## REVIEW

## Sleep-wake cycle, aging and cancer

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#### Summary

Disruptions in sleep-wake patterns have been linked to a variety of health problems, including an increase risk for obesity, type II diabetes, and hypertension. The link to increased risk of malignancy and premature aging is less clear, however. This manuscript reviews current epidemiological and experimental evidence linking alterations in sleep-wake patterns to malignancy and premature aging. Epidemiological evidence suggests that alterations in sleep-wake patterns (e.g.; night-shift or rotating-shift work) are associated with increases in leukemia, endometrial, breast, prostate, and colorectal cancers. Excessive long or short sleep duration is associated with increased mortality. These observations are further supported by experimental animal model systems: Sleep deprivation causes death in *Drosophila cycle<sup>01</sup>* mutants. Manipulations of light-dark cycle in rodents or mutations that knock out certain genes in the circadian pathway accelerate aging and neoplastic growth. Melatonin, the pineal hormonal signal of darkness appears to have evolved in part to protect against mutagenesis by synchronizing cellular proliferation, differentiation, and apoptosis to the circadian peaks and troughs of genotoxic stress. A model based on circadian-gating of sleep-wake cycles, therefore, links the circadian pathway to the mutational theories of senescence and neoplasia.

*Key words*: circadian – sleep – wake – cancer – mutation – aging

#### **INTRODUCTION**

Individuals in modern day industrialized nations experience a variety sleep derangements, more so than their ancestors. Increases in shift work schedules and the need to adjust sleep cycles for work, family, and social demands are practically mainstay in any busy individual's life. Sleep

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derangements have been linked to a variety of health problems, including an increase risk for obesity, type II diabetes, and hypertension. The link to increased risk of malignancy and premature aging is less clear, however. It is possible that changes in sleep-wake cycles and sleep disruption may promote aging and carcinogenesis. Exposure to ingested mutagens occurs during feeding periods and in relationship to the cycles of sleep and wakefulness. Alterations in diurnal wake and sleep patterns and sleep disruption may increase the rate of DNA damage by phase-shifting of cyclic exposure to mutagenic stress relative to the circadian peaks of DNA repair. The resulting accumulation of mutations may accelerate aging or lead to genomic instability and carcinogenesis (Shadan 2007a, b). This manuscript reviews current cepidemiological and experimental evidence linking alterations in sleep-wake patterns to malignancy and premature aging.

#### EPIDEMIOLOGICAL STUDIES LINK SLEEP ALTERATIONS TO MALIGNANCY

Epidemiological evidence suggests that alterations in sleep-wake patterns are associated with cancer (Mormont 1997). Irregular circadian cycles due to night-shift work are associated with increases in tumorigenesis (Hansen 2001, Pinheiro et al. 2006). Furthermore, the incidence of breast tumors in blind women is low, and an inverse relationship exists between breast cancer incidence and the degree of visual impairment (reviewed in Sanchez-Barcelo et al. 2003). It has been suggested that melatonin may play a protective role against breast cancer, and circadian disruption has been proposed as a risk factor for breast and colorectal cancer in women (Davis 2001, Pinheiro et al. 2006, Zhu et al. 2006).

Progressive decline of pineal melatonin secretion is observed in parallel to the growth of primary tumors of breast and prostate (Bartsch and Bartsch 1997). Altered-lighted environments, rotating shift-work and variations in the genes responsible for circadian rhythmicity may increase the risk of prostate cancer (Kubo et al. 2006, Zhu et al. 2006). This is further supported by inhibition of prostate cancer cell proliferation in response to melatonin (Fornas et al. 2000, Moretti 2000, Sanchez-Barcelo et al. 2003, Sainz et al. 2005). These epidemiological studies backed by experimental evidence link altered sleep-wake patterns and circadian shifts to carcinogenesis.

Molecular epidemiology links disruption of circadian clock gene expression to carcinogenesis as demonstrated in breast cancer, endometrial cancer, and leukemia. Over 95% of breast cancer cells exhibit disturbances in the expression of Per1, Per2, and Per3 circadian clock genes (Chen et al. 2005). A variant of Per3 genotype is associated with increased risk of breast cancer among premenopausal women, while expression of Perl is significantly reduced in endometrial carcinoma (Yeh et al. 2005, Zhu et al. 2005). Inactivation of Per1 or a neighboring gene may contribute to the pathogenesis of certain leukemias while disrupted circadian genes have been reported specifically in acute myeloid leukemia (Penas et al. 2003). Disruption of circadian gene expression may therefore be linked to carcinogenesis.

#### DOES ALTERED SLEEP DURATION PROMOTE MALIGNANCY AND PREMATURE AGING?

Epidemiological studies indicate that excessive long or short sleep duration may adversely impact longevity. Individuals who report both an increased (greater than 8 hours per day) or decreased (less than 7 hours per day) sleep duration are at increased risk of all-cause mortality (Alvarez and Ayas 2004, Tamakoshi and Ohno 2004, Youngstedt and Kripke 2004). In one study, men and women who reported usually sleeping less than 4 hours were 2.8 times and 1.48 times more likely to have died within 6 years than those who reported 7.0 to 7.9 hours of sleep. Persons who reported sleeping ten hours or more had about 1.8 times the mortality of those reporting 7.0 to 7.9 hours of sleep (Kripke et al. 1979). Sleep duration of 7 hours at night has been shown to be associated with the lowest mortality risk (Tamakoshi and Ohno 2004). Consumption of hypnotic medications has been argued to be predictive of increased mortality by some (Kripke et al. 1979, 1983, 1998, Allgulander et al. 1987, 1990, Rumble and Morgan 1992, Thorogood et al. 1992, Merlo et al. 1996, Sundquist et al. 1996, Kojima et al. 2000, Mallon et al. 2002, Ahmad and Bath 2005), but not all studies (Hays et al. 1996, Phillips and Mannino 2005). An American Cancer Society study of 1.1 million respondents demonstrated that sleeping longer than 7.5 hours was associated with about 5% of the mortality of the sample (Youngstedt and Kripke 2004). Three epidemiologic investigations noted that the use of hypnotic medications predicted death from cancer (Merlo et al. 1996, Kripke et al. 1998, Mallon et al. 2002). Case-control studies found that benzodiazepines may be associated with ovarian cancer (Harlow and Cramer 1995, Harlow et al. 1998). In a study of consumers of a new hypnotic, 42% of deaths were attributed to cancer (Hajak 1999). Whether circadian rhythm sleep disorders are associated with increased risk of cancer or premature aging remains to be determined. Excessive long and short sleep duration, therefore, appear to impact mortality.

#### SLEEP DEPRIVATION APPEARS TO PROMOTE PREMATURE AGING AND NEOPLASIA

The effects of sleep deprivation upon mortality have been studied in animal model systems. Sleep deprived *Drosophila cycle*<sup>01</sup> circadian clock mutants

die prematurely (Shaw et al. 2002). Death is preventable by activation of heat-shock genes, which are thought to protect against genome instability (Hunt et al. 2004). Sleep disruption, therefore, may promote DNA damage in the context of altered circadian clock function. Prolonged sleep deprivation in rats causes premature death (Rechtschaffen et al. 1983, 1989). Sleep-deprived rats appear debilitated, ataxic, and bear various ulcerative hyperkeratotic skin lesions. Tumors grow faster in jet-lagged mice as compared with controls (Filipski et al. 2004). Mice deficient in the circadian gene Period 2 (Per 2) accumulate mutations, age prematurely and are prone to neoplastic growth (Chen et al. 2005). 30% of Per 2 mutants die before the age of 16 months, with the first case occurring at 9 months of age. Consistent with mutational theories of aging, genetic lesions accumulate with accelerated senescence in knockout mice deficient in DNA repair (Gensler and Bernstein 1981, Wynford-Thomas et al. 1996, Ashok and Ali 1999, Vijg 2000, Shaw et al. 2002, Dufour et al. 2004, Pandita et al. 2004). When challenged with gamma radiation, Per 2 knockout mice show a marked increase in tumor development and rapid hair graying. Apparent accelerated aging, skin lesions, and shortened life span are somewhat reminiscent of the sleep-deprived rats (Rechtschaffen et al. 1983, 1989). Mice deficient in Bmall circadian gene have shorter life spans and display many signs of premature aging including sarcopenia, cataracts, reduced subcutaneous fat, organ shrinkage (Kondratov et al. 2006). Disruption of Bmall results in increased mortality after 26 weeks of age in mutant mice and a phenotype consistent with progressive arthropathy (Bunger et al. 2005). Early aging in these animals correlates with increased levels of reactive oxygen species (Kondratov et al. 2006). Disruption of sleep-wake patterns and altered circadian clock function appear to promote DNA damage, premature aging and tumorigenesis.

#### THE ROLE OF MELATONIN

Melatonin, the hormonal "signal of darkness," is an indolamine synthesized mainly by the pineal gland. Light inhibits melatonin secretion and its circulating levels increase with decreased light input. The suprachiasmatic nucleus (SCN) receives photic information via the retinohypothalamic tract (RHT) and regulates melatonin secretion from the pineal gland through a network of neurons.

Detection of melatonin or related metabolites across phyla suggests a fundamental role in circadian regulation. Melatonin and its metabolite 5-methoxytryptamine, have been detected in metazoans and all major non-metazoan taxa investigated (Bell-Pedersen et al. 2005). These include bacteria, dinoflagellates, euglenoids, trypanosomids, fungi, rhodophyceans, pheophyceans, chrolophyceans, and angiosperms (Hattori et al. 1995, Hintermann et al. 1995, Hardeland et al. 1995, 1996, Tilden et al. 1997, Hardeland et al. 1999, Ganguly et al. 2001, Bell-Pedersen et al. 2005, Bembenek et al. 2005, Vieira et al. 2005). Circadian secretion of melatonin or its metabolic enzymes is a significant component of diurnal rhythms in many vertebrate species and insects (Tamakoshi and Ohno 2004, Bell-Pedersen et al. 2005, Bembenek et al. 2005). Melatonin receptors have been detected in ducks, mice, chickens, and in the human gut (Lee and Pang 1993). Melatonin may have evolved to maintain synchronicity of cellular division and differentiation in multicellular organisms with respect to circadian time.

Cell culture and in vivo studies describe the influence of melatonin upon the cell cycle in various tissues. Melatonin and its metabolic enzymes are present in the gastrointestinal tract, suggesting *in-situ* biosynthesis by the gut tissues and a paracrine effect. Diurnal rhythm of melatonin in the gastrointestinal tissues of birds and rodents has been described with high levels present in the dark period. Melatonin inhibits the proliferation of the jejunal epithelium, consistent with local hormonal effects (Lee and Pang 1993, Hannibal and Fahrenkrug 2006). Pathways for the biosynthesis and degradation of melatonin have also been shown in skin fibroblasts, keratinocytes, hair follicles, and melanocytes (van der Horst et al. 1999, Slominski et al. 2002, 2005). Certain melatonin receptors appear to be linked to cellular growth and differentiation (Carlberg 2000).

Several studies implicate disruption of melatonin secretion to neoplastic growth. Alterations in circadian rhythm have been associated with cancer in animals (Mormont and Levi 1997). Manipulation of the light-dark cycle in rodents is associated with increases in tumorigenesis (Anderson et al. 2000). Implanted malignant tumors into SCN-lesioned mice grow at an accelerated rate (Filipski et al. 2004). Administration of exogenous melatonin reduces growth and the incidence of mammary tumors. Pinealectomy has the opposite effect. Melatonin reduces the incidence of spontaneous mammary tumors in *C-neu* and *N-ras* transgenic mice

(Mediavilla et al. 1997, Sanchez-Barcelo et al. 2003).

The antiproliferative properties of melatonin have been well established in animal studies. Melatonin in the physiological range reduces growth of androgen-dependent human prostate cancer (Moretti et al. 2000) and in pharmacological doses inhibits androgen-insensitive tumor cells (Sainz et al. 2005). It inhibits cellular proliferation and H3-thymidine uptake in SV-40 transfected or EGF-stimulated cells in culture and has an antineoplastic effect on a rat pituitary cell line (Fornas et al. 2000). The influence of melatonin on the regulation of cell cycle is therefore evident in cell culture and *in vivo*.

The antiproliferative effects of melatonin are investigated at the molecular level. Melatonin increases the expression of p53 and p21WAF1 proteins, reducing metastatic capacity and cell invasiveness in MCF-7 human breast cancer cells (Sanchez-Barcelo et al. 2003, Mediavilla and Sanchez-Barcelo 1999). Melatonin counteracts the stimulatory effect of estradiol on cell invasiveness. This effect is in part mediated by the induction of cell surface adhesion proteins E-cadherin and beta (1)-integrin. Melatonin down-regulates the expression of estrogen receptor-alpha and inhibits the binding of the estradiol-ER complex to the estrogen response element (Sanchez-Barcelo et al. 2003, Kiefer et al. 2005). It causes a decrease in proliferation cell nuclear antigen, *c-myc*, and *c-jun* expression. Melatonin increase of p53 is associated with the induction of apoptotic cell death in cancer cells (Fornas et al. 2000, Blask et al. 2002, Sainz et al. 2003, Qin et al. 2004). Increase in p53 is associated with down-regulation of cyclin E and the stimulation of Fas expression (Allgulander et al. 1987). Additional mechanisms implicated in melatonin's oncostatic action include the calcium/calmodulin and protein kinase C-mediated signal transduction cascades (Soto-Vega et al. 2004). Melatonin suppresses of epidermal growth factor receptor EGFR/mitogen-activated protein kinase (MAPK) activity (Blask et al. 2002). Molecular studies support a role for melatonin in the regulation of the cell cycle.

Melatonin may have evolved in part to protect against mutagenic stress. Circadian rhythmicity noted in apoptotic response to genotoxic stress may be due to melatonin (Ruifrok et al. 1998, Ijiri 1989). Antioxidant action of melatonin plays a significant role in countering DNA damage (Pawlikowski et al. 2002). As a scavenger of free radicals it augments the activities of anti-oxidant enzymes and can protect against carcinogens (Seidman et al. 1999, Karbownik 2002). Melatonin inhibits benzo(a)pyrene-induced two stage skin carcinogenesis in mice. It decreases the number of animals bearing papillomas and reduces the number of papillomas per animal (Kumar and Das 2000). DNA damage induced by paraquat or UV light exposure on calf thymus DNA appears to be prevented by melatonin (Yamamoto and Mohanan 2001). It protects human keratinocytes from UVB irradiation (Nickel and Wohlrab 2000) and partially protects oxidative damage to DNA by the carcinogen KBrO<sub>3</sub> (Cadenas and Barja 1999). Significant evidence implicates melatonin in the protection of DNA.

# CAUTIOUS INTERPRETATION OF THE EVIDENCE IS NEEDED

It is important to distinguish between sleep-wake cycles and circadian rhythmicity. Sleep-wake cycles may be altered by introduction of circadian shifts or by introduction of forced desynchrony under controlled conditions. Furthermore, certain processes may be regulated by a circadian clock component, but not be circadian. Cautious interpretation of the available evidence is therefore required.

Several factors may influence or confound interpretation of the clinical and epidemiological results presented. Depression and low socioeconomic status, for example, are strong candidates for producing some of the statistical association between long sleep and mortality (Patel et al. 2006). In one prospective study on habitual duration of sleep and incidence of breast cancer the authors did not find convincing evidence for an association between sleep duration and the incidence of breast cancer (Pinheiro et al. 2006). In another study, short sleep and insomnia appear to be associated with little risk of increased mortality (Kripke et al. 2002). Clinical epidemiological evidence, therefore, should not be considered as proof of an association or causality

#### CONCLUSIONS

The importance of balanced sleep patterns on good health is well documented in the literature. However, there is no clear link between disruption in sleep patterns and risk of aging and malignancy. A model based on circadian-gating of sleep-wake cycles enhances our understanding of this pattern in promotion of aging and malignancy. Alterations in sleep-wake cycles and circadian shifts create windows in time in which DNA becomes more vulnerable to genotoxic stress. During these periods cells are least capable of responding adequately to DNA damage by DNA repair or apoptosis. This may result in accumulated DNA damage, accelerated aging, and malignant transformation. The model proposed links the circadian pathway to the mutational theories of senescence and neoplasia, although careful interpretation of the data should be considered, and further studies are needed.

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