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Review article

# Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption

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ABSTRACT

Exposure to Artificial Light At Night (ALAN) results in a disruption of the circadian system, which is deleterious to health. In industrialized countries, 75% of the total workforce is estimated to have been involved in shift work and night work. Epidemiologic studies, mainly of nurses, have revealed an association between sustained night work and a 50–100% higher incidence of breast cancer. The potential and multifactorial mechanisms of the effects include the suppression of melatonin secretion by ALAN, sleep deprivation, and circadian disruption.

Shift and/or night work generally decreases the time spent sleeping, and it disrupts the circadian time structure. In the long run, this desynchronization is detrimental to health, as underscored by a large number of epidemiological studies that have uncovered elevated rates of several diseases, including cancer, diabetes, cardiovascular risks, obesity, mood disorders and age-related macular degeneration. It amounts to a public health issue in the light of the very substantial number of individuals involved. The IARC has classified shift work in group 2A of "probable carcinogens to humans" since "they involve a circadian disorganization". Countermeasures to the effects of ALAN, such as melatonin, bright light, or psychotropic drugs, have been proposed as a means to combat circadian clock disruption and improve adaptation to shift and night work. We review the evidence for the ALAN impacts on health. Furthermore, we highlight the importance of an in-depth mechanistic understanding to combat the detrimental properties of exposure to ALAN and develop strategies of prevention.



**Contents**



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## 1. Introduction: The internal clock and the circadian system

Circadian rhythms are endogenous rhythms with a periodicity of approximately 24 h (24 ± 4 h). They are widespread and regulate most, if not all, of the major physiological systems in mammals. Circadian rhythms are unquestionably the most studied in the literature though other periods exist that range from milliseconds (i.e. ultradian rhythms, for which the period extends from milliseconds to 20 h) to a year (i.e. infradian rhythms, for which the period extends from 28 h to a year) [1]. Circadian rhythms are dependent on an internal clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. Each of the paired suprachiasmatic nuclei is composed of a heterogeneous group of about 10,000 interconnected neurons that give rise to circadian rhythms through specific neuronal gene expression patterns and by the rate at which they fire action potentials.

In addition to this, peripheral clocks have been identified in numerous tissues such as cerebral cortices [2,3], liver, kidney, heart, skin, and the retina, and these are capable of acting in an autonomous manner [4,5]. The SCN subsequently synchronizes peripheral clocks with each other and thus aligns the entire circadian system to the external light-dark cycle. The possible interrelationships between the main clock located in the SCN and the peripheral clocks in other tissues are actively being investigated [6]. The SCN serves in part as a clock, synchronizing other clocks in peripheral tissues, and in part directly orchestrates circadian physiology [7].

The SCN generates circadian rhythms by means of a transcriptional-translational feedback loop. In short, the mechanism is formed by the basic helix-loop-helix (bHLH) Per-Arnt-Sim (PAS) domain containing transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1), which activate the expression of three *Period* (*Per 1–3*) and two *Cryptochrome* (*Cry 1–2*) genes by binding to their E-box (5′-CACGTG-3′) promoter elements. The PERIOD (PER 1–3) and CRYPTOCHROME (CRY1–2) proteins rhythmically accumulate, heterodimerize, and translocate to the nucleus to suppress their own transcription by interaction with the CLOCK:BMAL1 complex. CLOCK/BMAL1 also rhythmically control the expression of nuclear receptors, such as REV-ERBα/β (reverse transcript of erythroblastosis gene) and RORα/β/γ (retinoic acid related (RAR) orphan receptor), which in turn repress and activate *Bmal1* expression, respectively, conferring amplitude and robustness to the oscillations in the molecular clockwork. From a molecular point of view, light activates the expression of several genes in SCN with different expression patterns [8].

We critically review the evidence from a large number of epidemiological studies for an association between long-term exposure to light at night (ALAN) and detrimental effects on health, such as cancer, diabetes, overweight and obesity, mood disorders, and age-related macular degeneration. Furthermore, we underline the importance of an in-depth mechanistic understanding to limit and combat the detrimental properties of exposure to light at night and develop strategies to prevent deleterious effects on health.

## 2. Light control of melatonin secretion

The circadian system in human beings is a complex entity that starts in the eye and that terminates in the pineal gland, which produces melatonin (5-methoxy-*N*-acetyltryptamine), a neurohormone essential for functioning of the clock. In humans, melatonin is secreted during the dark phase of the light–dark cycle. Daytime melatonin levels are hence comparatively very low. Light is considered to be the most potent circadian synchronizer for humans, although non-photic time cues, such as meal times, physical activity and social interaction, also play a part in synchronization of the circadian system. Since the period of the internal clock in humans is not exactly 24 h but close to 24.2 h [10,11] daily exposure to light allows maintain the 24 h cycle of the internal clock.

The synchronizing effect of light on the clock begins at the fetal stage in mammals through secretion of maternal melatonin [12]. While light is a key factor that controls the secretion of melatonin, it differentially

affects the secretion of this hormone as a function of the time of day of the exposure, the intensity, the light spectrum, and the duration of the exposure. An exposure at night time, between midnight and 4 am, i.e. at the time of peak melatonin secretion, results in a complete inhibition of secretion for the full duration of the exposure [9]. Exposure to light in the morning results in a phase advance which means that the peak of melatonin secretion occurs earlier than it would otherwise. On the other hand, when the exposure takes place at the end of the afternoon i.e. prior to the nadir for core body temperature, the clock's phase is delayed. There is hence a phase response curve (PRC, Fig. 1) of the effect of the light [13] that can be used to treat desynchronized patients so as to reset the timing of the biological clock when it is either phase-advanced or phase-delayed [14,15]. The effect of light depends also on its intensity and duration [16,17], as well as its spectral properties, since intrinsically photosensitive retinal ganglion cells (ipRGCs) in the eye contain melanopsin, which is a photoreceptor that relays the light versus dark signaling signal in the retina. Melanopsin is particularly sensitive to blue light (i.e. wavelengths of 460–480 nm) [18,19] and is fundamental for the functioning of the circadian system and for SCN entrainment. This component of the retina has long been considered to be exclusively involved in non-visual functions, although there are recent indications that, in addition to being involved in multiple non-image-forming systems, melanopsin may also have a role in visual functions [20].

Even low intensity light, as emitted by recent technologies such as LEDs, computer screens or televisions, mobile phones, and tablets is capable of acting on the clock, thus leading to a phase delay and a slowing of melatonin secretion [21]. In addition to being exposed to light from a range of LED consoles throughout the day, adolescents are also avid users of such devices at night. The resulting circadian phase delay, which is often associated with a lack of sleep, is thought to underlie clock desynchronization disorders. This amounts to a type of chronic jet lag, also referred to as social jet lag - i.e. a misalignment between the clock and social time - and can jeopardize their health [22].

Our circadian clocks and therefore our circadian rhythms are temporally coordinated by internal and external rhythmic signals. When the signals are no longer in resonance with the clock then the whole system experiences a misalignment called disruption or desynchronization which corresponds to a state where the biological time (i.e. the internal clock) and astronomical time (i.e. the local time) become dissociated [23] thus resulting in alteration of circadian parameters (period, acrophase, amplitude and mean levels). Therefore, whenever the light-dark cycle is altered, as is the case with shift and night work [24–29], transmeridian flights that cover more than three times zones [30,31] or in case of blindness [32], the clock becomes disrupted in accordance with the duration of the desynchronization.

Regardless of the origin (cancer, shift work, jet lag, blindness, …), desynchronization becomes manifest through atypical clinical symptoms, such as persistent fatigue, sleep disorders leading to chronic insomnia, poor appetite, and mood disorders that can cause depression, though some desynchronized people do not experience any of these clinical signs [33,34]. To assess the rhythm synchronization or desynchronization of an organism marker rhythms are useful tools for decision making e.g. time of sampling, timing of therapy, assessing therapeutic responses (Figs. 2,3). A marker rhythm is a physiological rhythmic variable (cortisol, melatonin, body temperature…) with a prominent circadian rhythm, highly reproducible and reliable both on an individual basis and as a group phenomenon (Fig. 2) characterizing the timing of the endogenous rhythmic time structure [35–37].

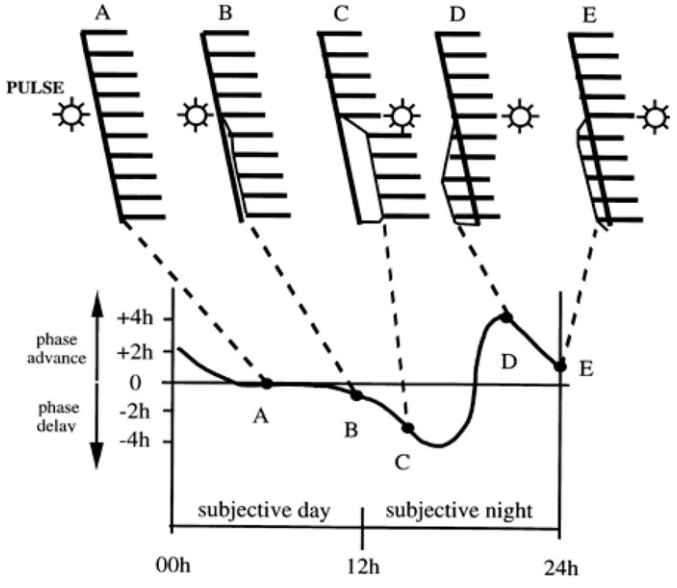


**Fig. 1.** Phase Response Curve (PRC) of motor activity of a nocturnal rodent: the same light pulse administered at different circadian stages (A, B, C, D, E) results in different responses according to the timing of light exposure: no effect (A); or phase advance (D and E); or phase delay (B, C). (From Moore-Ede 1982, (13)).

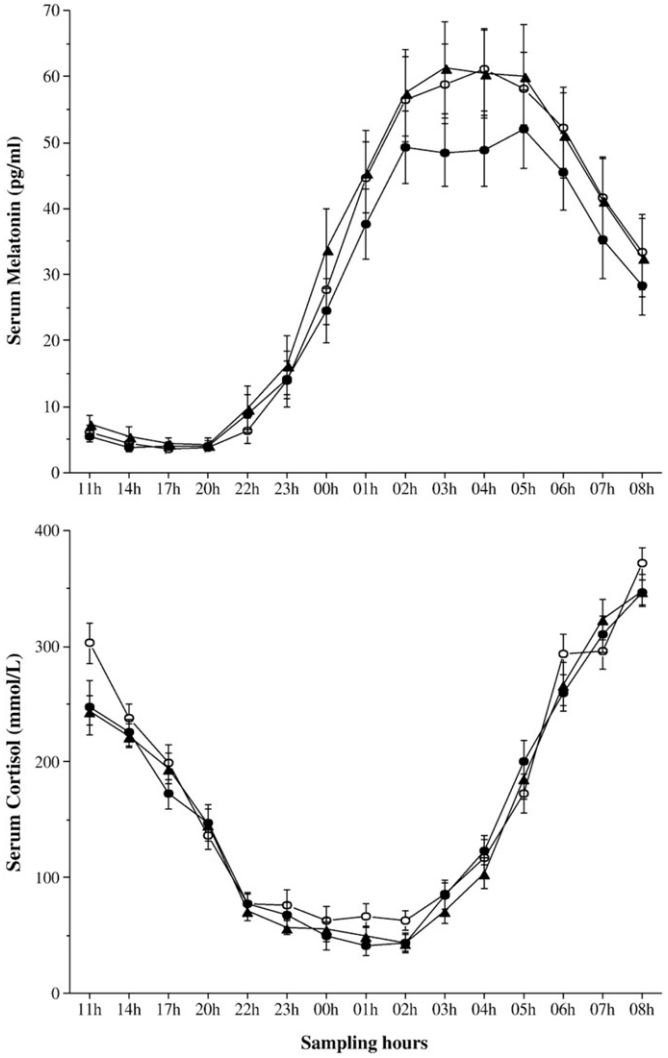


**Fig. 2.** Reproducibility of plasma cortisol and melatonin patterns in young healthy men. Each subject participated in three 24-h sessions (S1, S2, S3): S2 took place two weeks after S1 and S3 four weeks after S2. The circadian rhythms of the two hormones are highly reproducible from a day to another. Both are useful circadian markers of the time structure. S1 (○), S2 (●), and S3 (▲). Each time point is the mean ± SEM of 31 subjects. (From Selmaoui and Touitou 2003; [59]).

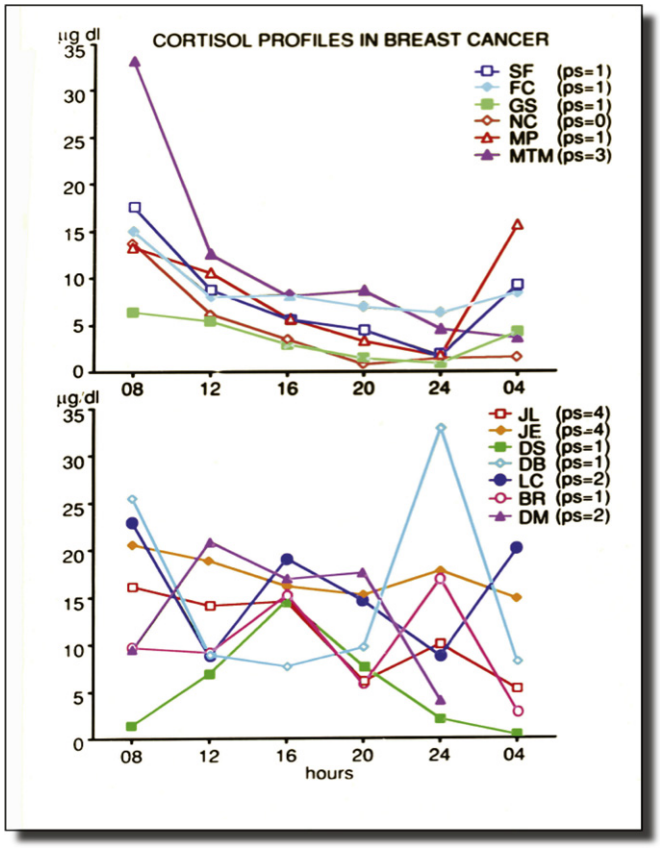


**Fig. 3.** Disruption of plasma cortisol pattern, a marker rhythm, in breast cancer patients (From Touitou et al. 1996, [60]). Upper part: patients with so-called normal circadian rhythm of cortisol. Lower part: patients with abnormal cortisol circadian pattern. ps values correspond to the performance status (ps) of the patients: 0 = normal; 1 = near normal; 2 = needs bed rest for <50% of time; 3 = needs bed rest for >50% of time; 4 = bedridden, needs help to perform normal activities.

## 3. Artificial light at night disrupts the circadian system

In order to accommodate production demands e.g. machines working 24/24 h, cost saving procedures, or specific issues related to security, approximately 20% of the working population in industrialized countries is engaged in shift and/or night work. This type of employment hence exposes a large number of workers to unusual light-dark cycles. Indeed, in our modern industrialized societies, regular 08 h to 17 h working hours for 5 days a week have become relatively rare (25%) compared to so-called atypical, non-standard work hours, such as shift work, night work, part-time work, working on weekends, etc. Those atypical work hours are common in the service industries, such as healthcare, transportation and communications, hospital staff, the police, the hospitality industry, etc. All work hours outside of the usual regular daily working hours are hence considered to be atypical and shift work and night work are therefore prime examples of atypical working hours. European guidelines (93/104/CE and2003/88/CE) provide the following definition of shift work: "all team work schedules whereby the workers are successively assigned to the same work setting".

In the majority of studies performed to date, shift work and night work have been shown to adversely affect the health of workers, for whom numerous health issues have been identified, such as an increased incidence of cancers, sleep disturbances, gastro-intestinal problems, neuropsychological issues, cardio-vascular impairments. These effects are thought to be linked to a loss of the synchronization between the internal clock and the light-dark cycle.

In 2007, the International Agency for Research on Cancer (IARC) emphasized that there is "limited proof for carcinogenic effects relating to the work place", but that "a positive association has been observed between exposure to shift work and cancer, for which a causal interpretation is considered as being credible; although chance, bias and other confounding factors cannot be eliminated". The IARC has hence classified shift and/or night work in group 2A of "probable carcinogens" since "they involve a circadian disorganization" [38,39].

## 4. Shift work, light at night and cancer risk

First hypothesized by Stevens (88), the relationship between exposure to light during shift and/or night work and the occurrence of cancer in workers has been the subject of numerous scientific studies [reviews in e.g. [40–42]].

### *4.1. Breast cancer*

The notion that light can have an effect on the incidence of breast cancer has gained indirect support from research that has shown that women who are blind have a lower rate of breast cancer, although caution is required in regard to this interpretation due to the low number of cases that were studied [43–46]. There also appears to be a positive association with the levels of domestic or outdoor (e.g. from street lights) night time lighting. It needs to be kept in mind, however, that bias can occur in these types of studies due to a reliance on declarative information [47,48]. A co-distribution of exterior light and a 73% higher incidence of breast cancer has been reported in two studies; one in Israel [49,50], the other in South Korea [51], in lit-up suburbs of a town compared to those that are not lit-up. These findings have led various authors to view light as a form of pollution.

Two prospective studies of nurses in the USA have been carried out (Nurse Health Study I and II) [52,53] to investigate the role of ALAN in breast cancer. The first study involved nurses who had worked at least three nights per month. For this study, 78,562 nurses were followed over a 10 year period. There was one case of breast cancer for every 2441 study subjects. The study showed that the risk of breast cancer increased with the number of years spent working night shifts, and there was a statistically significantly increase of 36% when individuals had been assigned at least three night shifts per month over a 30 year period [52]. In the second study, the same authors followed 115,022 nurses over a period of 12 years. Breast cancer was diagnosed in 1352 of them. The relative risk (RR) for breast cancer was 1.79 for women who worked at least 3 night shifts per month over a period of 20 years [53]. In a case control study of 813 women who worked at least once per week from 19 h to 9 h over a 10 year period, a statistically significant increase of 60% in the risk was noted [54]. A retrospective Danish case control study of 7565 women indicated that those who mainly work at night for >6 years had a statistically significant increase of 70% in the relative risk of breast cancer, with a tendency for the Odd Ratio (OR) to increase when the duration of the night work increased [55,56]. With a cohort of 43,316 nurses, a Norwegian study [57] has reported a significant increase in the risk of breast cancer (OR = 2.21) in nurses who worked night shifts for >30 years. In a subsequent study, the same authors described a significant increase in the risk among nurses who worked at least 5 years performing at least 6 consecutive night shifts per month (OR 1.8; confidence interval:1.1–2.8), which suggests the risk may be linked with the number of consecutive night shifts [58]. A case control study in France has reported a significant increase in the risk of breast cancer (OR = 1.40) among women who worked at night for at least 4 to 5 years, and particularly those who engaged in night work prior to their first pregnancy [61].

Overall, the majority of epidemiological studies of the link between breast cancer and shift work have reported an increase in the order of 50 to 100% for breast cancer among women who work night shifts [47,52–53,55–58,61–62]. Two studies did not, however, find such a

link [63,64], although one of these involved a very small number of cases and the authors acknowledged the low prevalence of night work in the study [63]. The positive studies of the risk of cancer and nurses performing night shifts are usually in regard to breast cancer [53,56–58], or radio operators, for example, in regard to other sites [65]. Meta-analyses of epidemiological studies on night work noted a statistically significant average increase around 50% in the risk of breast cancer among women who were chronically exposed to light at night [66,67].

### 4.2. Breast cancer in flight attendants: A specific case

Flight attendants, who regularly undertake transmeridian flights over several time zones present a particularly relevant example of circadian disorganization. They are subject to the effects of night light as part of their work schedules and they are also exposed to the effects of ionizing radiation, ozone and greater exposure to carbon monoxide.

A number of studies have been undertaken to investigate the risk of breast cancer in flight attendants working long routes that involve crossing several time zones. All of these studies indicate that there is a significant relative risk (RR: 1.2–5.4) [68–72] of cancer (e.g. melanoma, skin cancers, etc.), while studies of cabin crews working domestic flights revealed less of an effect [70,73]. In a study involving eight European countries, mortality was found to be slightly higher among flight attendants, without this increase being linked with the duration of the employment [74]. These findings have been confirmed in an Icelandic and a Finnish study [72,75]. It should be emphasized that with these studies of flight crews it is difficult to distinguish between the effects of repeated desynchronization linked with traversing numerous time zones several times per month, from effects of exposure to night light during the flights, or also from effects of ionizing radiation. A meta analysis regarding the incidence of breast cancer among flight attendants addressed this issue [76]. An increased risk of malignant melanoma has been also described among cabin attendants which seems to be occupationally related [68,70,71].

### 4.3. Cancer at sites other than the breast

There are relatively few epidemiological studies regarding the relationship between shift work and night work and the occurrence of cancer at sites other than the breast. As some of the data regarding this are contradictory, additional research with more controlled studies are required to confirm or refute these findings.

#### 4.3.1. Prostate cancer

The published studies on shift work and prostate cancer risk showed mixed results. In contrast, a Japanese prospective cohort study showed a significant 3-fold increased risk in rotating shift workers when compared with day workers [81]. The same authors, however, subsequently published results of a cohort study showing no increased risk of prostate cancer in rotating shift workers when compared to day workers [82]. The limitation of these 2 Japanese studies is that the increase in risk of developing prostate cancer observed among rotating shift workers is based on only seven cases in the first study and 17 prostate cancer cases in the second study.

In a Canadian population-based case-control study a significant but modest (19%) increased risk of prostate cancer was reported among men who normally worked full-time rotating shifts, when compared with men who had never worked full-time shift work [83]. In a case-control study in Spain including 1095 prostate cancer cases and 1388 controls, subjects who had worked ≥28 years had a significant 37% increased risk of prostate cancer [84].

Lastly, the incidence of prostate cancer among male pilots and flight crews has been the subject of a relatively sizeable number of studies. These have revealed an increased risk that, although it is statistically significant, was quite minor [77–80].

#### 4.3.2. Colorectal cancer

The relationship between working rotating night shifts and the risk of colorectal cancers has been looked for in 78586 female participants in the Nurses' Health Study. 602 incident cases of colorectal cancer were documented. The data suggest 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 [85]. Sleep is an important factor and short duration of sleep (<6 h per night) has been shown to significantly increase the risk of colorectal adenomas [86].

#### 4.3.3. Several sites

In a population-based case-control study conducted in Quebec, Canada, job histories, including work hours, were elicited from 3137 males with incident cancer at one of 11 anatomic sites and from 512 controls. A moderate, though significant increase (adjusted odd ratio ranging between 1.8 and 2.8) was observed for the following sites: prostate, colon, bladder, rectum, pancreas and lung. No evidence was observed for cancers of the stomach, esophagus, kidney and melanoma [87].

Cancer risk was evaluated in a cohort of 43, 316 female Norwegian nurses. Besides breast cancer (see above), a small but significantly increased risk was found for ovarian cancer, squamous cell carcinoma, and malignant melanoma with a standardized incidence ratio (SIR) of 1.14 [57].

## 5. Mechanistic approach of ALAN effects in cancer

Various mechanisms have been proposed to explain the effects of light at night on cancer, of which three seem to be essential in impacting various levels of the organism's metabolism: inhibition of night time secretion of melatonin by light, sleep deprivation, and chronodisruption. The reported rise in cancer risk may be a consequence of one -or most probably simultaneous effects- of these three major mechanisms.

### 5.1. Inhibition of night time secretion of melatonin

A possible link between melatonin and electrical power in breast cancer incidence (the melatonin hypothesis) has been suggested [88]. However, interference by other wavelengths with the clock has also been investigated, which allowed showing that low frequency magnetic fields (50 Hz) or radiofrequencies (800 and 1800 Ghz) do not affect melatonin secretion, nor do they have a desynchronizing effect on the clock in humans. This was found to be the case even for workers who were exposed chronically to magnetic fields for up to 20 years in the setting of their work environments [89–91].This strongly suggests that nocturnal melatonin secretion is inhibited by light rather than by magnetic fields.

As early as 1978, Cohen et al. [92] pointed out a role for the pineal gland in the etiology and treatment of breast cancer. This was followed by the finding that melatonin inhibition and pinealectomy enhance benzanthracene-induced mammary tumors in rats. This finding very much suggests that melatonin may suppress tumor development [93]. A large body of experimental studies has since shown that melatonin reduces the incidence and the growth of tumors in animal models [94,95]. Analogously, the growth of human breast cancer xenografts in nude rats was found to be stimulated by human melatonin-depleted blood [96]. Moreover, melatonin at the same levels as in human blood has been shown to inhibit the in vitro proliferation of the MCF-7 human breast cancer cell line. These effects were associated with substantial changes in the ultrastructure of the MCF7 cancer cells, and they suggest that exposure to melatonin causes sublethal, yet reversible, cellular injury [97]. Furthermore, melatonin was found to reduce the invasiveness of MCF-7 cells, due to a decrease in cell attachment and cell motility. These effects

appear to be the result of increased expression of beta1-integrin and E-cadherin as well as the promotion of differentiation of the tumor cells [98].

Inhibition of melatonin secretion upon exposure to light was hence one of the first cancer-promoting mechanisms to be proposed [88,99,100]. In women engaged in shift work this results in an increase in estrogens [101], which is a major risk factor for breast cancer [102]. A significant inverse relationship has been found between plasma melatonin levels and estrogen-receptor positive breast cancer [103]. It has hence been hypothesized that the oncostatic actions of melatonin on hormone-dependent mammary tumors are mainly due to its anti-estrogenic activity [104]. Melatonin is also a potent antioxidant as result of its ability to scavenge free radicals and to activate antioxidative enzymes such as glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase [105–109].

By affecting key genes involved in DNA damage response pathways, melatonin may increase the capacity to repair DNA [110,111]. It also acts as a stimulant under basal or immunosuppressive conditions while with exacerbated immune responses, such as acute inflammation, it acts as an anti-inflammatory compound [112,113]. An oncostatic action by regulation of the metabolism of linoleic acid, which is a promoter of tumorigenesis in mammals such as humans and mice has been documented [114–116].

Melatonin has been proposed to have a role in epigenetic regulation of breast cancer cells. Such a role is supported by numerous properties of the hormone [117,118] such as anti-estrogenic effects by interaction with estrogen-receptor ER alpha and hormone receptor status [119]; aromatase and telomerase inhibition [120,121]; effects on the cell cycle [122]; and deregulation of *PER2* which acts as a tumor suppressor gene [123]. The development of environmental epigenetic biomarkers may allow the risk of future disease to be predicted, including the risk of breast and other cancers.

### 5.2. Sleep deprivation

Many shift workers who have a misaligned circadian rhythm due to working nights are at higher risk with respect to their night work of developing shift work disorder (SWD). SWD is characterized by excessive sleepiness and/or sleep disturbances associated with work schedule, although some night workers are able to adjust their circadian rhythm to night work [25,34].

According to the International Classification of Sleep Disorders [124], shift work disorder is a condition characterized by: 1) excessive sleepiness and insomnia associated with an individual's work schedule over the course of at least one month; 2) evidence that the circadian and sleep-time misalignment were present for for 7 days using sleep log or actigraphic recording; and, 3) the sleep disturbance cannot be explained by another sleep, medical, neurological or mental disorder, or the result of medication or substance abuse [124].

Shift and/or night workers tend to have 2 to 4 h less sleep on a daily basis, which in the long run results in sleep deprivation. Some factors that are responsible for the short sleep duration are longer working hours, a rise in night work, less physical activity, more urbanization with accompanying stress factors like noise and especially television viewing and 'surfing' on the net. Additionally, sleep during the day provides less rest since it is generally of lower quality, interrupted, shorter, and disturbed by the goings-on outside.

Sleep deprivation results in drowsiness, as well as decreased levels of attention and alertness that underlie a doubling in the risk of traffic accidents [125]. The accident rate is higher for getting to work for a morning shift and for returning home after a night shift, while it also increases with work schedules that exceed 10 h. It is interesting to note that the best adaptation to shift work seems to be linked with the evening chronotype, an individual characteristic, that may relate to night work adaptation [126,127].

### 5.3. Potential mechanisms of the effects of sleep deprivation on cancer

Sleep deprivation has a profound impact on the neuro-immune-endocrine axis, which plays an important role in the regulation of cell proliferation and immune protection, including the production of cytokines [128–131]. Accordingly, it has been reported that long sleepers have a lower risk of breast cancer [132], although, since this report was published, a similar study has failed to duplicate this finding [133]. However, a recent review paper synthesizing experimental data and meta-analyses of sleep duration, napping or quality of sleep and cancer incidence among 1,500,000 study individuals in 13 countries reported that the data were inconclusive [134].

A single night of total sleep deprivation thus mimicking the first night of night shift work has been used under controlled laboratory conditions to examine both the effect of increased sleep pressure on metabolite levels (i.e. a metabolomic approach) and the masking effect of sleep in healthy subjects. During sleep deprivation, some plasma metabolites (e.g. tryptophan, serotonin, taurine, and lipids) exhibited significantly increased levels that may exert an effect on the circadian system [135].

The potential deleterious effects of sleep deprivation on health need therefore further investigations taking in account all of the work parameters (see below) to ascertain the role of sleep debt in shift and night work.

## 6. Circadian misalignment and cardiovascular risks

### 6.1. Epidemiology

Based on the prospective cohort study of the Nurses' Health Studies, a longer duration of rotating night work was associated with a small yet statistically significant absolute increase in the risk of coronary heart disease [136]. In a systematic review and meta-analysis shift work was significantly associated with myocardial infarction (RR 1.23), ischaemic stroke (RR 1.05), coronary events (RR 1.24) but was not associated with increased rates of mortality (whether vascular cause specific or overall) [137].

### 6.2. Potential mechanisms

Effects of shift work on carotid atherosclerosis (e.g. carotid plaque, based on ultrasound measurement of the thickness of the carotid artery intima-media complex) in 1543 young adults (24–39 years old) suggest that shift work accelerates the atherosclerotic process in men even before age 40, and not in women [138].

Even a short-term circadian misalignment (12-h inverted behavioral and environmental cycles for three days) adversely affects cardiovascular risk factors in healthy adults with increased 24-h systolic and diastolic blood pressure, and increased inflammatory markers which may explain, at least in part, why shift work increases hypertension, inflammation, and cardiovascular disease risk [139]. Furthermore, high triglyceride levels and low concentrations of HDL cholesterol, which are markers of cardiometabolic risks, have been noted in shift workers and these findings may indicate an association between shift work and a metabolic syndrome [140].

## 7. Circadian misalignment and diabetes

ALAN appears to favor cardio-metabolic risks [141] which are themselves risk factors for cancers.

### 7.1. Epidemiology

Epidemiologic data suggest an association between metabolic syndrome and diabetes, especially type 2 diabetes mellitus and breast cancer. Exposure to shift work may therefore be considered as a risk factor for diabetes [142].

A mismatch in sleep timing between workdays and free days (referred to as 'social jet lag') has been linked to a higher cardiometabolic risk in adults, and specifically so with components of glycemic control, serum lipids, and adiposity that predispose to diabetes and atherosclerotic cardiovascular disease [143]. This relationship between shift work and lipids has however not been found in other studies [144].

The association between diabetes and shift work has been recently reviewed: while sleeping <6 h has been associated with a moderate risk (RR 1.28) for type 2 diabetes in the general population, in the case of shift workers who are lacking sleep or who are sleep deprived the data in the literature on the risk of diabetes are contradictory. Consistent association supported by experiments on animals and humans between shift work and type 2 diabetes have been published [145]. However, due to the scarcity of epidemiological studies the strength of the evidence is moderate which indicates that such a relationship has not been formally proven [146]. However and for the sake of completeness, a very recent paper showed that Danish nurses working night and evening shifts have increased risks for diabetes with the highest risk associated with current night shift work (RR: 1.58) [147].

### 7.2. Potential mechanisms

Circadian misalignment reduces glucose tolerance. This effect may help explain the moderate increase in the risk of diabetes in shift workers [148,149]. The dysregulation of glucose metabolism with insulin resistance, hyperinsulinemia, and fat-induced chronic inflammation are potential mechanisms [150,151]. Furthermore, recent studies suggest an association between cancer incidence and anti-diabetic medications e.g. metformin, a drug of choice in type 2 diabetes mellitus, with its anti-neoplastic and tumor-suppressing activity [152,153], though confounders and methodological biases cannot be ruled out [154].

Lastly, a mismatch between chronotype, which is the preferred sleep timing, and work schedule has been looked for: in early chronotypes, type 2 diabetes risk increased with increasing duration of shift work exposure, whereas late chronotypes had the highest diabetes risk working daytime schedules [155].

## 8. Circadian misalignment, overweight and obesity

### 8.1. Epidemiology

The association of exposure to light at night and being overweight has been found statistically significant [156] in a study using data on countries worldwide (satellite images of night time illumination). Another study of the same kind in South Korea provided epidemiological evidence that ALAN is moderately but significantly associated with obesity and various sleep health issues such as delayed sleep pattern, short sleep duration, insomnia and habitual snoring [157]. Besides, sleeping <6 h daily is associated with weight gain and an increase in BMI [158,159]. It has recently been shown that the risk of obesity in male shift workers was not related to the length of exposure, speed of rotation and tolerance to shift work [160]. Major effects are likely to relate to a sedentary lifestyle and to a nocturnal nibbling of carbohydrates. Tobacco use, uncontrolled food intake, and a decrease in physical exercise are also factors that promote the risks for cardiovascular diseases among shift workers.

### 8.2. Potential mechanisms

Several mechanisms have been put forward to explain why shift workers tend to gain weight. These comprise effects of light, melatonin inhibition, and sleep deprivation.

#### 8.2.1. Light effects

Light undoubtedly plays a crucial role. Even dim light (e.g. 5 lux) at night was found to be able to suppress expression of Per1 and Per2 at both the gene and protein levels in the SCN of mice. This was associated with alterations in feeding behavior, metabolic functions, and increased weight gain [158,161–163].

#### 8.2.2. Melatonin effects

Melatonin (10 mg/kg/day for 6-weeks) has been shown to affect the body weight of Zücker diabetic fatty rats. These rats are used as a model of obesity-related type 2 diabetes. Melatonin reduces obesity and improves metabolic profiles in this strain of rats, without affecting food intake and activity. Oral administration of melatonin to rats has been shown to induce browning of inguinal white adipose tissue. This may at least in part explain the control of body weight by melatonin, and its metabolic benefits [164–166] .

#### 8.2.3. Sleep deprivation effects

There is experimental evidence showing a strong relationship between sleep deprivation, circadian disturbances and increased metabolic risk. The association between sleep deprivation and obesity in shift workers has led to the assumption that sleep deprivation may be a direct consequence of night shift workers being overweight [167,168].

#### 8.2.4. Peptide hormones involved in food intake

Another proposed mechanism is the modulated secretory pattern of peptides that are involved in food intake. Sleep restriction is associated with elevated ghrelin, an orexigenic hormone mainly produced in the stomach, reduced leptin, the satiety hormone, and increased body mass index [169]. The orexigenic neuropeptides orexin-1 and 2 (also known as hypocretin-1 and 2) for example not only centrally stimulate food intake but also exert wake-promoting effects [170].

## 9. ALAN, cognition and mood disorders

### 9.1. Epidemiology

Exposure to light at night may impair cognitive performances and induce excessive sleepiness and mood changes associated with the work schedule. Shift work has been associated with impaired cognition and the association was stronger for exposures lasting >10 years [171]. Shift workers are at higher risks of fatigue, anxiety and depressive symptoms than day workers. This can result in absenteeism and a decline in work productivity [172–174].

A subsample of individuals (21–73 years old), who had been followed annually for 10 years, was selected from the British Household Panel Survey [175]. For men, being engaged in night work for ≥4 years was associated with an increased risk of having poor mental health and of reporting anxiety or depression [odds ratio: 2.58). Gender differences have been noted in regard to the mental health effects of different types of shift work. The mental health of men was adversely affected by engaging in night shift work for ≥4 years, while working varied shifts for ≥4 years had a negative impact on the mental health of women [175].

### 9.2. Potential mechanisms

In humans exposure to blue light increases hippocampal activity compared with longer wavelength green light, and the differences are

detectable almost immediately upon exposure to light. This indicates that light is a modulator of cognitive brain function in humans [176]

In an effort to establish the mode of action of ALAN on the circadian system, examination of the effects of ALAN exposure on different rodent species (rats, mice, hamsters) has focused on cognition and depressive-like responses of the animals. Exposure of diurnal Nile grass rats to dim ALAN (5 lx) decreased the latency to float in the forced swim test, and it impaired learning and memory as assessed by the Barnes maze test [177]. These responses have been associated with reduced dendritic lengths on CA1 neurons [177]. The same low levels of dim light (5 lx) exposure at night have been reported to increase depressive-like responses in Siberian hamsters [178] and mice [179], as assessed by a sucrose anhedonia and the forced swim test (5 lx). These findings strongly suggest that low level illumination at night may alter cognitive brain functions and affective responses. It is likely that these effects are mediated by melanopsin-expressing retinal ganglion cells (ipRGCs) which are much more sensitive to blue light (460–480 nm) than red wavelength light (>600 nm), since exposure to red LAN, to which melanopsin exhibits little sensitivity, has been shown to exert no effect [180].

## 10. ALAN and age-related macular degeneration

### *10.1. Phototoxicity*

Age related macular degeneration (AMD), the leading cause of blindness in subjects older than 65 years of age, is a complex neurodegenerative visual disorder caused by the loss of retinal pigmented epithelium (RPE) cells and the light-sensitive photoreceptor cells that they support. The severe visual loss affects around 12% of the population of industrialized countries. Among the potential risk factors that have been documented in this multifactorial disorder, genetic factors are major with the important role of human leukocyte antigen (HLA) and complement system genes. Oxidative stress and smoking are the environmental risk factors most consistently associated with AMD [181, 182]. Blue light which is known to induce photochemical and cumulative damage to the retina may be associated with age-related macular degeneration [183]. Light wavelengths from 415 to 455 nm (blue-green range) had the highest toxicity in an in vitro porcine model of AMD [184].

### *10.2. Potential mechanisms*

Results from a study whereby albino and pigmented rats were exposed to domestic levels of various Light Emitting Diodes (LEDs; cold-white, blue and green), indicate that white LEDs induce more pronounced retinal degeneration than control fluorocompact lamps, and that pigmented rats are not protected from the deleterious effects of the LEDs. This study also found that exposure to LEDs induced breakdown of the external blood-retinal barrier [185]. The effects of other factors like diet, cardiovascular factors, and alcohol are more controversial [186].

### *10.3. Preventive measures*

The consequences of ophthalmic lens filtering that blocks these toxic wavelengths from reaching the retina should be assessed. Preventive measures require precise etiological knowledge, however. This is quite difficult to attain since AMD is a multifactorial disease with intricate relationships between causes and risk factors.

## 11. Methodological limitations of the studies

Some inconsistencies in results of the different studies devoted to the effects of ALAN on cancer risk are related to the fact that the definition of shift work and night work is itself different from a country to another which leads to differences in exposure classification and exposure contrast across studies and makes it difficult to compare and interpret results, and conduct meta-analyses [187]. Shift work and night work are characterized by a specific set of factors, and these should be taken into account in all studies so as to be able to reach reliable and definitive conclusions on cancer risk [40,48,187–190]. Among the items that need to be considered are: the length of the shift, the direction (e.g. the direction of the hands on a clock, hence referred to as clockwise, that is to say: morning-afternoon-night; or anti-clockwise that is to say: night-afternoon-morning), the number of nights worked in a row, the total number of nights per month and per year, the start and finishing times of the shift, the number and the scheduling of days off, the regularity or the irregularity of the shifts, a continuous or discontinuous system, the speed of the rotation (e.g. fast or slow) (Table 1). The current trend for shift work has gone from a standard rotation system (e.g. rotation every week or every fortnight) to a faster-paced rotation system (e.g. from 1 to 3 days). This new type of rotation has largely had a positive impact on the functioning of the circadian rhythm and its desynchronization, sleep deprivation, etc.

The methodological limitations of epidemiological studies regarding the link between shift work or night work and cancer are numerous. Examples of these are the retrospective studies; the lack of control groups in some studies; self-assessments of parameters such as fatigue, drowsiness, and the duration or the quality of sleep, etc. Bias can occur due to the nature of the work itself when it is prone to compromising the organism by exposure to radiation, chemicals, etc. Furthermore, a major potential problem with studies of shift work is in regard to the bias called the healthy worker effect (HWE). HWE consists of two selection processes: healthy worker hire and healthy worker survivor. Healthy worker hire effect arises when people with greater than average health are recruited to work in industrial jobs. Sickness absence in workplaces may reflect a "healthy hire effect," i.e., that workplaces recruit individuals with experience of sickness absence differently. The *healthy worker*

**Table 1**
Methodological limitations of epidemiological studies: parameters that should be taken into account.

| Parameters | Observations |
|---|---|
| Consensus on a framework | Consensus to be reached |
| Definition of night work | Consensus to be reached regarding the definition |
| Permanent or fixed-term position | A permanent position is less harmful |
| Length of exposure to night work | Number of successive nights, total number of nights per month, number of years |
| Duration of the shift work cycle | Continuous, semi-continuous, discontinuous system |
| Direction: clockwise or counterclockwise | In the same direction as, or in the opposite direction of the hands of a clock. An anti-clockwise direction can represent a greater risk in the absence of sufficient rest periods between the shifts to allow for circadian readjustment |
| Speed of the rotation: fast or slow | If a slow rotation: a greater number of successive sequences of night work, giving rise to desynchronization of multiple functions |
| Specific work conditions | Shift starting and ending times |
| Regularity or irregularity of the work performed | Rarely reported |
| Lifestyle of the shift worker | Rarely reported |
| Age at which shift or night work was commenced | Rarely reported |
| Number of days off work and their scheduling relative to the work shifts | Rarely reported |
| Risk factors linked to the nature of the work | Exposure to radiation, chemical entities, handling of anti-neoplastic medications… |
| Biological markers | Melatonin, cortisol, motor activity, body temperature, metabolomic profile … |
| Exposure cut-off threshold | Still unknown; depending on the specific study: from a few years to 20–30 years |

*survivor effect* is a bias that occurs in occupational studies when less healthy workers are more likely to reduce their workplace exposures. Thus, due to selective factors, a shift worker is someone who is often in better health, at least initially, than those working regular daytime shifts. Studies comparing the two groups of workers can hence, in fact, underestimate the adverse health effects of shift work [48].

As even the definition of shift work and night work can differ between one country and another, it becomes necessary for researchers to identify and meticulously describe all of the factors or parameters that define shift work schedules in their studies (Table 1). While a certain number of effects on health have been highlighted by the various studies that have been carried out, no exposure threshold (e.g. 5, 10 or 15 years, and even more) above which the appearance of adverse effects takes hold has been established.

## 12. Preventive measures to combat circadian disruption and alleviate circadian misalignment

One of the long-term aims of researchers is to counter circadian misalignment and reduce its resulting deleterious effects on health. Testing has involved agents that are likely to resynchronize the clock, such as light and melatonin, as well as specific psychotropic medications with the aim of improving sleep, or conversely to enhance alertness, depending on the work requirements [188].

### 12.1. Bright light

Exposure to bright light (approximately 10,000 lx), in an appropriate time frame, can be used due to its ability to shift the circadian phase and to reset the timing of the clock, with an ensuing improvement in performance and alertness. Exposure to bright light before starting an early morning shift or prior to a nightshift allows for an improvement in performance and alertness. The appropriate intensity and duration of the exposure still remain to be determined. Efficient treatments to phase-advance human circadian rhythms are needed to attenuate circadian misalignment and the associated negative health outcomes that accompany early-morning shift work, early school start times, jet lag, and delayed sleep phase disorder. A 30-min morning bright-light exposure with afternoon or early evening melatonin has been proposed to phase-advance human circadian rhythm [191,192] though association of melatonin and light did not, however, improve adaptation to shift work.

On the other hand, following a night shift, workers should as much as possible avoid all exposure to light, whether natural or at home, so as to facilitate being able to get to sleep. Glasses that filter out blue light appear to be beneficial in this regard [193–195], although this could be difficult to implement in practice.

### 12.2. Melatonin

Taking melatonin by night workers was proposed in the USA [196], since it is a chronobiotic i.e. an agent that adjusts the timing of the central clock and that can reset the sleep-wake cycle [197]. Melatonin is not indicated in France for issues relating to shift or night work.

### 12.3. Napping

30 to 50 min napping is a strategy to combat drowsiness for workers who carry out night work, and it has been associated with a decrease in accidents and an improvement in alertness and performances [189] due to its beneficial recuperative effect. What still needs to be established is the right duration and when it should take place in relation to the night shift.

### 12.4. Use of psychostimulants

The most commonly used stimulant is caffeine. It has been proposed as a psychostimulant to increase alertness among night shift workers. Thus, they can be advised to drink a cup of coffee at the beginning of a shift to increase alertness during night work [196].

### 12.5. Specific psychotropic medications

Hypnotics (triazolam and temazepam) for sleep disturbances or modafinil for problems with daytime sleepiness have been used in some countries to counter issues related to shift or night work. While medications that enhance alertness (armodafinil and modafinil) have been associated with a greater level of alertness during shift work, they have also been associated with headaches and nausea [198]. Due to their side effects and the potential for their misuse, psychotropic medications should be avoided.

## 13. Conclusions and future perspectives

Approximately 75% of the active population in industrialized countries, work atypical hours; that is to say outside of the so-called normal let us say 08 h to 17 h business hours. By exposing workers to artificial light at night, shift and/or night work decreases the time spent sleeping, and it disrupts the circadian structure, the sleep cycle, social life, and meal times. This results in a perturbation of the functioning of the biological clock that is often called “social jet lag” because of the misalignment between the biological clock and social time. In the long run, this rhythm desynchronization is detrimental to health, as underscored by a large number of epidemiological studies, particularly in regard to the risk of breast cancer in women who do shift or night work. It amounts to a bona fide public health issue in light of the very substantial number of individuals involved.

Circadian disruption, sleep deprivation, melatonin suppression, and social misalignment experienced by shift and night workers result in detrimental effects on health with an increased incidence of cancers, cardiovascular risks, diabetes, obesity, mood disorders, and age-related macular degeneration, as assessed in a large number of epidemiological studies. Whether one or several of the numerous potential mechanisms documented is/are the cause(s) of the deleterious effects of ALAN remains an open question. More experimental data are hence needed to ascertain the causality for these effects.

It is paramount in this regard that researchers act on establishing an agreed framework that will allow definitive validation of the risk of breast cancer in women who are exposed to artificial light at night in the setting of their work. Future epidemiology should consider a collection of factors, including - but not limited to - aspects such as the shift system with the type of rotation, the direction of the rotation, the number of years worked, the number of night worked per month, and all of the exposure metrics used etc. (Table 1) which are able to influence melatonin secretion, sleep deprivation and the circadian system. Well-controlled studies with more detailed aspects are needed to ascertain the relationship between exposure to light at night and the risk of cancer and to identify the underlying mechanisms. Counter measures could then be investigated and validated to combat the adverse health effects of atypical work schedules, and shift work and night work in particular. Given the large number of night workers in the world preventing the circadian disruption caused by light at night and its potential effects on health might become an important matter of public health.

Practically speaking, behaviors that should be avoided are: exposure to light up to 30 min prior to going to sleep; opting for a morning shift that starts before 07 h; undertaking more than three successive night shifts; and, in light of the potential risks with pregnancy, performing shift work or night work when pregnant cause adverse effects in an intact organism, or its progeny, or (sub) populations.

Lastly, it should be emphasized that since ALAN interferes with the endocrine system, it can be considered to be a new endocrine disruptor. It differs fundamentally in nature, however, from typical endocrine disrupting chemicals, which have been defined by WHO as “exogenous compounds or mixtures that alter function(s) of the endocrine system and that consequently cause adverse effects in an intact organism, or its progeny, or (sub) populations”.

## Conflict of interest

The authors declare that they have no conflict of interest.

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