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Associations of Circadian Disruption of Sleep and Nutritional Factors with Risk of Cancer

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Abstract: *Background*: Daily entrainment of the human circadian clock is important for good human health. In previous studies, shift work has been linked to higher risk of chronic diseases, including certain types of cancers. Exposure to light at night suppresses the physiologic production of melatonin, a hormone that has antiproliferative effects on intestinal cancers. In the present review, we examine the available evidence on sleep disruption, changes in nutrient intake and nutritional factors and risk of cancers.

Methods: Internet search of PubMed and discussion with colleagues.

Results: Recent studies indicate that night shift work appears to have independent influence on the function of the endocrine system, gastrointestinal tract and circadian brain function. Sleep disruption enhances cortisol secretion and ghrelin release from the stomach and decreases melatonin and leptin which interfere with functioning of beta cells of pancreas. Apart from biological dysfunctions, behavioral changes, increased intake of refined carbohydrates, w-6 fats and low w-3 fats, physical inactivity, excess of tobacco and alcoholism appear to be common among night shift workers. Leptin signals the brain to feel satiety whereas ghrelin, produced in the stomach, signals hunger. Recent studies also indicate that sleep-deprived individuals with hormonal changes have greater cravings for sweet and fatty foods. Apart from this, stress hormone cortisol, which increases with sleep deprivation also contribute to hunger. In addition to altered hormone levels, late night awakening provides greater opportunity to eat, smoke and drink alcohol and eating often includes high-caloric foods. Epidemiological studies indicate that sleep disruption may be associated with obesity and other chronic diseases including cancers. Since electric light at night has adverse effects among night shift workers compared to day shift workers, it has been proposed that a portion of the high and rising risk of breast and prostate cancer worldwide may be because of night shift work. The suppression of melatonin by exposure to light at night may be one reason for the higher rates of breast, prostate and colorectal cancers in the developed world. Suppression of nocturnal melatonin by exposure to light at night results in lack of protection by melatonin on cancer cell receptor sites which allows the uptake of linoleic acid (LA) which in turn enhances the growth of cancer cells. Melatonin is a protective, oncostatic hormone and strong antioxidant having evolved in all plants and animals over the millennia. It is possible that rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer and other cancers.

Conclusions: Experimental evidence and limited human evidence allowed the International Agency for Research on Cancer (IARC) to classify circadian disruption of sleep, as a probable human carcinogen, group 2A. Behavioral changes, intake of fast foods, physical inactivity, excess of tobacco and alcoholism are common among night shift workers which may also apart from deficiency of melatonin.

Keywords: Light at night, night shift, melatonin, diet, nutrient.

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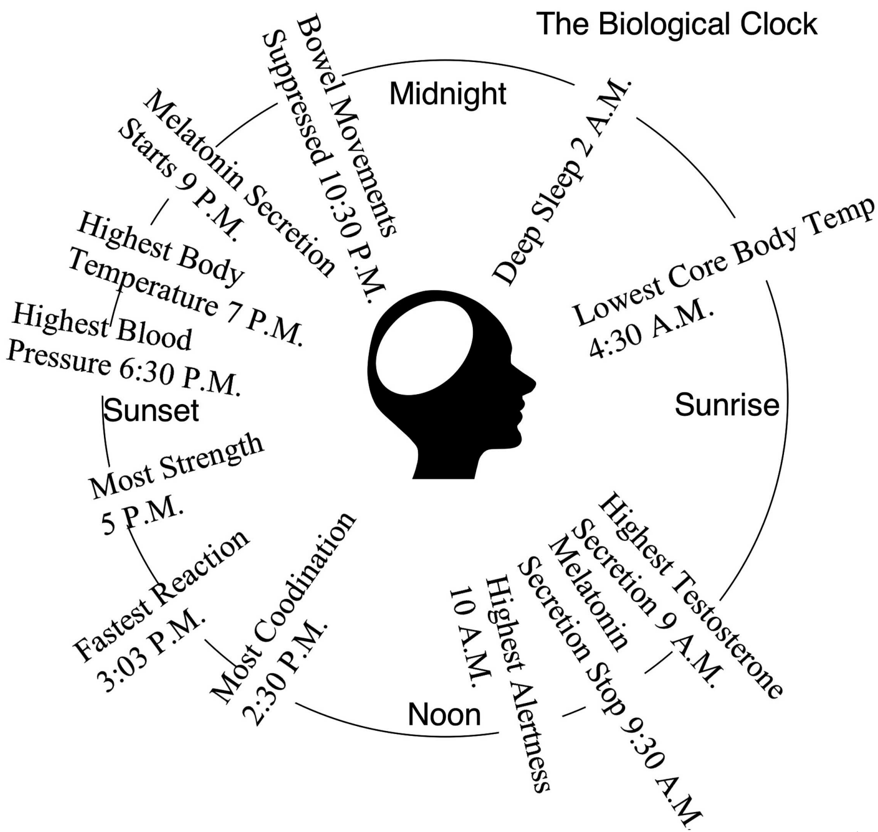
INTRODUCTION

Life in industrialized societies is primarily life inside buildings. Illumination from electric lighting in the built environment is quite different from solar radiation in intensity, spectral content, and timing during the 24-hour daily period. Humans evolved over millions of years with the day-night pattern of solar radiation as the primary circadian cue. Working rotating night shift disrupts circadian rhythms and may have a wide range of physiologic, psychological and social effects leading to behavioral changes and biological dysfunctions among night shift workers [1-6] (Figs. **2**-**4**). In previous studies, shift work has been linked to higher risks of some chronic diseases, including cardiovascular disease, type 2 diabetes and certain types of cancers [2-6]. Exposure to light at night suppresses the physiologic production of melatonin, a hormone that has antiproliferative effects on intestinal cancers [7-14]. The rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer [1-11] (Figs. **2**-**4**).

A large number of studies have addressed numerous health concerns associated with shift work. However, only recently has a new candidate effect been added to the list, namely cancer. The International Agency for Research on Cancer [IARC] has provided the incentive for epidemiological studies which investigate "probable" cancer hazards



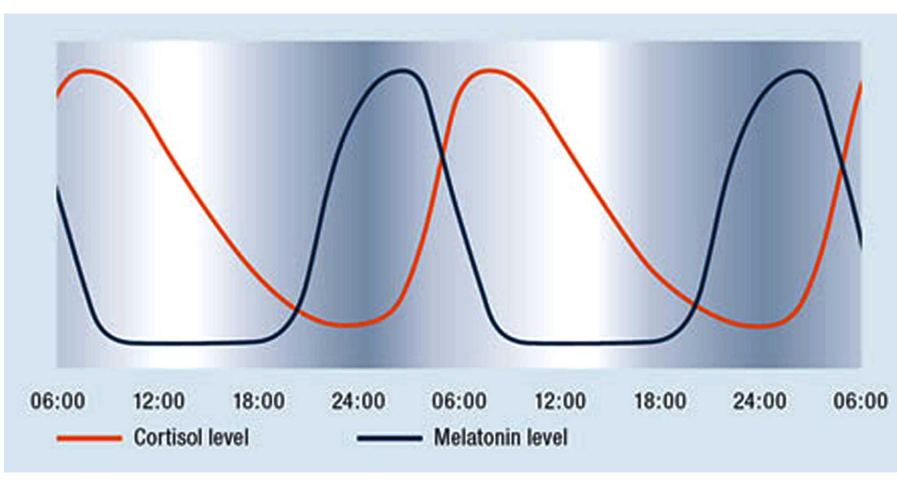


Fig. (1). (**A**) Many physiological functions, such as body temperature, hormone secretion, sleep, wakefullness, blood pressure, heart rate and alertness rise and fall with a cycle of approximately 24 hours circadian rhythm. (**B**) Normal circadian rhythm of cortisol and melatonin hormones.

Type of Cancer	Odds Ratio	95% Confidence Interval
Breast cancer		
Night shift ≥ 0.5 year[a]	1.5	1.3 – 1.7
Night shift 6 years[a]	1.7	1.3 – 1.7
"Graveyard shift" (any) [b]	1.6	1.0 – 2.5
Shift work ≥ 5.7 hours/week[b]	2.3	1.0 – 5.3
Rotating nights; 1-14 years[c]	1.08	0.99 – 1.18
Rotating nights; 15-29 years[c]	1.08	0.90 – 1.30
Rotating nights; ≥ 30 years[c]	1.36	1.04 – 1.78
Rotating night shift work: > 20 years[d]	1.79	1.06 – 3.01
Prostate cancer		
Rotating shift work[e]	3.0	1.2 – 7.7

a. Hansen J. *Epidemiology*. 2001;12:74-77.
b. Davis S, et al. *J Natl Cancer Inst*. 2001;93:1557-1562.
c. Schernhammer ES, et al. *J Natl Cancer Inst*. 2001;93:1563-1568.
d. Schernhammer ES. *Epidemiology*. 2006;17:108-111.
e. Kubo T, et al. *Am J Epidemiol*. 2006;164:549-555.

Fig. (2). Odds Ratio for breast and prostate cancer among shift workers.

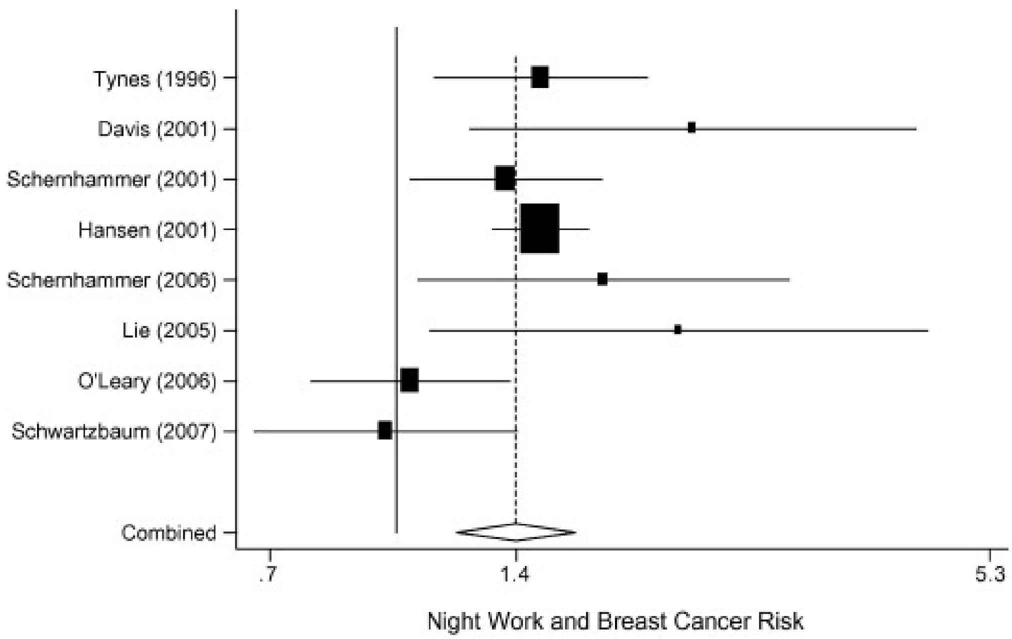


Fig. (3). Risk of breast cancer in night shift workers. (Ref no. 3, 4, 53, 58, 60 in the text) By Eva S Scherhamer *et al.,* 2009.

associated with shift work [6]. After a critical review of published data relevant to an assessment of carcinogenicity, the following was stated: (i) "There is sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)". (ii) "There is limited evidence in humans for the carcinogenicity of shiftwork that involves night work". On the basis of (i) and (ii), the 22 working group participants concluded [6], (iii) "Shiftwork that involves circadian disruption is probably carcinogenic to humans (Group 2A)". On the one hand, shift work is inevitable today as there is work to do for people over 24 hours, everyday. To deliver such work at unusual times, 15-20 percent of male and female workers in developed countries are engaged in regimens involving night work, i.e., in time-windows that contain the so-called biological night [6]. On the other hand, possibly associated breast and prostate cancers are two of the most common cancers in the world. Given the fact that many shift workers may be exposed to circadian disruption or chronodisruption, even small risk elevations could translate into numerous attributable cases.

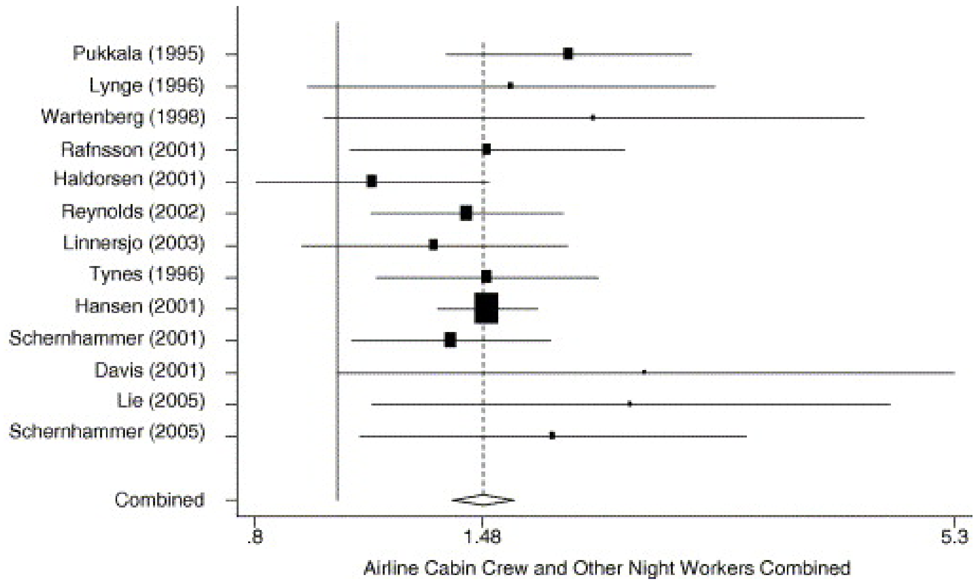


Fig. (4). Risk of breast cancer in night shift workers. (Ref no. 3, 4, 53, 56, 58 in the text).

MECHANISM OF CANCERS AND MELATONIN

Many physiological functions, such as body temperature, hormone secretion, sleep, wakefulness, blood pressure, heart rate and alertness rise and fall with a cycle of approximately 24 hours which is called a circadian rhythm [7-14] (Fig. **1A** & **1B**). A group of cells in the brain, the Suprachiasmatic Nucleus (SCN), acts as a pacemaker and drives the circadian rhythms. Environmental factors, called synchronizers or Zeitgebers, help reset circadian rhythms to the 24 hour day-night cycle. Among those factors, light is the most powerful synchronizer. However, when exposure occurs at a time when the body would normally not be exposed to light, that is, at night, then it disrupts the circadian rhythms [7-15]. The disruption of circadian rhythms may result in biological dysfunctions, decreased alertness and poor sleep leading to increased risk of chronic diseases [6-15].

Exposure to light at night disturbs the circadian system with alterations of the sleep/activity patterns, suppression of melatonin production, and deregulation of circadian genes involved in cancer related pathways [7-14]. Most of the studies that have analyzed the relationship between nocturnal exposure to light (and shift work) and cancer have focused on the role of melatonin [2-6] (Figs. **2**-**4**). Melatonin is a hormone mainly secreted at night by the pineal gland. Peak melatonin levels usually occur during sleep in the middle of the night (Fig. **1A** & **B**). It has been demonstrated that melatonin is involved in regulation of circadian rhythms, sleep and potentially in restraining tumor growth [14]. Melatonin has a direct antiproliferative effect which stops cancer cells from growing and spreading, and it may also increase the expression of a gene that acts as a tumor suppressor. Melatonin is a potential free-radical scavenger, and could thus protect by shielding DNA from oxidative damage. Finally, melatonin could also act as an immune-modulating agent.

Light exposure during the night suppresses nocturnal melatonin secretion, which may be in a dose response manner: the brighter the light, the greater the suppression. The decrease in melatonin production has been suggested to induce an increase in the levels of reproductive hormones such as estrogens, which would then stimulate the growth and proliferation of hormone-sensitive cells in the breast, prostate, colon and rectum where cancer is more common among night shift workers [14-16].

NUTRITIONAL AND BEHAVIOURAL CHANGES

Light, including artificial light, has a range of effects on human physiology and behavior and can therefore alter human physiology when inappropriately timed. The internal rhythms can become desynchronized from both the external environment and internally with each other, impairing our ability to sleep and wake at the appropriate times and compromising physiologic and metabolic processes [16]. There is increased consumption of ready prepared foods rich in calories, refined carbohydrates and total fat, trans fat and w-6 fat which are well known risk factors of obesity and other chronic diseases [17-21]. Apart from dietary changes, night shift workers have tendency to avoid spare time physical activity and there is a tendency to consume more tobacco and alcohol and eat more foods due to increased hunger. Niedhammer *et al.*, [17] conducted a longitudinal observational study in nurses that incorporated two 5-year periods between 1980–1985 (n = 363) and 1985–1990 (n = 285). They reported that weight gains exceeding 5 and 7 kg were more frequent in nurses on night work compared to daytime work during the 5-year period 1985–1990. And the subjects of the study were differed from those in Niedhammer's study as they were male workers engaged in alternating shift work. Morikawa *et al.*, [18] conducted a longitudinal cohort study over a 10-year period in 1,529 Japanese male workers and reported significantly increased body mass index in shift workers during the observation period.

The type of job schedule was significantly associated with all three BMI endpoints (5% increase in body mass index; odds ratio (OR) for comparison between alternating shift workers and regular day workers, 1.14; 95% confidence

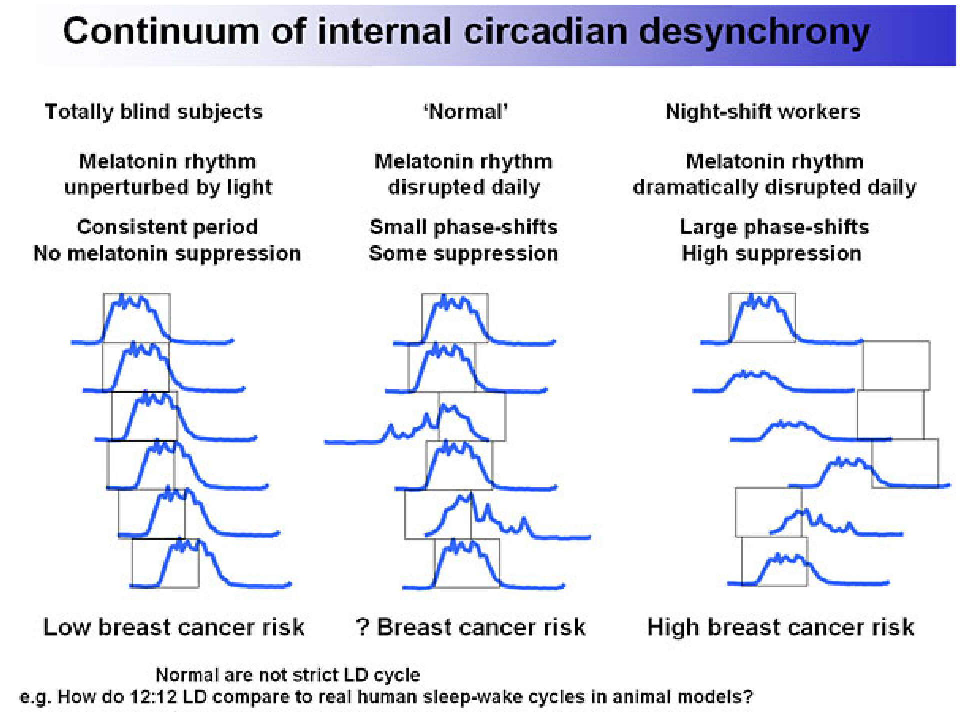


Fig. (5). Risk of breast cancer caused by melatonin rhythm disruption (suppression) due to phase shifting.

interval (CI), 1.06–1.23): (7.5% increase in body mass index; OR, 1.13; 95%CI, 1.03–1.24: 10% increase; OR, 1.13; 95%CI, 1.00–1.28). Body mass index at study entry was also positively associated with the 5, 7.5, and 10% increases in body mass index during the study [19]. It is possible that life style alterations such as eating habits and exercise in conjunction with disruption of circadian rhythm may have contributed to shift work related weight gain. Kivimaki *et al*., examined the association between the shift work and health habits. They studied a population of 689 nurses (age 22- 60 years) working night and day shifts. Smoking, Alcohol consumption, sedentary life style and being overweight were the considered habits. There was an increased incidence of smoking and overweight among those who worked during the night, compared to those who worked only day time hours [20]. Persson *et al.,* conducted qualitative interviews with 27 nurses (2 men and 25 women) between the age of 25 and 63 to determine the impact of night work on diet and exercise habits. Many of the nurses reported eating food high sugar in order to override the feelings of tiredness. Sweet foods and junk food were readily consumed due to ease of access compared to an alternatively healthy snack. In addition, nurses reported that it was difficult to select healthy foods the day after working night shift [21].

DIETARY INTAKE

Chronobiologists, nutrionists and physicians have been interested in finding out the eating habits of shift workers. Altered eating behaviour is a manifestation of altered relationship between internal 24 hours rhythms and external work schedule of persons. Eating behavior might be altered by working shifts, especially when night work is involved [22, 23], due to a diverse range of biological, social, and cultural factors [24]. Nocturnal eating causes disturbances of intestinal motility, affecting the digestion, absorption, and utilization of pharmacological drugs and nutrients [25, 26]. Refined carbohydrates, w-6 fat, trans fat and high saturated fat diets particularly low in w-3 fats, antioxidants, vitamins and amino acids may have greater adverse effects on physiological functions leading to poor availability of protective nutrients.

Several studies have demonstrated that shift work affects circadian distribution of food intakes, regularity of meals and the number of meals eaten during different phases of shift cycles [27, 28]. Several studies [29-34] have evaluated food intake characteristics or nutritional aspects in shift workers. In a comparison between shift and day work, one study [29] observed a lower intake of energy and nutrients in female shift workers because of less frequent and poorer quality meals, although another two studies [30, 31] failed to observe these differences. A comparison between Type of work shifts in shift workers showed no significant difference in daily intake of energy [32, 34]. The total number of eating events per day was significantly higher in night shift workers [33], although these workers had a reduced energy intake during the 8-h night shifts [34]. In 2002, a detailed questionnaire survey was conducted in the same company [35]. A preference for fried food was significantly more frequent in shift workers (46%) than in day workers (42%). However, there was no significant difference in the preference for either sweet or salty food and therefore suggested that the preference for fried food was another potential factor.

A cross-sectional survey examined the associations of various nutrients and dietary factors as well as food groups with creatinine-adjusted first morning urinary melatonin (6-sulfatoxymelatonin; aMT6s) concentrations [36]. Although no specific nutrients were associated with altered concentrations of melatonin, the findings pose the possibility that

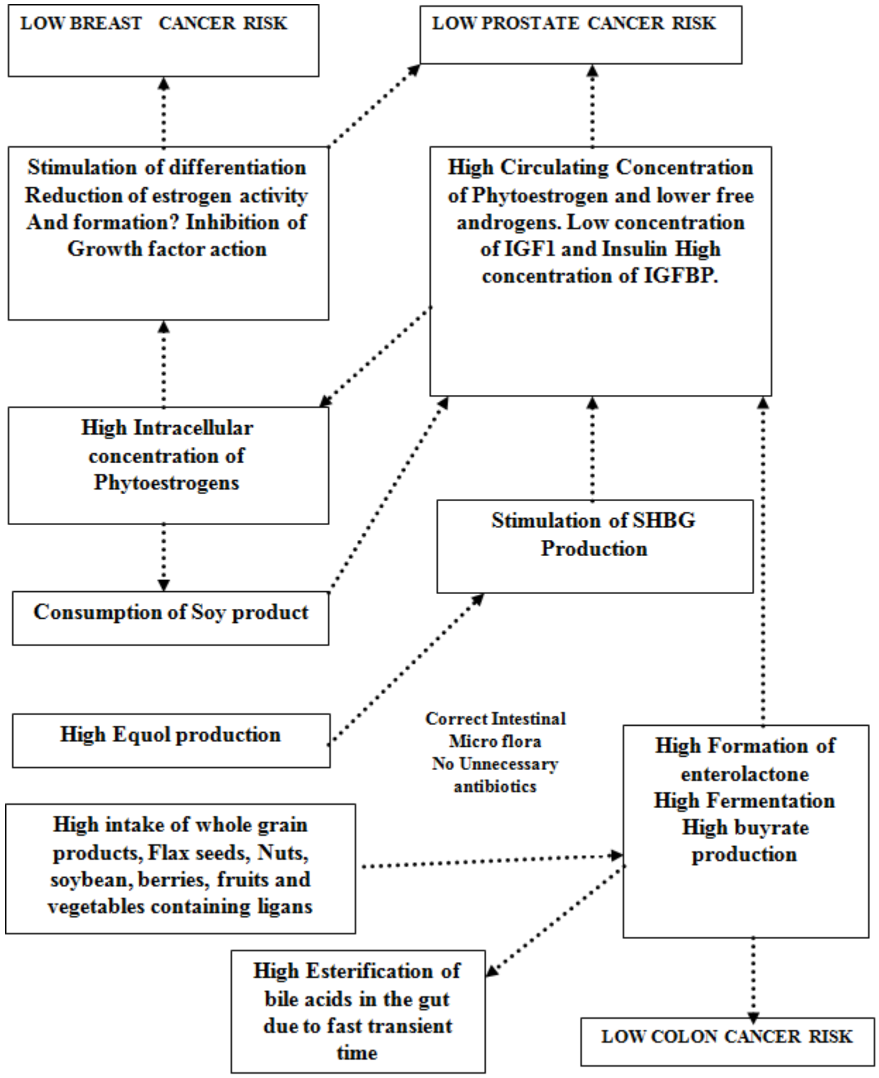


Fig. (6). A working hypothesis for the role of diet in the prevention of breast, prostate, and colon cancers. This model deals with some of the the possible mechanisms for the protective role of dietary phyto-oestrogens (isoflavonoids and lignans) in association with other biological events.

several specific foods, including red meat, could affect cancer risk through the lowering of melatonin concentrations [36].

DRINKING AND TOBACCO CONSUMPTION

Alcohol drinking habits are usually assumed to be a risk factor for obesity as alcohol itself is high in calories and drinkers also tend to eat high-calorie meals. Night shift workers are more likely to smoke and drink alcohol during night shift work, in order to pass their time and maintain awakening during work. However moderate alcohol intake may be protective. A study in Japanese male workers found that drinking alcohol more than five times per week decreased the risk of developing obesity compared to abstinence [37].

EXPERIMENTAL STUDIES

Results from *in vitro* and animal studies suggest that the antiproliferative effect of melatonin is not limited to breast cancer, but may also affect other cancers, especially intestinal cancers [38-43]. For example, melatonin substantially inhibited the growth of cell lines derived from hormone-independent colon carcinomas, and the anticarcinogenic properties of melatonin have repeatedly been demonstrated in chemically induced colon cancers in rodents [44-47].

The growth of rat hepatoma 7288CTC *in vivo* is stimulated by the uptake of linoleic acid (LA) and its metabolism to 13-hydroxyoctadecadienoic acid (13-HODE), an important mitogenic signaling molecule within this tumor. This study tested the hypothesis that the mechanism of melatonin's anticancer action *in vivo* involves the inhibition of tumor LA uptake and metabolism to 13-HODE in hepatoma 7288CTC and results support a novel mechanism of tumor growth inhibition by melatonin involving a melatonin receptor-mediated suppression of cAMP levels, resulting in diminished tumor FA transport, possibly *via* decreased Fatty-acid transport protein (FATP) function. The inhibition of these signal transduction events by melatonin culminates in the suppression of LA uptake and LA metabolism to the mitogenic signaling molecule 13-HODE, and cancer growth [48].

Exposure of (SR-) xenograft-bearing rats to increasing intensities of polychromatic white light at night suppresses melatonin while increasing tumor growth rates, DNA content, [3H]thymidine incorporation into DNA, LA uptake, 13-HODE formation, cAMP levels and Extracellular signal-regulated kinase (ERK1/2) activation a dose-dependent manner. Similar effects occur in SR- human breast cancer xenografts perfused in situ with melatonin-depleted blood from healthy female subjects after their exposure to a single bright intensity (2800 lux) of polychromatic light at night. Additionally, SR- human breast cancer xenografts exhibit robust circadian rhythms of LA uptake, 13-HODE formation and proliferative activity. Exposure of xenograft-bearing rats to dim light at night results in the complete elimination of these rhythms which culminates in unfettered, high rates of tumor metabolism and growth. This biological mechanism may partially explain the higher risk of breast and other cancers in women working rotating night shifts and possibly others who also experience prolonged exposure to light at night [48, 49] (Fig. **5**).

EPIDEMIOLOGICAL STUDIES ON SHIFT WORK AND CANCERS

The multilevel endocrine changes caused by circadian disruption with melatonin suppression through light at night lead to the oncogenic targeting of the endocrine-responsive breast in women and possibly the prostate in men. Repeated phase shifting with internal desynchronization may lead to defects in the regulation of the circadian cell cycle, thus favoring uncontrolled growth. Sleep deprivation leads to the suppression of immune surveillance that may permit the establishment and/or growth of malignant clones [50].

The relationship between cancer and shift work is relatively recent. The IARC report talks about the results of eight studies in humans. A meta-analysis performed in 2005 evaluated 13 studies [51]. Some of the studies have evaluated a large number of individuals (for example, the studies based on the Nurses' Health Study included 78,586 women who were followed for ten years). Usually the studies include a group of individuals who have worked shifts (and night shift), and a control group, that is, individuals who were not employed on any night shift work. The majority of studies have focused on women and risk of breast cancer, and found an increased risk of breast cancer associated with exposure to light at night and night work [3, 52-57] (Figs. **2**-**4**). There was also a trend of increased risk with increased years of night shifts and more hours per week of work during the night. For example, one study found that, compared with those who had never worked at night, nurses who had done nightwork for between 1 and 29 years, showed an 8% increase in relative risk of breast cancer, and nurses with 30 years or more of night work showed a 36% increase in relative risk [4]. Another study found that women who worked more than 20 years of rotating night shifts had a modestly elevated risk of breast cancer, and there was no increased risk with fewer years of shiftwork [58] (Figs. **2**-**4**).

A few studies have evaluated other types of cancer [5]. This study reported a possible relationship between rotating night shift and risk of colorectal cancer and concluded that working a rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer in women [5]. Another study [56] (Fig. **4**) found that flight attendants had increased risk of breast cancer and melanoma. Although the majority of studies focused on women, two studies found and increased risk of prostate cancer among male rotating shift workers.

Most studies have taken into account confounding variables such as reproductive history, family history of breast cancer, use of oral contraceptives and hormone replacement therapy, social class and alcohol consumption. However, the epidemiological studies also have some significant limitations, as previously described. While the majority of studies published indicate a relationship between shiftwork and increased risk of cancer, some studies did not find such a relationship [59]. A recent study [60] (Fig. **3**) used registry data that included nearly the entire Swedish working population, had a follow-up for 19 years (between 1971 and 1989). However, it should be noted that only a small proportion of the population were shiftworkers, and therefore the power of the study is limited.

Effect of night shift work on lifestyle indicate that there is an increased risk of accidents and error, increased sleepiness and fatigue due to deprivation of sleep, increased health problems; and disruption to family and social life. Strategies to limit the risk associated with these hazards are also reviewed and required advance knowledge of circadian pattern of blood pressure, heart rate, cortisol, melatonin and reproductive hormone levels. Melatonin, which is a potent marker of the primary circadian oscillator, displayed a phase shift that differs widely among night shift workers. Body temperature on the other hand was found to be more regularly adapted despite the persistence of a small decrease or leveling off during the night. Although no relationship was found between the melatonin increase and nocturnal PRL (prolactin) peak, a concomitance with this transient temperature decreases [4]. Plasma concentration of melatonin and prolactin were significantly lower in nurses of the working groups during night. The results indicate that night shift suppresses ovarian function by affecting the circadian rhythm of melatonin and prolactin [5]. There is considerable influence of sleep in driving the Circadian growth hormone rhythm as revealed by its acute shift in the sleep period. They also provide evidence of an incomplete adjustment of growth hormone rhythms in night workers [61]. Melatonin shows a potential oncostatic action, and light exposure during night suppresses melatonin production. There is little information, however, about the direct effect of night work on the risk of cancer. Women who work on rotating night shift with at least three nights per month, in addition to days and evenings that month, appear to have a moderately increased risk of breast cancer after extended period of working rotating night shift [62]. Higher age, BMI and heavy smoking were significantly related to lower levels of melatonin whereas it was significantly associated with higher aMT6s levels. Melatonin levels may be one mechanism through which these factors influence the development of cancer [63]. The adjustment to permanent night work of the circadian rhythm in the secretion of melatonin, which is generally considered to be the best known indicator of the state of the endogenous circadian body clock.

In brief, in a normal environment, permanent night shift systems are unlikely to be results in sufficient circadian adjustment in the most individuals to benefit health and safety [64].

A single morning urinary melatonin measurement is a reasonable marker for long term melatonin levels among premenopausal women. Women who work on rotating night shifts seem to experience changes in hormone levels that may be associated with the increased cancer risk observed among night shift workers [65]. Temporal endocrine structure (TES), may be defined as the combination of predictable hormonal changes that are time-related. Regarding their frequency, endocrine rhythms may be circadian, ultradian and infradian. The endocrine circadian time structure (ECTS) that is closely dependent on some areas of hypothalamus, is of particular interest [66] There is insufficient knowledge about the relationship of other lifestyle factors or endogenous sex steroid hormones with melatonin levels [63]. Together with body temperature, TSH acrophase is adapted to regular night work, suggesting that TSH may be a good index for evaluating the orientation of the endogenous clock [67]. The endocrine profiles of night shift workers were compared to those of day active subjects during their usual sleep wake schedule. During usual day sleep, despite an adapted structure, cortisol levels among night workers were abnormally enhanced, whereas TSH decreased in comparison to the plateau observed among day-active subjects. During usual work time, some hormonal disturbances persisted, in particular concerning cortisol and PRL (two hormones reflect the level of activation). Among night workers the work time was associated with the quiescent period of cortisol secretion normally occurring during the first hour of sleep and with a transient PRL increase [68]. PRL & TSH exhibit opposite phase relationship with delta waves, PRL increasing and TSH decreasing when delta waves developed. Delta waves never increase during cortisol secretion, however, pulses of prolactin and GH are positively linked to increase in delta wave activity, which is the deepest phase of sleep occurring primarily during the first third of the night. Pulses of TSH and cortisol are related to superficial phases of sleep [69]. Exposure to light at night, including disturbances of the circadian rhythm, possibly mediated via the melatonin synthesis and the clock genes, has been suggested as a contributing cause of breast cancer. Persons who engaged in night shift work may exhibit altered night time melatonin levels and reproductive hormone profiles that may increase the risk of hormonal related disease, including breast cancer [70]. There is evidence in humans, that the endogenous melatonin rhythm is stronger for persons in a bright-day environment than in a dim-day environment; and the light intensity necessary to suppress melatonin at night continues to decline as new experiments are done. Melatonin suppression can increase breast tumorigenesis in experimental animals, and altering the endogenous clock mechanism may have downstream effects on cell cycle regulatory genes pertinent to breast tissue development and susceptibility. Therefore, maintenance of a solar day-aligned circadian rhythm in endogenous melatonin and in clock gene expression by exposure to a bright day and a dark night may be a worthy goal [70, 71]. Several studies have been conducted world wide recently, to investigate the effects of factors that can disrupt circadian rhythm and alter normal production of melatonin and reproductive hormones on breast cancer risk [72].

Reduced melatonin may increase breast cancer risk through several mechanisms, including increased estrogen production and altered estrogen receptor function. The genes that drive the circadian rhythm are emerging as central players in gene regulation throughout the organism, particularly for cell-cycle regulatory genes and the genes of apoptosis. Aspects of modern life that can disrupt circadian rhythms during the key developmental periods (eg, in utero, infancy and during adolescence) may be particularly harmful. Epidemiologic studies should consider gene and environment interactions such as circadian gene variants and shift work requirements on the job [73]. The molecular biological research on the circadian clock and on mechanisms of phototransduction makes it clear that light for vision and light for circadian function are not identical systems. In particular, if electric lighting as currently employed contributes to 'circadian disruption' it may be an important cause of 'endocrine disruption' and thereby contribute to a high risk of breast cancer in industrialized societies [74]. Associations between night work and breast cancer risk were investigated in a nested case-control study within a cohort of 49,402 Norwegian nurses. Significantly increased risks were seen in nurses who worked ≥5 years with ≥6 consecutive night shifts (OR = 1.8, 95% confidence interval: 1.1, 2.8) and suggest that risk may be related to number of consecutive night shifts [75]. The suppression of melatonin by exposure to light at night may be one reason for the higher rates of breast and colorectal cancers in the developed world deserves more attention. The literature supports raising this subject for awareness as a growing public health issue. Evidence now exists that indirectly links exposures to light at night to human breast, prostate and colorectal cancers in shift workers [76, 77].

Furthermore, the finding that colorectal cancer patients had lower plasma levels of melatonin than healthy control subjects suggests a possible link between low melatonin levels and the enhanced development of colorectal cancer in humans [78, 79]. In other studies, a 70% and 40% increase in the risk of breast cancer in flight personnel and shift personnel, respectively, and excess relative risks of prostate cancer in flight personnel were calculated. Moreover, the two studies of prostate cancer in male shift workers available at the time were both compatible with increased risks [80, 81]. Other mechanisms may be involved in the influence of night work on cancer risk, such as the loss of normal diurnal variation in cortisol [82]. Results from two mortality studies [83, 84] among male shift workers provided the first suggestions that an increased cancer risk was associated with night-shift work.

MANAGEMENT

Alternating few night shifts with day shifts provided some benefit in heart rate and blood pressure variability among those undertaking day shift compared to frequently rotating night shift. A limited number of nights should recommended for safety reasons. A study of the impact of shift pattern on junior doctors showed that the poorly designed shift schedules cause excessive disruption to shift workers' circadian rhythms [85]. Circadian rhythms are under the influence of, and physiological variables are mediated by, the activation of the adrenals, sympathetic/parasympathetic, hypothalamic and pituitary activity [86-89]. An intrinsic body clock residing in the suprachiasmatic nucleus (SCN) within the brain regulates a complex series of rhythms in humans, including sleep/wakefulness. The individual period of the endogenous clock is usually >24 hours and is normally entrained to match the environmental rhythm. Misalignment of the circadian clock with the environmental cycle may result in sleep disorders. The environmental light-dark cycle provides the principal entraining signal to the SCN, which in turn produces synchronized rhythms of behaviour and physiology through alignment of circadian gene oscillation within both extra-SCN neurons and peripheral tissues [88, 89]. Circadian rhythms, coordinated in part by the parietal hypothalamic-pituitary and adrenal mechanisms, have been reported in almost all variables examined thus far, including the circulation. It is possible that all metabolic functions undergo circadian rhythms [87-89]. Adapting to shift work is easy for some people while others never adjust. Exercise and a well balanced diet will probably help any adjustment. It is possible that shift workers may benefit by doing active prayer, although such sub-study could not be done in this subset of shift workers. Singh *et al*., also reported for the first time in the literature, a circadian decline in antioxidant vitamins, nitrite, coenzyme Q10 and magnesium and increase in oxidative stress during second quarter of the day compared to values in the evening [90]. The adverse effects of shift work have been reviewed but no study has reported if shift work would be associated with greater decline in vitamins, melatonin and greater increase in oxidative stress, because such findings may explain the pathogenesis of increased blood pressure variability, type 2 diabetes mellitus, hypertension insulin resistance and mortality among shift workers [91].

Nonpharmacological management of circadian rhythm with yoga, physical activity, moderate alcohol intake, and functional foods such as almonds, walnuts, rape seed oil, and Nutraceutical eg coenzyme Q10 and w-3 fatty acids appear to be protective against circadian rhythms of cardiovascular events. Brain is quite rich in w-3 fatty acids, hence function of certain areas of the brain, responsible for circadian rhythm and neurotransmitters release, may be altered by supplementation of these agents [90-93]. The Indo-Mediterranean Diet Heart Study was a single blind randomized study that assessed the effect of a diet rich in alpha-linolenic acid, the parent n-3 fatty acid, on the occurrence of myocardial infarction and sudden cardiac death [92, 93]. Of one thousand subjects of the Indo-Mediterranean Diet Heart Study, we focus on the 115 patients from both control and intervention groups in which cardiac events occurred [92]. The timing of cardiac events throughout the day was compared between the intervention and control groups. The distribution of cardiac events along the four quartiles of the day was compared between groups as well as against equal distribution. The risk ratio for a cardiac event was lowest between 4:00 and 8:00 hours in the morning for the intervention group. The control group had a higher rate of events in the second quartile of the day, which deviated from an equal distribution, as expected (P=0.013). In the intervention group events were equally distributed along the day. No statistically significant difference was found in daily event distribution between the groups. The findings indicated that a diet rich in alpha-linolenic acid may abolish the higher rate of cardiac events, normally seen in the second quartile of the day. This alteration in the circadian rhythm of cardiac events appears to be due to beneficial effects of w-3 fatty acids on brain function especially on suprachiasmatic nucleus, as well as on cardiovascular function. The beneficial effect of Mediterranean diets have also been demonstrated in the Lyon Heart Study and other studies [94, 95].

A diet comprising of low w-6/w-3 ratio of fatty acids appears to be protective, whereas a high ratio of these fatty acids in the neurons, endothelial cells, liver cells and cardiomyocytes can predispose metabolic syndrome as well as circadian rhythm of cardiovascular events [95-98]. Effect of shift work on diet and lifestyle has also been observed by other investigators (Fig. **6**) [90-98]. Omega-3 rich foods are fish, fish oil, flax seeds, walnuts, leafy vegetables and whole grains and w-6 rich foods are corn oil, sunflower oil, safflower oil and soybean oil. It is possible that eating 400g per day of fruits, vegetables and nuts and another 400 grams of whole grains in conjunction with 30-50g per day of olive oil + mustard/canola oil may be protective against circadian disruption of sleep and therefore possibly against cancers. There are specific guidelines for shift workers; eat breakfast before day sleep to avoid wakening due to hunger. Stick as closely as possible to a normal day and night pattern of food intake with adjustment of time as suggested elsewhere and in the Nordic Nutrition Recommendations [99-101]. Divide the 24-hour intake into eating events with three satiating meals each contributing 20–35% of 24-hour intakes. The higher the energy needs, the more frequent the eating should be. Avoid over-reliance on (high-energy content) convenience foods and high-carbohydrate foods during the shift. Instead choose vegetable soups, salads, fruit salads, yoghurt, wholegrain sandwiches, cheese or cottage cheese (topped with slices of fruits), boiled egg, nuts, and green tea (promoting antioxidant activity), although this may not be palatable to some. Design shift schedules so as to allow adequate time between shifts for sleep, meal preparation, amongst others, avoid quick returns. Avoid sugar-rich products such as soft drinks, bakery items, sweets, and non-fiber carbohydrate foods (high glycemic load) like white bread. In an early study by Halberg's group [101], effects of competing photic and nonphotic synchronizers of circadian rhythms were tested in lifetime studies on mice subjected to calorie restriction and/ or to weekly shifts of the lighting regimen, repeatedly reviewed. A prolongation of tenth-decile survival time beyond that achieved by calorie restriction alone was observed among mice subjected to shifts in lighting but not in feeding, so that in alternate weeks, food was offered during the rest (light) span. Murine mammary carcino-genesis, under controlled conditions, was reduced in this group ($X^2 = 4.15$, $P<0.05$). Further studies also support that night shift may be associated with decreased melatonin and abnormal dietary habits due to circadian disruption of sleep [102-104].

In brief, the strategies now available to reduce the potential for circadian disruption, include extending the daily dark period, appreciate nocturnal awakening in the dark, using dim red light for night time work and avoid frequently rotating shifts. It may be easier to adjust to a schedule that rotates from day shift to evening to night rather than the reverse order and unless recommended by a physician, not taking melatonin tablets. Diet and lifestyle guidelines should be provided to shift workers to change their behavior related to diet and lifestyle factors.

CONFLICT OF INTEREST

Declared none.

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