lab	2 days	Appetite	0–9 Likert scale 1×/h from 0800 to 2300 h	None
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	3 days	Appetite	0–10 Likert scale 1×/h from 0700 to 2200 h	None
Reynolds et al. [30]	n = 14 men	Baseline = 10 h Short = 4 h	Baseline = 2200–0800 Short = 0400–0800	Fixed, standardized meals; 2,000 kcal/ day	5 days	Appetite	VAS at 1100, 1230, 1630, and 1930 h	None

VAS visual analogue scale

significantly increased hunger as assessed continuously across the day when a group of men were exposed to 4-h TIB (0100–0500 h) compared to 10-h TIB (2200–0800 h) for 2 days [29]. Similarly, Brondel and colleagues reported significantly increased preprandial hunger values before breakfast and dinner after 2 days of short (4-h TIB, 0100–0500 h) vs. habitual (8-h TIB, 0000–0800 h) sleep [25]. No differences in hunger were observed in studies by Schmid et al. [27] and St-Onge et al. [18] comparing sleep durations of 4.25 h/night (0245–0700 h) vs. 8.25 h/night (2245–0700 h) and 4 h/night (0100–0500 h) vs. 9 h/night (2200–0700 h), respectively. Reynolds and colleagues exposed a group of men to 4-h TIB (0400–0800 h) for 5 days and found no change in hunger assessed throughout the day when compared to the baseline sleep condition of 10-h TIB (2200–0800 h) [30]. A similar study by van Leeuwen and colleagues exposed men to 4-h TIB (0300–0700 h) and 8-h TIB (2300–0700 h) for 5 days and found no difference in hunger when assessed at 0730 h in a fasted state [31].

The effects of total sleep deprivation on subjective hunger have also been investigated. Schmid et al. assessed hunger in a group of men at 0730 h in the fasted state after a night of 7.5-h TIB (2230–0600 h), a night of 5-h TIB (2230–0330 h), and after total sleep elimination. The authors noted an incremental impact of sleep restriction on subjective hunger: compared to the full sleep episode, participants reported double the hunger rating after total sleep elimination and ~50 % increased hunger (though not statistically significant) after short sleep compared to habitual sleep [22]. The study by Benedict et al., exposing men to 1 night of total sleep deprivation, also found increased hunger when compared to measures taken after habitual sleep length [20]. On the other hand, a study by Pejovic and colleagues including both men and women found no effect of sleep elimination on hunger when compared to an 8-h sleep opportunity [23].

Differences in experimental design may account for some of the discrepancies observed in the results on the impact of sleep restriction on subjective hunger. In the studies which compared short and habitual sleep conditions, those which anchored the short sleep episode to the time of habitual awakening reported no effect on hunger [27, 28, 30, 31]. Conversely, the studies which did observe a significant increase in hunger during restriction anchored short sleep timing to the midpoint of the habitual sleep episode, thereby cutting off the last 2–3 h of the sleep episode in the short sleep condition [25, 29]. Recalling the aforementioned circadian variation of REM sleep [41], it is assumed that the elimination of the latter portion of the sleep episode to achieve partial restriction will result in a significant decrease in the expression of REM sleep. This is important, since a recent study from our laboratory observed that REM sleep duration is inversely related to hunger [42]. Increased hunger under sleep curtailment in the Spiegel et al. [29] and Brondel et al. [25] studies may therefore be explained by the reduction of REM sleep, which is not expected to be observed in the other sleep restriction studies which maintained a similar wake-up time between short and habitual duration conditions. A caveat to this hypothesis is that the restricted sleep condition in the St-Onge et al. study was also anchored to the midpoint of habitual sleep and no effect of sleep duration was noted on hunger and appetite ratings [18]. Nevertheless, the inclusion of women in that study

complicates a direct comparison with the Spiegel and Brondel studies, which were done exclusively with male participants. Interestingly, out of the three studies which compared hunger between total sleep elimination and habitual sleep conditions, those which included men exclusively observed significant effects of sleep deprivation [20, 22], whereas no differences were observed between elimination and habitual conditions when women were also included [23].

Subjective appetite after partial sleep restriction was assessed in four studies to date [18, 27, 29, 30]. No effect of 2- and 5-day partial sleep restriction was observed on appetite ratings in the studies by Schmid et al. [27] and Reynolds et al. [30], which included only men and anchored the short sleep episode to the time of habitual awakening (wake times in both conditions maintained at 0700 h and 0800 h, respectively). Similar to what was observed for hunger ratings, Spiegel et al. reported increased appetite for sweet, salty, and starchy food in men exposed to 2 days of short sleep (episodes anchored to the midpoint of sleep) [29]. No changes in appetite were observed by St-Onge et al. who exposed men and women to 3 days of short sleep (episodes anchored to the midpoint of sleep) [18].

As was seen for EE, the effects of a night of total sleep deprivation appear to induce substantial increases in hunger and appetite ratings, whereas the effects of partial sleep restriction remain less defined. In the study by Spiegel and colleagues, which was the first to report increased hunger and appetite after sleep restriction, participants were fed via constant intravenous glucose infusion throughout the measurement period [29]. The findings of that study are the most robust of all reported, and their particular method of administering calories could have amplified the effects of sleep restriction above what was induced by others. The effects of sleep restriction on subjective perceptions of hunger and appetite may also be modulated by sex, since differences between short and habitual sleep are more commonly observed in studies which included only male participants.

Sleep Restriction and Appetite-Regulating Hormones

Methodological details and findings of studies which have focused on the effects of sleep restriction on appetite-regulating hormones are summarized in Table 11.3.

Various circulating peptides and hormones have been demonstrated to play a role in the regulation of hunger, appetite, satiety, and food intake. These include hypothalamic factors (e.g., neuropeptide Y and agouti-related peptide), gut hormones (e.g., ghrelin, glucagon-like peptide-1 [GLP-1], peptide YY [PYY], and cholecystokinin), and adiposity signals (e.g., leptin and adiponectin) [72]. Leptin and ghrelin have been the most widely studied appetite-regulating hormones within the context of experimental sleep restriction studies. In fact, of all the energy balance-related parameters discussed in this chapter, the effects of sleep restriction on leptin have probably been studied the most. Though they will not be discussed here, two studies with inconsistent findings have investigated adiponectin levels in response to sleep restriction [23, 51], and PYY and GLP-1 have been sampled after sleep curtailment in one study [51].

Table 11.3 Methodological details and findings of studies of the effects of sleep restriction on appetite-regulating hormones

Reference (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Meal presentation conditions during study	Duration of sleep restriction preceding measure	Measure	Sampling frequency	Significant effect of restricted sleep
Omisade et al. [28]	n = 15 women	Baseline = 10 h Short = 3 h	Baseline = 2200–0800 Short = 0500–0800	Fixed, standardized meals; matched	1 day	Salivary leptin	830 and 2000 h	Morning level increased in short sleep vs. baseline, no change in evening level
Spiegel et al. [29]	n = 12 men	Extended = 10 h Short = 4 h	Extended = 2200–0800 Short = 0100–0500	Intravenous glucose infusion at constant rate of 5 g/kg of body weight	2 days	Leptin	1×/20 min from 0800 to 2100 h	Decreased in short vs. extended
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–700 Short = 0245–0700	Ad libitum energy available; in lab	2 days	Leptin	1×/h from 800 to 2300 h	None
St-Onge et al. [51]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	3 days	Leptin	Continuous over 24 h	None
Simpson et al. [32]	n = 71 men n = 65 women	Baseline = 10 h Short = 4 h	Baseline = 2200–0800 Short = 0400–0800	Ad libitum energy available; in lab	5 days	Leptin	Single draw from 1030 to 1200 h	Increased in short vs. habitual sleep, response greater in women and those with higher BMI
Reynolds et al. [30]	n = 14 men	Baseline = 10 h Short = 4 h	Baseline = 2200–0800 Short = 0400–0800	Fixed, standardized meals; 2,000 kcal/day	5 days	Leptin	0900, 1000, 1200, 1400, 1600, 1800, 2000 h	Increased in short vs. habitual sleep
van Leeuwen et al. [31]	n = 15 men	Habitual = 8 h Short = 4 h	Habitual = 2300–700 Short = 0300–0700	Fixed, standardized meals	5 days	Leptin	0730 h	Increased in short vs. habitual sleep

(continued)

Table 11.3 (continued)

Reference (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Meal presentation conditions during study	Duration of sleep restriction preceding measure	Measure	Sampling frequency	Significant effect of restricted sleep
Spiegel et al. [33]	n = 11 men	Habitual = 8 h Short = 4 h Extended = 10 h	Baseline = 2300–0700 Short = 0100–0500 Extended = 2100–0900	Fixed, standardized meals	6 days	Leptin	Continuous over 24 h	Decreased in short vs. extended, 2-h advance of peak level in short vs. extended, values at baseline sleep duration were "intermediate between those recorded under 4-h and 12-h conditions"
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	Ad libitum energy available during fixed meal times; in lab	14 days	Leptin	Continuous over 24 h	None
Schmid et al. [22]	n = 9 men	Habitual = 7.5 h Short = 5 h Elimination = 0 h	Habitual = 2230–600 Short = 2230–0330	Intake not monitored during free living/ eating outside lab	1 day	Leptin	0700 and 0730 h	None
Pejovic et al. [23]	n = 10 men n = 11 women	Habitual = 8 h Elimination = 0 h	Habitual = 2230–0630	Chose hospital cafeteria meals at fixed times in lab	1 day	Leptin	Continuous over 24 h	Increased during daytime in sleep elimination vs. habitual
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	Fixed, standardized meals	1 day	Leptin	1800 h; 2100 h; 1×/90 min between 2400 and 0900; 1×/h from 1000 to1300; 1500 h; 1800 h	None

Mullington et al. [24]	n = 10 men	Habitual = 8 h Elimination = 0 h	Baseline = 2330–0730	Fixed, standardized meals (extra snack at served in deprivation days)	3 days	Leptin	1×/90 min over 120 h (baseline day and 3-day deprivation)	Amplitude reduced during deprivation vs. habitual
Spiegel et al. [29]	n = 12 men	Extended = 10 h Short = 4 h	Extended = 2200–800 Short = 0100–0500	Intravenous glucose infusion at constant rate of 5 g/kg of body weight	2 days	Total ghrelin, n = 9	1×/20 min from 0800 to 2100 h	Increased in short vs. extended
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–700 Short = 0245–0700	Ad libitum energy available; in lab	2 days	Total ghrelin	1×/h from 800 to 2300 h	None
St-Onge et al. [51]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	Fixed, standardized meals	3 days	Total ghrelin	Continuous over 24 h	Fasting and morning levels increased in short sleep in men
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	Ad libitum energy available during fixed meal times; in lab	14 days	Total ghrelin, n = 9	Continuous over 24 h	None
Schmid et al. [22]	n = 9 men	Habitual = 7.5 h Short = 5 h Elimination = 0 h	Habitual = 2230–600 Short = 2230–0330	Intake not monitored during free living/ eating outside lab	1 day	Total ghrelin	0700 and 0730 h	Increased in sleep elimination vs. habitual
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	Fixed, standardized meals	1 day	Total ghrelin	1800 h; 2100 h; 1×/90 min between 2400 and 0900; 1×/h from 1000 to 1300; 1500 h; 1800 h	Reduced in sleep elimination vs. habitual at 0130 h, increased in elimination vs. habitual at 0430–0730 h

BMI body mass index

In their innovative study, Spiegel and colleagues [29] were among the first to report altered leptin in response to partial sleep restriction. They exposed men to 2 days of 4-h TIB (0100–0500 h) or 10-h TIB (2200–0800 h) and noted a significant decrease in leptin, as measured continuously throughout the day, after short sleep. In a similar study by the same group [33], leptin levels were again compared between 4-h TIB and 10-h TIB, but the exposure was extended to 6 days. Samples were obtained regularly over 24 h. The authors noted a decrease in leptin levels and a 2-h advance in the time of leptin peak in response to short sleep. Schmid et al. [27] observed no difference in leptin levels across the day after short (4.25 h, 0245–0700 h) or habitual (8.25 h, 2245–0700 h) sleep for 2 days. Similarly, studies by St-Onge et al. [51] and Nedeltcheva et al. [19] found no effect on leptin levels sampled across 24 h in response to short sleep for 3 [51] or 14 days [19].

Some studies, however, noted increases in leptin after partial sleep restriction. A study by Omisade and colleagues [28] exposed women to 3-h (0500–0800 h) or 10-h TIB (2200–0800 h) for 1 day and sampled salivary leptin at 0830 h and 2000 h to approximate a diurnal variation of the hormone. They observed an increase in morning leptin levels compared to baseline sleep, but no change in evening levels. Simpson and colleagues [32] studied men and women under 4-h TIB (0400–0800 h) and 10-h TIB (2200–0800 h) for 5 days. They obtained a single blood draw between 1030 and 1200 h and observed an increase in response to short sleep. Reynolds and colleagues [30] utilized a similar design (sleep durations, schedule, and length of exposure) as Simpson et al. [32] and also noted an increase in leptin after short sleep when sampling across the day in men. Another similarly designed study by van Leeuwen et al. [31], comparing 4-h TIB (0300–0700 h) to 8-h TIB (2300–0700 h) for 5 days, sampled leptin at 0730 h and observed an increase in short vs. habitual sleep episodes.

Comparing between 1 day of 7.5-h TIB (2230–0600 h), 5-h TIB (2230–0400), and sleep elimination, Schmid et al. [22] found no difference in leptin when sampled in the morning. Similarly, Benedict et al. [20] compared between one night each of sleep elimination and habitual sleep in men and noted no change in leptin levels sampled across 24 h. On the contrary, Pejovic et al. [23] compared leptin levels sampled across 24 h in men and women after one night of sleep elimination or habitual sleep and observed an increase in levels after total sleep deprivation. In a slightly different design, Mullington and colleagues [24] sampled leptin levels continuously over a baseline day and 3 days of total sleep deprivation and noted that the amplitude of the circadian variation was reduced during sleep elimination compared to habitual sleep. The authors concluded that sleeping may have a role in controlling the nocturnal rise in leptin levels and that increased nocturnal eating may be a consequence of this attenuated nocturnal increase [24].

Thus, while widely studied, the effects of sleep curtailment on leptin secretion are inconsistent, and the reasons for this are not clear. Feeding protocols utilized in these studies varied and included either controlled feeding [20, 28, 33, 51], participant self-selection [19, 22, 23, 27], or constant intravenous glucose infusion [29]. Unfortunately, a pattern is not apparent between feeding protocols. Likewise, differences in the timing and frequency of sampling (either morning fasted, throughout the day, or across 24 h) are also likely to systematically contribute to disparate results.

Nevertheless, increased awakening during sleep restriction intervention is associated with prolonged light exposure, which can delay the central circadian pacemaker [6]. It would therefore be important to sample continuously throughout the 24-h cycle to observe the dynamics of the secretory profile. Interestingly, each of the partial restriction studies that observed increases in leptin anchored the timing of short sleep episode to habitual wake-up time [28, 30–32], whereas the two studies by Spiegel et al. (exclusively studying men), which found a decrease in leptin, anchored short sleep to the center of the night [29, 33]. Similar decreases might have been expected in the St-Onge et al. [51] and Nedeltcheva et al. [19] studies which anchored the short sleep episode to the center of the night. However, these latter studies included both men and women. Together, the results may suggest that the effects of sleep restriction on leptin secretion are affected by the timing of sleep or subtle alterations in sleep architecture. A modulatory effect of sex is also possible.

In a finding mechanistically consistent with their initial observation of decreased leptin, Spiegel and colleagues [29] reported an increase in ghrelin in a group of men in response to 2-day exposure to 4-h TIB (0100–0500 h) compared to 10-h TIB (2200–0800 h). The ghrelin findings reported by St-Onge et al. [51] are somewhat consistent with that report: studying men and women, after 3-day exposure to 4-h TIB (0100–0500 h) and 9-h TIB (2200–0700 h), increases in fasting and morning levels were observed after short sleep, selectively in men but not women. Neither Schmid et al. [27] nor Nedeltcheva et al. [19], on the other hand, reported any changes in ghrelin after restricting sleep to 4.25 h/night for 2 days or 5.5 h/night for 14 days, respectively. Sampling in the morning between 0700 and 0730 h, another study by Schmid et al. [22] observed a trend for increased ghrelin in response to 5-h TIB (2230–0330) compared to 7.5-h TIB (2230–0600 h) and a significant increase in ghrelin in response to total sleep deprivation compared to habitual sleep. Sampling across 24 h during a day of habitual sleep and a day of total sleep elimination, Benedict et al. [20] observed reduced ghrelin levels at 1300 h but increased ghrelin levels at 0430–0730 h in sleep elimination compared to habitual sleep duration.

While the findings are mixed, increased ghrelin is often reported in response to sleep length curtailment, particularly in the morning [20, 22, 51]. Sex appears to have a modulatory role in regulating the effects of sleep restriction on ghrelin levels. St-Onge et al. [51] found a strong sex effect for ghrelin, with increased levels in response to short sleep in men but not women, which is in agreement with others who studied men exclusively [20, 22, 29]. The Nedeltcheva et al. study [19], which also included both men and women, reported no effect of sleep duration on ghrelin levels. Importantly, the study by St-Onge et al. was large enough to allow separate analyses by sex (males, $n = 14$; females, $n = 13$), whereas the study by Nedeltcheva et al. may have been underpowered to allow separate sex comparisons (males, $n = 6$; females, $n = 5$). The studies which observed increased ghrelin in men anchored either the short sleep episode to the middle of the night [29, 51] or the time of habitual lights-out [22], thereby eliminating sleep from the final 2–3 h of the night, whereas the study not observing a change in ghrelin in men anchored short sleep to the time of habitual awakening [27]. Thus, again, a role of sleep timing or the expression of sleep architecture influencing the effects of sleep length curtailment on appetite-hormone levels is possible.

Sleep Restriction and Food Intake

Methodological details and findings of studies which have focused on the effects of sleep restriction on food intake are summarized in Table 11.4.

A critical aspect that should be accurately measured when researchers are concerned with energy balance is food intake. Accordingly, in addition to measuring subjective ratings of hunger/appetite and the circulation of appetite-regulating hormones, five laboratory-based sleep restriction intervention studies have measured food intake [18–20, 25, 27]. In the study by Brondel and colleagues [25], food intake was measured after 1-day exposure to short (4-h TIB, 0200–0600 h) or habitual sleep length (8-h TIB, 0000–0800 h). Afternoon and evening food intake was self-recorded, and ad libitum intake of in-lab breakfast and lunch was assessed. Energy intake was significantly increased in restricted compared to habitual sleep. In the study by Schmid and colleagues [27], food intake was measured after 2-day exposure to short (4.25-h TIB, 0245–0700 h) or habitual sleep length (8.25-h TIB, 2245–0700 h). Food was presented as a buffet breakfast until 1100 h, a snack buffet from 1100 h onward, and free access to meals on request. No differences in energy intake were observed. St-Onge et al. [18] included both men and women and measured food intake after 4-day exposure to short (4-h TIB, 0100–0500 h) or habitual (9-h TIB, 2200–0700 h) sleep duration. Participants were given free access to a variety of foods available in the lab and were given $25 to purchase food from local markets. The amount and timing of eating was decided by the participant. Energy intake was significantly increased after sleep restriction. Nedeltcheva and colleagues [19] also measured food intake in both men and women after exposure to 14 days of short (5.5-h TIB) or habitual (8.5-h TIB) sleep duration (timing centered at the midpoint of sleep). Participants were served meals at fixed times in excess and also had unlimited access to a snack bar with palatable snacks and soft drinks. Energy intake from snacks was increased after short sleep, compared to habitual sleep duration. Benedict and colleagues [20] compared food consumed by men from a buffet offered at 1730 h after one night of total sleep deprivation or a night of habitual sleep (2300–0700 h). No difference in energy consumed from this dinner buffet was seen.

Increased energy consumed under ad libitum conditions after sleep curtailment compared to habitual sleep duration was observed in three out of four studies which utilized partial sleep restriction. The Schmid et al. study [27] was the only partial curtailment study which did not report increased energy consumed. Interestingly, it is also the only study which anchored short sleep timing to habitual wake-up time, whereas the remaining three studies [18, 19, 25] centered restricted sleep to the midpoint of habitual sleep. This may imply that sleep timing or subtle changes in the expression of sleep architecture may influence food intake, or an interaction between sleep timing and sleep duration is important. The specific food presentation of the Benedict et al. study [20], namely, a single eating opportunity at 1730 h instead of access throughout the day, may account for the unexpected lack of a significant effect of total sleep deprivation on food intake.

Table 11.4 Methodological details and findings of studies of the effects of sleep restriction on food intake

Reference (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Duration of sleep restriction preceding measure	Times of measure	Method of food presentation	Measure	Significant effect of restricted sleep
Brondel et al. [25]	n = 12 men	Habitual = 8 h Short = 4 h	Habitual = 0000–0800 Short = 0200–0600	1 day	Food intake during free living and served breakfast and lunch	Free living: ad libitum access to foodin lab, standardized meals at fixed times served in excess for ad libitum intake	Energy	Increased in short vs. habitual
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–0700 Short = 0245–0700	2 days	Food intake during breakfast buffet and snack buffet for remainder of day	Standardized breakfast buffet and snack buffet refilled when necessary for ad libitum intake, also access to meals on request	Energy	None
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	4 days	Food intake throughout full waking period	Free access to food available in lab and $25 to purchase food from local market, amount and timing of eating decided by participant	Energy	Increased in short vs. habitual
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	14 days	Food intake during served breakfast, lunch, dinner, and free access to snacks	Standardized meals at fixed times served in excess for ad libitum intake, also unlimited access to snack bar with palatable snacks and soft drinks	Energy	Increased in short vs. habitual [from snacks)
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	1 day	Food intake during dinner buffet	Buffet offered at 1730 h for ad libitum intake	Energy	None

(continued)

Table 11.4 (continued)

Reference (reference #)	Participants	Time in bed conditions	Lights out/on clock times	Duration of sleep restriction preceding measure	Times of measure	Method of food presentation	Measure	Significant effect of restricted sleep
Brondel et al. [25]	n = 12 men	Habitual = 8 h Short = 4 h	Habitual = 0000–0800 Short = 0200–0600	2 days	Food intake during served breakfast, lunch, and dinner	Standardized meals at fixed times served in excess for ad libitum intake	Macronutrients	Increased fat intake in short vs. habitual
Schmid et al. [27]	n = 15 men	Habitual = 8.25 h Short = 4.25 h	Habitual = 2245–0700 Short = 0245–0700	2 days	Food intake during breakfast buffet and snack buffet for remainder of day	Standardized breakfast buffet and snack buffet refilled when necessary for ad libitum intake, also access to meals on request	Macronutrients	Increased total fat intake in short vs. habitual
St-Onge et al. [18]	n = 14 men n = 13 women	Habitual = 9 h Short = 4 h	Habitual = 2200–0700 Short = 0100–0500	4 days	Food intake throughout full waking period	Free access to food available in lab and $25 to purchase food from local market, amount and timing of eating decided by participant	Macronutrients	Increased fat and saturated fat intake in short vs. habitual
Nedeltcheva et al. [19]	n = 6 men n = 5 women	Habitual = 8.5 h Short = 5.5 h	Centered at habitual sleep midpoint	14 days	Food intake during served breakfast, lunch, dinner, and free access to snacks	Standardized meals at fixed times served in excess for ad libitum intake, also unlimited access to snack bar with palatable snacks and soft drinks	Macronutrients	Increased carbohydrate intake in short vs. habitual
Benedict et al. [20]	n = 14 men	Habitual = 8 h Elimination = 0 h	Habitual = 2300–0700	1 day	Food intake during dinner buffet	Buffet offered at 1730 h for ad libitum intake	Macronutrients	None

Macronutrient composition of the food eaten was also measured in each of the five aforementioned studies that assessed ad libitum energy consumption [18–20, 25, 27]. Increased fat intake was observed in response to partial sleep restriction in the Brondel et al. [25], Schmid et al. [27], and St-Onge et al. [18] studies, and increased saturated fat intake was also observed in the latter [18]. The Nedeltcheva et al. study [19] reported increased intake of carbohydrate, but not fat, after short vs. habitual sleep duration and selective increase in snack food intake but not meals. The Benedict et al. study [20] which failed to detect differences in energy intake after a night of total sleep deprivation compared to a night of habitual sleep also did not detect any between-condition differences in macronutrient intake. This is likely due to its distinct methodological approach, described above.

Increased consumption of energy and fat seems to be the most consistently observed changes in an energy balance parameter in response to partial sleep restriction. Increases in energy intake beyond the energy which is expended by either metabolic processes or PA are therefore a viable link in establishing a causal pathway from sleep restriction to the development of obesity. Data obtained from the laboratory-based intervention studies described above support much of the epidemiological data, showing that short sleep is associated with a high-fat diet [73] and excess snacking [74].

Conclusions: Considerations and Future Steps

The results from the laboratory-based clinical intervention studies described in this chapter lend support to the epidemiological evidence showing an association between short sleep duration and increased prevalence of obesity. Although some results remain equivocal, experimental reduction of sleep duration was demonstrated to causally relate to parameters which would support a positive energy balance. As described in the introduction, a state of energy imbalance would exist when energy intake is not equal to energy output. Positive energy balance arises when food intake is excessive enough to surpass EE or, conversely, when EE is reduced to a level below normal energy intake. Based on the evidence described here, it appears that sleep restriction may affect energy balance mainly via energy input rather than EE. Specifically, the intervention studies have been convincing in demonstrating a causal link between reduced sleep duration and increased food intake. Reduced PA (which would be a logical consequence of increased daytime sleepiness) has been reported by some, although partial sleep restriction does not appear to affect RMR. To date, only one study has utilized a metabolic chamber to investigate 24-h EE in response to total sleep restriction. This tool should be used in the context of partial sleep curtailment to look more closely at TEE but also sleeping metabolic rate and non-exercise activity thermogenesis, which have not yet been described under short sleep conditions.

As far as the mechanism by which reduced sleep duration leads to increased food intake, the authors have mainly considered an alteration in the hormonal control of

appetite and hunger. Conflicting results have been presented for leptin, a satiety-signaling hormone, although increases in ghrelin, an appetite-stimulating hormone, may be more uniformly observed. A potential modulation by sex on the interaction between short sleep and appetite hormones may exist, however, indicating a need for more intervention studies which are powered to detect differences between men and women. Indeed, within young, ovulating females, the menstrual cycle and its associated variations in hormones and physiology may further influence food intake or possibly EE in response to sleep restriction. Energy balance state itself is known to influence leptin and ghrelin. Under unrestricted feeding conditions, sleep-deprived participants are expected to consume excess food, leading to a positive energy balance state. Going forward, then, it will be important to conduct studies under highly controlled energy intake conditions which help determine the interaction between short sleep and energy balance on the hormonal control of food intake.

In real-life conditions, individuals who are habitually exposed to short sleep may have increased daily food intake because their prolonged wake episodes may afford them increased opportunities to eat. While this has not been extensively studied in the laboratory, one study considering this observed that nocturnal eating episodes (past the time of habitual bedtime) were present in ~27 % of participants [18]. It has recently been reported in observational studies that the timing of food intake is related to increased BMI [44] and reduced weight loss effectiveness [75]. This observation may be related to a study in mice showing that animals fed a high-fat diet during their inactive phase gained more weight than mice fed during their habitual active phase [76]. The effects of sleep restriction on the temporal distribution of food intake, under ad libitum and unrestricted conditions, should therefore be further pursued. Such studies may also have practical ramifications for the health of night shift workers, since these individuals often experience shortened sleep episodes, unusual feeding-fasting behavior characterized by nocturnal eating, and increased risk of weight gain and cancer.

As discussed in this chapter, small differences in the scheduling of the sleep within the intervention studies may influence specific energy balance outcomes. This implies that not just sleep duration alone but also the timing of sleep episodes should be considered as playing a role in the regulation of metabolism and body weight. Indeed, researchers have been paying increasing attention to this: an observational study found that individuals with later sleep schedules tended to have higher energy intakes throughout the day than those whose midpoint of sleep was earlier [44], and a laboratory-based manipulation study illustrated that sleep restriction combined with a chronic circadian misalignment resulted in reduced RMR and altered glucose homeostasis [52]. The problem of circadian misalignment, short sleep, and delayed sleep and meal timing is not limited to shift workers and presents an important health risk for a large portion of the population. More work should be done to determine if sleep timing affects energy balance and how it may be involved in the causal pathway to obesity.

Chronic partial sleep restriction likely leads to a state of positive energy balance, which can ultimately result in excess weight gain and obesity. Furthermore, obesity is associated with increased risk of a variety of cancers [2], which may suggest a role of

sleep restriction in cancer as well. This role may be directly causal or indirectly, via increased risk of obesity. As described, shift workers, who experience reduced sleep duration combined with a circadian disruption, are at an increased risk of obesity and cancer development. Related to this, recent epidemiological work has shown an association between "social jet lag" (i.e., the discrepancy between sleep episode timing between work and free days that often results in sleep loss) and obesity [77], and chronic jet lag conditions increase tumor progression in mice [78]. An important angle of research may be to further assess the markers of cancer risk in the context of experimental sleep restriction studies. The effects of sleep episode schedule, in addition to duration, on the development of obesity, adverse metabolic outcomes, and cancer should be further studied with controlled laboratory interventions.

In conclusion, accumulating evidence from intervention studies has been delineating the ways in which restricted sleep duration may lead to obesity, corroborating much of the epidemiological studies on this sleep-obesity link. Nonetheless, many inconsistencies and questions within the laboratory-based data still remain, owing mainly to important methodological differences between studies. It is necessary that researchers continue to explore the mechanisms underlying the relationship between sleep and energy balance, as this line of research will continue to have major public health implications for various medical conditions, including, but not limited to, obesity and cancer.

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S. Redline and N.A. Berger (eds.), *Impact of Sleep and Sleep Disturbances on Obesity and Cancer*, Energy Balance and Cancer 8, DOI 10.1007/978-1-4614-9527-7,