Exposure to artificial light at night: A common link for obesity and cancer?

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Abstract Exposure to artificial light at night (ALAN) has been associated with disruption of the circadian system, which has been pointed out to have detrimental effects on health. Exposure to outdoor ALAN is very frequent in industrialised countries due to nocturnal light pollution and the relevant involvement of the total workforce in shift work and night work. Ecological and epidemiologic studies highlight the association between exposure to ALAN and several diseases, mainly obesity and cancer. More recently, also indoor ALAN exposure has been investigated. Among several multifactorial mechanisms linking ALAN exposure and health risks, suppression of melatonin secretion plays a pivotal role leading to alterations in circadian rhythm patterns, that are detrimental in terms of appetite regulation, and dysfunctions in metabolic signalling and cell growth in cancer. In addition, gut dysbiosis, inflammation, hypovitaminosis D, imbalance in cytokine secretion and levels are responsible for the multiple relationship linking circadian dysregulation due to ALAN exposure and obesity, and cancer. Therefore, the current manuscript summarises human and basic studies pointing

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1. Introduction

In recent years, artificial light at night (ALAN) emitted by residential areas, road illumination and non-stop economic activities has been recognised as one of the major and novel risk factors for obesity [1], with trends in nocturnal light pollution paralleling demographic trends in obesity [2]. Analogous associations emerged between ALAN and certain types of cancer [2,3]. In urban settings, an increase in ALAN exposure and especially an increase in the blue light spectrum emissions have been observed due to a switch to the use of white light emitting diode technology as the new urban light standard [4]. In addition to light emitting diode lighting, artificial light encompasses different types of illuminating sources, i.e. fluorescent or incandescent lights. Though all these types of artificial light are perceived as white by the retina, they are different technologically speaking and in terms of electromagnetic spectra. Notably, this heterogeneity is responsible for variability in the entrainment of the circadian clock. Indeed, the relevance of ALAN to health is mainly due to its interference with the circadian system [5]. Ambient light, through its spectral composition, is the most relevant 'zeitgeber' (namely, an environmental cue able to synchronise the endogenous rhythm) of the circadian system. The wavelength of light, perceived by the eye photoreceptor, triggers the first step in circadian modulation [6]. The retina input reaches the SNC that orchestrates the peripheral clocks by endocrine regulation (mainly through 5-methoxy-N-acetyltryptamine- melatonin- and cortisol) or through the autonomic nervous system [7]. Furthermore, the wavelength captured by the skin, by the ultraviolet (UV)-sensitive photopigment neuropsin ($\lambda max = 380$ nm), regulates directly skin clocks [5,7]. The link seems to be mediated by melatonin. Another pivotal player in this scenario is represented by melatonin. Melatonin is secreted by the pineal gland during the biological night, following the retina stimulations of a specific photoreceptor named melanopsin, different from rods and cones, and sensitive to blue light (460–480 nm). ALAN exposure may suppress melatonin production and blunt its circadian rhythmicity through sleep pattern disruption and reduction of sleep duration [8]. Nevertheless, alterations in sleep duration and architecture can only partially account for the complex connections linking ALAN to obesity and cancer, as summarised in Fig. 1. Beyond melatonin actions, a reciprocal connection has been shown between the circadian system an inflammation, with the circadian clock acting on the inflammatory system and inflammation regulating clock genes [9]. This results in alterations in circadian rhythms that are strictly correlated with the state of inflammation. Inflammation is considered to be a common soil of both obesity and cancer. Hence, imbalances in cytokine production and activity may underpin tumour initiation and progression. Nonetheless, adipokines are able to affect tumour cell energy metabolism and their metabolic reprogramming, a well-known factor in cancer progression [10]. Obesity is involved in endothelial-related mechanisms in cancer via insulin/IGF signalling, oestrogens, chronic inflammation, and increased leptin-mediated activation of PI3k/Akt/mTOR signalling [11,12]. In turn, cancer cells produce various factors of inflammation, including interleukin 1 beta (IL-1β), IL-6 and tumour necrosis factor alpha (TNF-α), which modify the physiological sleep structure and affect numerous neurotransmitters involved in sleep (adenosine, prostaglandins, nitric oxide, GABA). Tumours can also alter the physiological functioning of the serotonergic, dopaminergic, GABAergic and noradrenergic circuits, resulting in sleep disturbances (especially insomnia and circadian rhythm disturbances), as well as anxious-depressive symptoms, very often present in cancer patients [13]. In addition, the tumour-suppressor Ink4a/Arf acts as a mediator of RAS oncogene-induced changes in the circadian system, thereby mediating the interplay between the clock and the cell cycle [14,15]. Another relevant connection has been described between obesity and cancer due to a pivotal role played by gut dysbiosis. Notably, obesity is associated with changes in the intestinal microbiome composition and intestinal barrier permeability. These conditions promote inflammation through the upregulation of some inflammatory cytokines (e.g. IL-6, TNF-α, IL-17 and IL-23), favouring carcinogenesis in some types of cancer, such as colorectal cancer [16]. Gut dysbiosis has also been observed in the disruption of the circadian clock, either via dietary manipulation or phase shift, like sleep–wake cycle shift. Beyond changes in diversity and/or abundance of bacterial species, circadian disruption resulted also in alterations in some metabolic functions of gut microbiota metabolism [17].

Vitamin D deficiency also seems to play a role in ALAN-related diseases. Vitamin D deficiency and inadequacy are widespread, showing relevant associations with both cancer and obesity [18,19]. According to evidence from ecological and epidemiological studies, the

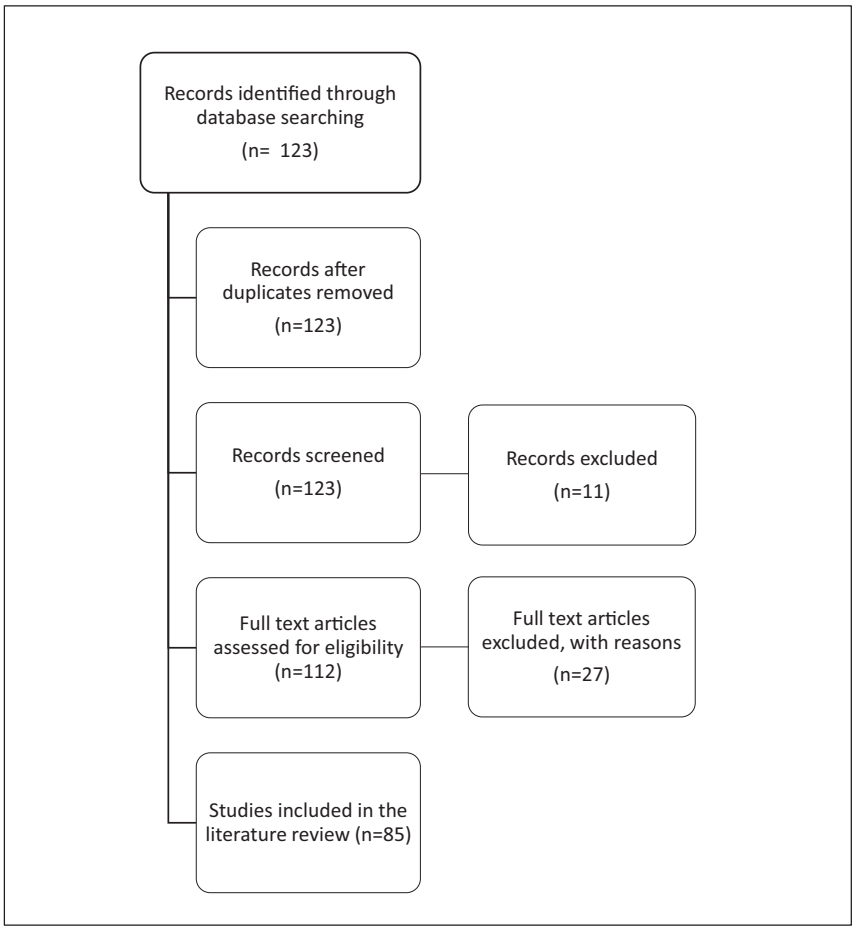

Fig. 1. Diagram of search strategy and the screening process.

link connecting poor vitamin D status and circadian rhythm disruption is represented by solar ultraviolet-B irradiance [20]. Interestingly, daytime sunlight exposure entrains the circadian system through the blue-violet (446−484 nm λ) spectrum and induces vitamin D synthesis through the ultraviolet-B (290−315 nm λ) spectrum. As sunlight and darkness are the primary zeitgebers of the circadian system in humans, time-of-day variation of sunlight exposure, latitude and ALAN, as well as alterations in sleep duration may act synergistically in promoting mechanisms leading to chronodisruption with unfavourable health consequences in terms of risk of obesity and/or cancer development [21]. Similarly, daylight saving time and artificial time zones have been acknowledged to be associated with circadian misalignment, alterations in epigenetic and transcriptional regulation of core clock genes, and reduced sleep, mainly due to extended exposure to evening light. Acute effects and, to a lesser extent, long-term influence of daily saving time have been clearly related to public health risks [22,23]. Conversely, interventions based on morning bright light exposure provided beneficial effects in terms of body weight regulation, hormonal control of appetite and glucose homeostasis [24]. While light is the main regulator of the central circadian clock, other factors regulate clocks in peripheral tissues such as time of meal consumption and diet composition [25]. The environmental circadian rhythm disruption and genetic perturbation of the molecular clock cause intestinal microbiota dysbiosis, especially through a high-fat diet and alcohol consumption [26]. Furthermore, diet quality seems to be another mediator of circadian rhythmicity, especially in the case of rewarding food consumption: novel observations pointed out the fascinating role of dopamine in the regulation of circadian entrainment, with animal studies showing alterations in light-induced phase shifts and central dopamine signalling linked to ingestion of palatable, rewarding foods [27]. The aim of the present article is to summarise extant evidence connecting ALAN exposure to obesity and cancer in humans and animals.

2. Search strategy

The current review critically analyses the basic and translational evidence concerning the role of ALAN in obesity and cancer by describing the available literature from 2000 to 2021. The relevant literature was screened from PubMed (MEDLINE), by using the following

search terms: 'obesity', 'light at night', 'artificial light', 'cancer', 'melatonin', 'circadian rhythm', 'melatonin and circadian rhythm', 'melatonin and cancer', 'melatonin and obesity', 'shift work'. The selection had no data or language limit. Articles not found were requested to their respective authors via email or the Research Gate website twice. The criteria included in the literature review were original research articles that reported the methods used for the evaluation of exposure of ALAN exposure assessment in human subjects. Studies that did not include the assessment of the effect of artificial light were excluded. The data of each article were reviewed by two researchers. Any disagreements were resolved through consensus with a third researcher. The reference lists of obtained relevant articles and review articles were hand-searched to identify any further studies. Among the 123 collected, 38 were excluded and ultimately 85 were included in the review article (see Fig. 1 for details).

3. ALAN and obesity: human evidence

Concerning overweight and obesity, a wealth of studies reported a relationship between night shiftwork or short sleep duration and indicators of adiposity, such as body mass index (BMI) or waist circumference (WC) [28–30]. Beyond traditional determinants of obesity, i.e. energy intake and expenditure, mounting interest has been directed to environmental factors. Recent evidence focused on the association between exposure to ALAN and health outcomes. Though epidemiological studies exploring ALAN and excess adiposity are scarce, they are crucial in overcoming the hurdle of sleep duration and night shift work as hypothetical proxies of ALAN exposure. Here, we summarise evidence from human studies investigating the connection between ALAN and overweight/obesity.

3.1. Outdoor ALAN

In the last decades, mounting interest has been directed to the biological impacts of artificial night-time lighting and ecological light pollution [31,32]. At the spatial level, two different forms of artificial light at night can be distinguished: light emissions coming directly from sources (e.g. street lighting, commercial and domestic sources) and diffuse skyglow, which is due to the scattering of artificial light emissions in the lower atmosphere. Urbanisation, population density and economic activities are the main determinants of the spatial distribution of ALAN explored in ecological studies focusing on outdoor ALAN generally speaking. Secondarily, also the timing and the spectral composition of night-time lighting have been investigated [31,32]. Data from 8526 Korean participants in the KoGES study (47% men, mean age: 52.9 ± 9.0 years) revealed that high ALAN exposure (i.e. living in bright areas) were significantly associated with obesity (definition based on BMI) after adjustment for confounding variables (odds ratio [OR] 1.20, 95% CI 1.06–1.36, p = 0.003]) [27]. Similar findings were obtained by Abay and Amare [33] in 33586 Nigerian women (age 15–49 years), showing a significant non-linear relationship between satellite-based night light intensity (above 50–75th, 75–90th and above 90th percentiles of ALAN) and overweight as well as obesity according to BMI classification, regardless of potential confounders [33]. In an elegant study, Rybnikova *et al.* investigated the association between outdoor ALAN (data from the US Defense, database) and prevalence rates from a WHO country-wide database in men and women from more than 80 countries [34]. Outdoor ALAN was found to be a significant risk factor for women (B = 0.002–0.009, t = 2.739–2.877, P < 0.01) and men (B = 0.003–0.043, t = 1.972–2.658, P < 0.1). Including other explanatory variables (i.e. country-level development indicators), ALAN explained 72–73% of overweight and obesity prevalence rates worldwide in women and 67–68% in men [34]. In addition, a study was carried out on a sample of 239781 men and women (aged 50–71) from the NIH-AARP Diet and Health Study without obesity at baseline (1995–1996). Outdoor ALAN exposure was estimated from satellite imagery. Outdoor ALAN exposure at baseline was associated with higher odds of developing obesity over 10 years. The longitudinal association between ambient light exposure and the subsequent changes in obesity parameters have been also investigated in the HEIJO-KYO Cohort [36]. Data from 1110 elderly participants at baseline (mean age, 71.9 years) and data from 766 at follow-up (median, 21 months) were included in this prospective population-based study.

The main finding of the study was a significant association between light exposure and the %WHtR gain. In particular, night-time or evening exposure to a higher light intensity was significantly associated with subsequent % WHtR gain. Morning exposure to a longer time ≥500 lux or night-time exposure to a longer time <3 lux was significantly associated with subsequent %WHtR loss.

3.2. Indoor ALAN

In a Japanese study including 528 elders (47% men, mean age: 72.8 ± 6.5 years), ALAN exposure while sleeping was measured through a portable photometer [37]. Body weight, BMI and WC were significantly higher in the ALAN group (≥3 lux) than in the dim group (<3 lux) [37]. Notably, ALAN exposure was associated with higher OR for obesity (BMI: OR, 1.89; P = 0.02; abdominal obesity: OR, 1.62; P = 0.04) independent of demographic and socioeconomic variables [37]. Analogous findings were obtained from McFadden *et al.* [38] in a large cohort (n = 113,343, mean age: 47.2 ± 13.6 years) of women living in the United Kingdom: self-reported lightness during bedtime was associated with increased OR for overweight and obesity

Table 1
Summary of human studies on exposure to outdoor ALAN and cancer.

Cancer							
ALAN Source	Authors	Year	Reference	Ethnicity	Participants	Age	Main findings
Night-time satellite images	Kloog I, *et al.*	2008	45	Israeli-Jewish	Women (n: NA*) (ASR for 100,000 persons)	NA*	Strong positive association between ALAN intensity and BC rate (B = 0.121,t = 1.932, p < 0.05). No association between ALAN intensity and lung cancer rate. Estimated 73% higher BC incidence in the highest ALAN exposed communities than the lowest ALAN exposed communities.
Night-time satellite images	Kim YJ, *et al.*	2015	46	Korean	Women	NA*	Significant association of prevalence rates for BC with ALAN in urban areas (RR:1.007, 95% CI: 0.0025−0.0038) and in rural areas (RR: 1.017, 95% CI: 0.0048, 0.0099). No association with ALAN in female lung, liver, cervical, gastric and colon cancer.
Night-time satellite images	Kim KY, *et al.*	2017	47	Korean	Men (n = NA*) ASR	NA*	Incidence of prostate cancer significantly associated with ALAN (risk ratio = 1.02, 95% CI: 0.0006, 0.0192, p = 0.0369) and urbanisation (risk ratio = 1.06, p = 0.0055). Comparing the prostate cancer incidence at 25% and 75% level of ALAN, the risk ratio was 1.726. No significant association between ALAN and other cancers, including stomach, oesophageal, liver, pancreatic, laryngeal, lung and tracheal, bladder, and brain and central nervous system cancers, as well as lymphoma and multiple myeloma.
Night-time satellite images	Rybnikova N, *et al.*	2015	48	180 countries	Women (n:NA*)	NA*	Positive BC-ALAN association (t > 2.2; p < 0.01), explaining, along with other factors, about 65−85% of BC ASR variability worldwide
Night-time satellite images	Rybnikova N, *et al.*	2015	48	180 countries	Men (n: NA*)	NA*	Prostate cancer ASR and ALAN were marginally significantly associated (t = 1.886, p < 0 .1). Together with other variables, ALAN explained up to 79% of prostate cancer ASR variability.
Night-time satellite images	Al-Naggar RA, *et al.*	2016	49	158 countries	Men and women (n = NA*)	NA*	PALI and PAHI were positively associated with ASR of cancers of all forms of cancer: lung, prostate, breast, and colorectal cancers (p < 0.05).
Night-time satellite images	Kloog I, *et al.*	2010	50	164 countries	Women (n = NA*) (ASR)	NA*	Positive association between BC and ALAN (b = 0.150, t = 2.365;p <0.05). No association for all other cancer types (colorectal, larynx, lung, and liver cancers).
Night-time satellite images	Kloog I, *et al.*	2009	51	164 countries (GLOBOCAN database)	Men (n = NA) (ASR for 100,000 persons)	NA*	Positive association between prostate cancer and ALAN (B = 0.150, t = 2.916 P = 0.01). 110% higher risk of prostate cancer in the highest ALAN-exposed countries than in the lowest ALAN exposed countries. No association between lung/colon cancer and ALAN.
Night-time satellite images	Bauer SE, *et al.*	2013	53	US (White and Black populations)	34053 BC cases and 14458 lung cancer referents (women)	NA*	BC incidence was associated with high ALAN exposure (OR = 1.12, 95% CI [1.04, 1.20]). When stratified by race, ALAN exposure was associated with increased BC risk among whites (OR = 1.13, 95% CI [1.05, 1.22]), but not among blacks (OR = 1.02, 95% CI [0.82, 1.28]).
Night-time satellite images	Kim YJ, *et al.*	2016	54	Korean	3373121 individuals as	NA*	Prevalence rates for breast cancer significantly associated with ALAN in urban and rural areas.

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Table 1 (*continued*)

Cancer							
ALAN Source	Authors	Year	Reference	Ethnicity	Participants	Age	Main findings
					total population of the study area		OR: 1.383 95% CI: 0.013−0.265 without spatial effects, OR: 2.4 95% CI: 0.149−0.613 with spatial effects.
Self-reported ALAN exposure (Questionnaire)	Keshet-Sitton A, *et al.*	2017	55	Israeli-Jewish	252 women (110 BC patients and 142 controls)	36−79	In urban population BC risk increases with residence near strong ALAN sources (OR = 1.51, 95% CI = 0.99−2.30, $P < 0.06$).
Light-meter	Keshet-Sitton A, *et al.*	2017	56	Israeli-Jewish	266 new breast cancer cases	35−74	SMR was significantly and positively strongly correlated with mean, median, and SD light intensity per road length ($r = .79$, $P < 0.01$, $R^2 = .63$; $r = 0.77$, $P < 0.01$, $R^2 = 0.59$; and $r = 0.79$, $P < 0.01$, $R^2 = 0.63$).
Night-time satellite images	Rybnikova N, *et al.*	2018	57	US (Connecticut)	Women (n = NA*)	NA*	BC incidence rates positively associated with ALAN at spatial analysis (B = 0.074, z = 5.091, P = 0.01)
Night-time satellite images	Garcia-Saenz A, *et al.*	2018	58	Spanish	1,219 BC cases, 1,385 female controls, 623 prostate cancer cases, and 879 male controls	20−85	Exposure to outdoor ALAN in the blue light spectrum was associated with BC [adjusted OR for highest versus lowest tertile, OR = 1.47; 95% CI: 1.00, 2.17] and prostate cancer (OR = 2.05; 95% CI: 1.38, 3.03). In contrast, those exposed to the highest versus lowest intensity of outdoor ALAN were more likely to be controls than cases, particularly for prostate cancer.
Night-time satellite images	Rybnikova N, and Portnov BA.	2018	59	Israeli- Jewish	Women (BC incidence, reported as areal density of BC cases per km^2)	NA*	Positive association between ALAN and BC incidence (B = 0.361, t = 226.543, $p < 0.01$). Positive association between BC incidence and short-wavelength (blue) ALAN subspectrum ($z = 2.462$, $p < 0.05$) while reporting insignificant associations between BC and either green ($z = 1.425$, $p > 0.1$) or red ($z = -0.604$, $p > 0.1$) subspectra.

Abbreviations: ALAN (artificial light at night), BC (breast cancer), OR (odds ratio), RR (risk ratio), CI (confidence interval), PALI (Protected Area Light Pollution Indicator) PAHI (Protected Area Human Influence Indicator) ASR (age-standardised rates), SMR (standard morbidity ratio), SD (standard deviation), ASR (age standardised rates). NA (non-available)* Either age or number of participants are not specified when incidence/prevalence rates have been considered ans standardised for age and/or a selected unit of population (e.g. age-standardised rate for 100,000 persons).

(regardless of the definition based on either BMI or waist-to-hip ratio) [38]. Those observations are consistent with results from another cohort of 43 722 women from the Sister Study (involving subjects from the US and Puerto Rico, mean age: 55.4 ± 8.9 years), showing a positive association between self-reported ALAN exposure while sleeping and higher prevalence ratios of obesity as identified using BMI (prevalence ratio: 1.03, 95% CI 1.02−1.03), as well as measures of visceral adiposity (WC, waist-to-hip ratio and waist-to-height ratio) [1]. After a 5.7- year follow-up, the prospective analysis revealed that sleeping with an ALAN source was associated with incident obesity (relative risk: 1.19, 95%CI: 1.06−1.34) [1]. Another longitudinal study, including 766 Japanese participants who were followed up over 21 months, showed that both evening (≥100 lux) and night-time (≥3 lux) exposures to higher light intensity objectively measured were significantly associated with percent waist-to-height gain and BMI augmentation even in fully adjusted models [37].

4. Future directions

The emerging role of ALAN as a risk factor for obesity has been hypothesised to be mostly linked to alterations in sleep duration; however, interestingly, the association between ALAN and obesity/adiposity parameters was kept even when sleep duration or sleep characteristics were taken into account [1,37]. Hence a role of ALAN per se could be hypothesised as an independent factor influencing mechanisms underlying the development of overweight and obesity. Further research should be prompted in order to allow a more comprehensive understanding of the direct associations between ALAN and excess adiposity, performing studies using objective measures of ALAN such as satellite measures for outdoor ALAN and light meter/photometer for indoor ALAN and taking into account potential confounders such as sleep duration, sleep patterns and energy balance.

Moreover, in adulthood evidence is lacking regarding the interference of artificial light emitted by small electronic devices (i.e. tablets, smartphones, computers, etc.) at night and adiposity outcomes [39]. Importantly, also the type of wavelength and the timing of exposure seem to be pivotal details due to different interplays with melatonin production and thus with circadian disruption [40,41]. Finally, the potential impact of ALAN exposure in different periods of life (from early life to the elderly) on health outcomes such as obesity and cancer needs to be thoroughly understood.

5. ALAN and cancer: human evidence

The majority of studies investigating the relationship between ALAN and cancer encompasses ecological studies carried out at the population level based on exposure to outdoor ALAN, whereas evidence is scarce with regard to the indoor light intensity at night-time (Table 1). As well known, night shift work, as a real-life model for ALAN exposure, has been considered by the International Agency for Research on Cancer as a probable risk factor for breast, prostate, and colorectal cancers [42]. Prevalence or incidence rates of several cancers were considered, with breast cancer (BC) in women and prostate cancer (PC) in men as the most frequent types of cancers evaluated. Evidence from animal studies and limited epidemiology on night-shift work suggests that hormone-dependent cancers are especially affected by circadian disruption likely due to the potential role of melatonin as a modulator of cell proliferation [43,44].

5.1. Outdoor ALAN

The use of data gathered from satellites allowed us to explore the association between outdoor ALAN and cancer in large regional areas and worldwide [45−59], (see Table 1). Based on extant population-level evidence, findings from regional as well as worldwide analyses support exposure to outdoor ALAN as an independent risk factor for BC in women and PC in men, after controlling for potential confounding variables (Table 1). Most studies, save the article by Al-Naggar *et al.* [49], did not describe any significant association between ALAN and other non-hormone responsive cancers, including stomach, oesophageal, liver, pancreatic, laryngeal, lung and tracheal, bladder, and brain and central nervous system cancers, as well as lymphoma and multiple myeloma [50,51]. The association between outdoor ALAN and thyroid cancer incidence has been reported in the National Institutes of Health−American Association of Retired Persons Diet and Health Study [52]. ALAN exposure was estimated from satellite data and was linked to residential addresses. A positive association was found between ALAN exposure and thyroid cancer risk. Specifically, in comparison with the lowest quintile of ALAN exposure, the highest quintile was associated with a 55% risk increase. The association was primarily found for papillary thyroid cancer and was stronger in women than men. In women, the association was mostly for localised cancer, whereas in men, for advanced stages.

Race and ethnicity differences have been poorly investigated; Bauer *et al.* reported divergent associations between BC incidence and outdoor ALAN exposure when stratifying the analysis by race in White and Black women [53]. The authors hypothesised that this finding was explained by racial differences in naturally occurring melatonin production and secretion. In addition, the sensitivity of melatonin to light suppression may be influenced by eye pigmentation, which can vary due to race or ethnicity. The percentage of melatonin suppression secretion after light exposure was significantly

larger in light-eyed than individuals with darker eye pigmentation. The common occurrence of lighter iris colour is found almost exclusively among Caucasians. Based on these observations, white women may be at an increased risk of melatonin suppression after exposure to outdoor ALAN [53]. However, most of the global and regional data (mainly from South Korea, Israel and the US) are indeed consistent supporting ALAN as a relevant risk factor for some cancers (Table 1). However, there are discrepancies in the results of studies carried out in urban versus rural areas in identifying ALAN as a risk factor for cancer [54–56]. Moreover, it would seem that even rural areas and therefore apparently protected by ALAN are still partially at the risk of outdoor ALAN interference on health outcomes such as different types of cancer [49]. Two studies performed a sub-analysis considering different wavelengths in the light spectrum [57,58]. Interestingly, BC incidence was positively associated with short wavelength sub-spectrum (i.e. blue) while no associations were found for green or red subspectra [59]. Similarly, exposure to outdoor ALAN in the blue light spectrum was associated with BC and PC in a Spanish study [58]. Given that a long latency period has been shown between risk factor exposure and cancer onset, some studies relied on night-time satellite images for ALAN collected several years (approximately one decade) before disease prevalence or incidence observations. From a methodological standpoint, spatial effects of light pollution, i.e. the distance from the area taken into account into the study to the area where there is light pollution, on cancer should be acknowledged and preferred rather than relying on a general, unique regression model [54], and only some studies used to adjust the data for this confounding factor.

5.2. Indoor ALAN

Just a minority of studies assessed indoor ALAN exposure (58, 60–64, see Table 2), mainly through either in-person interviews or self-reported questionnaires. Compared to robust data from outdoor ALAN exposure, domestic ALAN exposure resulted in heterogeneous findings: residential bedroom light intensity while sleeping was associated with PC [57], whereas for BC, a couple of studies reported just marginally significant associations [60,61]. However, other studies found a positive association between BC and domestic ALAN [62–64]. Conflicting findings may be due to non-objective data based on self-reporting and variability in terms of time frame exposure (ranging from 5 to 10 years).

6. Future directions

Objective measures of residential ALAN exposure need to be used to strengthen epidemiological evidence concerning the connection between domestic ALAN and risk for cancer. It should be also acknowledged that the association of outdoor ALAN with shorter sleep duration may be affected by the potential impact of seasonality on ALAN. Noteworthy, individuals living furthest away from the equator would experience greater variations in outdoor ALAN exposure due to seasonality and this could explain the different results detected in studies on ALAN carried out in different populations. Further research is warranted to allow a better understanding of mechanisms underpinning cancer pathogenesis and its interplay with environmental and hormonal factors related to chrono-disruption (i.e. melatonin and sex-hormone interplay, different effects of intensity and wavelengths, analysis of confounders such as obesity and the type of cancer diagnosed in terms of staging and grading).

7. Basic science evidence

Experimental studies in rodents were mainly based on different protocols of exposure to ALAN, encompassing either dim light or white light exposure during the dark cycle as well as constant light exposure. The duration of the studies ranged from days to weeks, representing animal models of chronic exposure to ALAN to be translated to human health.

7.1. ALAN and obesity

Data from evidence based on animal studies suggest a strong relationship between ALAN exposure and the risk of developing obesity. Aubrecht *et al.* carried out an experimental study in twenty female Swiss-Webster mice (~8 weeks of age) [65], exposing them to dim light at night (dLAN, 16:8 light/dim light cycle at ~150 lux during the day and ~5 lux during the night) or a traditional light:dark cycle (LD 16:8 light/dark cycle; ~150 lux during the day and ~0 lux at night) for 6 weeks. Mice in the dLAN group had significantly increased body mass, despite energy intake was not higher and total daily activity level was not increased compared to the LD group [65]. Moreover, another study by the same group showed that ninety male Swiss-Webster mice (8 weeks of age) exposed to dLAN and high-fat diet over four weeks gained weight, reduced glucose tolerance, impaired insulin secretion and increased inflammatory cytokines such as TNFα compared with male mice in a standard light/dark cycle, clearly underscoring the detrimental synergistic effect of chronodisruption related to dLAN in addition to an obesogenic diet [66]. Another study investigating the acute effects of white ALAN on glucose and insulin metabolism on forty-one male Wistar rats undergoing either i.v. glucose or insulin tolerance tests while exposed to 2 h of white ALAN in the early or late dark phase, found that white ALAN exposure early in the

Table 2
Summary of human studies on exposure to indoor ALAN and cancer.

Cancer							
ALAN Source	Authors	Year	Reference	Ethnicity	Participants	Age	Main findings
Self-reported	Garcia-Saenz A, *et al.*	2018	58	Spanish	1,219 BC cases, 1,385 female controls, 623 PC cases, and 879 male controls	20−85	Compared with those who reported sleeping in total darkness, men who slept in "'quite illuminated" bedrooms had a higher risk of PC (OR = 2.79; 95% CI: 1.55, 5.04), whereas women had a slightly lower risk of BC (OR = 0.77; 95% CI: 0.39, 1.51).
In-person interview for bedroom ambient light (10-y exposure)	Davis S, *et al.*	2001	60	US	813 case patients and 793 control subjects.	20−74	Increased risk of BC among subjects with the brightest bedrooms, not statistically significant (OR: 1.4; 95% CI:0.8−2.6).
Domestic exposure to ALAN, in-person interview, bedroom ambient light, (10-y exposure)	Li Q, *et al.*	2010	61	US	363 incident BC cases and 356 age frequency-matched controls	30−80	A non-significantly increased risk of BC was observed among postmenopausal women for those keeping lights on while sleeping (OR = 1.4, 95% CI 0.7, 2.7), those who reported mainly sleeping in the daytime (OR = 1.4, 95% CI 0.5, 4.3), and those not drawing the curtains/window shades while sleeping at night (OR = 1.2, 95% CI 0.8, 1.9).
In-person interview, bedroom ambient light (5-y exposure)	O'Leary ES, *et al.*	2006	62	US	576 women with BC and 585 population-based controls	<75	Turning on lights at home during sleeping time (≥twice/week and ≥twice/night) associated with increased risks (OR: 1.65, 95% CI: 1.02, 2.69) of BC.
Bedroom light	Keshet-Sitton A, *et al.*	2016	63	Israeli-Jewish	278 women, BC patients (n = 93), and controls (n = 185)	27−91	Women moderately exposed to ALAN as a result of reading using bed light (reading lamp) illumination and women who had slept with closed shutters reduced their BC risk: OR = 0.81, 95% CI = 0.67 −0.97, P < 0.02, and OR = 0.82, 95% CI = 0.68 −0.99, P < 0.04, respectively. Women exposed to ALAN as a result of living near strong illumination sources were at a significantly higher BC risk (OR = 1.52, 95% CI = 1.10−2.12; P < 0.01).
Bedroom light	Kloog I, *et al.*	2011	64	Israeli-Jewish	1679 women		Exposure to ALAN in the "sleeping habitat" significantly associated with BC risk (odds ratio [OR] = 1.220, 95% confidence interval [CI] = 1.118 −1.311; p < 0.001), controlling for education, ethnicity, fertility, and alcohol consumption.
Cellphones	Keshet-Sitton A, *et al.*	2017	55	Israeli-Jewish	252 women (110 BC patients and 142 controls, of whom: urban population: 92 BC patients and 72 controls; rural population: 18 BC patients and 66 controls)	36−79	In urban population BC risk increased with daily use of cellphone (OR = 2.13, 95% CI = 1.01−4.49, P < 0.05). In rural women BC risk decreased with reading with room light illumination before retiring to sleep (OR = 0.55, 95% CI = 0.29−1.06, P < 0.07), and sleeping with closed shutters during the night (OR = 0.66, 95% CI = 0.41−1.04, P < 0.08).

Abbreviations: ALAN (artificial light at night), BC (breast cancer), PC (prostate cancer), OR (odds ratio), CI (confidence interval).

dark phase caused increased glucose response during the first 20 min after glucose infusion, whereas white ALAN exposure at the end of the dark phase caused increased insulin response during the first 10 min, indicating that LAN acutely induces glucose intolerance in rats [67]. A recent study from Borck *et al.* investigated whether altered miRNAs expression in the liver underlies metabolic disorders caused by disrupted biological rhythms demonstrated that C3H/HePas mice exposed to eight weeks of constant ALAN (12:12 light/light condition) compared to controls on 12:12 light/dark cycles (lights on at 6hr/lights off at 18hr), developed obesity and hepatic steatosis, which was paralleled by decreased expression of Rev-erbα and increasing miR-140−5p, 185−5p, 326−5p and 328−5p liver expression [68].

7.2. ALAN and cancer

In a recent study evaluating the effects of ALAN on carcinogenesis, Agbaria et al. investigated the effects of 1 × 30 min/midnight ALAN (134 μWcm−2, 460 nm) with or without nocturnal melatonin supplementation on tumour development and epigenetic responses in BC 4T1 tumour-bearing BALB/c female mice [69]. Mice exposed to ALAN significantly reduced 6- sulfatoxymelatonin levels and increased tumour volume and lung metastasis compared with controls [69]. The effects on carcinogenesis induced by ALAN also involved the intra-tumour enzymatic expression by changing the DNA methylation with a clear epigenetic effect [69]. These effects were diminished by melatonin supplementation [69] and similar results were reported also by a previous study by Schwimmer .et al. [70]. In addition, Blask *et al.* first observed the property of constant light exposure to suppress melatonin production in female nude rats and to stimulate the growth of tissue-isolated Michigan Cancer Foundation-7human BC xenografts via increased tumour linoleic acid (LA) metabolism [71,72]. Moreover, the same study group study investigated the effects of ALAN on the alteration of the biological rhythm and the potential role in carcinogenesis and Warburg effect [73] evaluating tissue-isolated human BC xenografts grown in nude rats, and showing that circulating systemic factors in the host along with Warburg effect, LA uptake/metabolism and growth signalling activities in the tumour are dynamically regulated, coordinated and integrated within circadian time structure over a 24-h light/dark cycle by the suprachiasmatic nucleus-driven nocturnal pineal production of the anticancer hormone melatonin [73]. In addition, Cos *et al.* investigated whether light exposure at night influences the growth of mammary tumours, administering single intragastric doses of dimethylbenzanthracene (20 mg in 1 ml of sesame oil) in thirty-two female Sprague−Dawley rats, 55 days of age, in order to induce mammary tumours. Rats exposed to ALAN, especially those under a constant dim light during the darkness phase, showed significantly higher rates of tumour growth as well as lower survival than controls, higher concentration of serum oestradiol and lower nocturnal excretion of 6-sulfatoxymelatonin [74]. Furthermore, exposure to ALAN also influences and determines resistance against various chemotherapies [75−77]. In particular, a study aimed to evaluate the ALAN induction of Doxorubicin resistance in tissue-isolated oestrogen receptor alpha-positive (ERa+) Michigan Cancer Foundation-7 human BC xenografts, grown in nude rats and maintained on a light/dark cycle of LD 12:12 in which ALAN is present during the dark phase (suppressed endogenous nocturnal melatonin), demonstrated a significant shortening of tumour latency-to-onset, increased tumour metabolism and growth and complete intrinsic resistance to Doxorubicin therapy [75]. The same study group showed first that circadian disruption of melatonin by ALAN exposure led to intrinsic resistance to Paclitaxel [76]. In both cases, melatonin administration can re-establish the sensitivity of breast tumours to Doxorubicin and Paclitaxel, respectively [75,76]. Consistently, it has been demonstrated that ALAN confers intrinsic resistance to tamoxifen therapy in rats BC cells [77]. Although, BC is the most studied cancer related to ALAN exposure. However, numerous further types of cancer have been assessed and considered potentially inducible by exposure to ALAN: lung adenocarcinomas, leukemias, hepatocarcinomas [78] and uterine cancer [79]. Moreover, Anisimov *et al.* found a higher incidence of several cancers in mice with continuous exposure to ALAN for 24 h compared to controls exposed for 12 h [80]. The age of the animal was considered to exclude a possible bias. Specifically, male and female rats were exposed to constant light started at the age of one month and at the age of fourteen months on the survival, life span, tumorigenesis and age-related dynamics of antioxidant enzymes activity in various organs in comparison to the rats maintained at the standard (12:12 light/dark) light/dark regimen [81]. Authors found that exposure to constant light started at the age of 1 month accelerated spontaneous tumorigenesis and shortened lifespan both in male and female rats as compared to the standard regimen [81]. At the same time, the exposure to constant light started at the age of fourteen months failed to influence the survival of male and female rats. While delaying tumours in males, constant light accelerated tumours in females [81]. Lastly, another study assessed the exposure to ALAN of different wavelengths and cancer development in female BALB/c mice (4−5 weeks, 20 + 1 g), and reported that short wavelength (<500390 nm) increased tumour growth, promoted lung metastases formation and advanced DNA hypomethylation, while long wavelength lessened these effects; melatonin treatment counteracted these effects and resulted in reduced cancer burden [82]. The connection between obesity and cancer development

under ALAN exposure has been investigated in few studies [76,83]. Guerrero-Vergas *et al.* demonstrated that ALAN exposure induced weight gain, altered circulating lipid and glucose profiles, increased levels of pro-inflammatory cytokines in rats and tumour cell inoculation resulted in increased tumour volume compared with rats non-exposed to ALAN, suggesting that circadian disruption by ALAN provides a favourable condition for tumour growth by promoting an anabolic metabolic response in the host [84]. A recent study evaluated ALAN effects on differentiation and cell cycle in eight male Wistar rats with autonomic nervous system denervation compared with five controls [83]. The significant differentially expressed genes were screened by the protein−protein interaction network analysis STRING database and the study demonstrated that several essential functions such as differentiation, cell cycle, ribosome assembly and splicing are altered by ALAN suggesting a potential role of ALAN in cancer and metabolism regulation [76].

8. Conclusion

The current findings provide evidence that exposure to ALAN represents a remarkable risk factor for weight gain, overweight and obesity, as well as for cancer. The main limitation of the present review article is represented by the translational potential of the evidence summarised: most of the evidence come from animal models that, however, do not fully mirror the circadian disruption in humans due to the shift in feeding rhythms in order to accommodate work time and social habits [86]. However, the novelty of the manuscript lies in the fact that are provided with both evidence on clinical and basic aspects and that is hypothesised a vicious cycle including ALAN, obesity and cancer, thus highlighting insights on this physiopathological interplay. In addition, ALAN exposure may be a predisposing factor for unfavourable health outcomes such as obesity and cancer promoting non-classical mechanisms underpinning obesity and/or cancer development, mainly due to circadian disruption of circadian disruption have primarily focused on shifting the LD cycle to imitate human jet lag or shift work. These light shifting protocols have merit in examining the negative effects of shifting the circadian clock; however, given the detrimental effects of ALAN on health, public health strategies to decrease obesity and cancer should be prompted considering interventions aimed at reducing long-term ALAN exposure.

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Conflict of interest statement

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References

[1] Park YM, White AJ, Jackson CL, Weinberg CR, Sandler DP. Association of exposure to artificial light at night while sleeping with risk of obesity in women. JAMA Intern Med 2019 Aug 1; 179(8):1061−71.

[2] Jones RR. Exposure to artificial light at night and risk of cancer: where do we go from here? Br J Cancer 2021. https://doi.org/10.1038/s41416-020-01231-7.

[3] Fonken LK, Nelson RJ. The effects of light at night on circadian clocks and metabolism. Endocr Rev 2014;35(4):648−70.

[4] Kyba CCM, Kuester T, Sanchez de Miguel A, Baugh K, Jechow A, Holker F, et al. Artificially lit surface of Earth at night increasing in radiance and extent. Sci Adv 2017;3(11):e1701528.

[5] Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. Somnologie 2019;23(3): 147−56.

[6] Vandewalle G, Archer SN, Wuillaume C, Balteau E, Degueldre C, Luxen A, et al. Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. J Biol Rhythm 2011;26(3):249−59.

[7] Buhr ED, Vemaraju S, Diaz N, Lang RA, Van Gelder RN. Neuropsin (OPN5) mediates local light-dependent induction of circadian clock genes and circadian photoentrainment in exposed murine skin. Curr Biol 2019;29(20):3478−34787 e4.

[8] Touitou Y, Reinberg A, Touitou D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: health impacts and mechanisms of circadian disruption. Life Sci 2017;173:94–106.
[9] Petrzilka S, Taraborrelli C, Cavadini G, Fontana A, Birchler T. Clock gene modulation by TNF-alpha depends on calcium and p38 MAP kinase signaling. J Biol Rhythm 2009;24(4):283–94.
[10] Gu W, Chen C, Zhao KN. Obesity-associated endometrial and cervical cancers. Front Biosci 2013;5:109–18.
[11] Chen J, Zhao KN, Li R, Shao R, Chen C. Activation of PI3K/Akt/mTOR pathway and dual inhibitors of PI3K and mTOR in endometrial cancer. Curr Med Chem 2014;21(26): 3070–80.
[12] Walker 2nd WH, Borniger JC. Molecular mechanisms of cancer-induced sleep disruption. Int J Mol Sci 2019;20(11).
[13] Lashinger LM, Harrison LM, Rasmussen AJ, Logsdon CD, Fischer SM, McArthur MJ, et al. Dietary energy balance modulation of Kras- and Ink4a/Arf+/–driven pancreatic cancer: the role of insulin-like growth factor-I. Cancer Prev Res 2013;6(10): 1046–55.
[14] El-Athman R, Genov NN, Mazuch J, Zhang K, Yu Y, Fuhr L, et al. The Ink4a/Arf locus operates as a regulator of the circadian clock modulating RAS activity. PLoS Biol 2017;15(12): e2002940.
[15] Liu Z, Wei ZY, Chen J, Chen K, Mao X, Liu Q, et al. Acute sleep-wake cycle shift results in community alteration of human gut microbiome. mSphere 2020;5(1).
[16] Rani A, Dasgupta P, Murphy JJ. Prostate cancer: the role of inflammation and chemokines. Am J Pathol 2019;189(11): 2119–37.
[17] Hong F, Pan S, Xu P, Xue T, Wang J, Guo Y, et al. Melatonin orchestrates lipid homeostasis through the hepatointestinal circadian clock and microbiota during constant light exposure. Cells 2020;9(2).
[18] Rafiq S, Jeppesen PB. Body mass index, vitamin D, and type 2 diabetes: a systematic review and meta-analysis. Nutrients 2018; 10(9).
[19] Grant WB. Ecological studies of the UVB-vitamin D-cancer hypothesis. Anticancer Res 2012;32(1):223–36.
[20] Smolensky MH, Sackett-Lundeen LL, Portaluppi F. Nocturnal light pollution and underexposure to daytime sunlight: complementary mechanisms of circadian disruption and related diseases. Chronobiol Int 2015;32(8):1029–48.
[21] Roenneberg T, Winnebeck EC, Klerman EB. Daylight saving time and artificial time zones- A battle between biological and social times. Front Physiol 2019;10:944.
[22] Rishi MA, Ahmed O, Barrantes Perez JH, Berneking M, Dombrowsky J, Flynn-Evans EE, et al. Daylight saving time: an American Academy of Sleep Medicine position statement. J Clin Sleep Med 2020;16(10):1781–4.
[23] Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism 2018;84:11–27.
[24] Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A 2014;111(47):16647–53.
[25] Voigt RM, Summa KC, Forsyth CB, Green SJ, Engen P, Naqib A, et al. The circadian clock mutation promotes intestinal dysbiosis. Alcohol Clin Exp Res 2016;40(2):335–47.
[26] Grippo RM, Guler AD. Dopamine signaling in circadian photoentrainment: consequences of desynchrony. Yale J Biol Med 2019;92(2):271–81.
[27] Koo YS, Song JY, Joo EY, Lee HJ, Lee E, Lee SK, et al. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. Chronobiol Int 2016; 33(3):301–14.
[28] Saulle R, Bernardi M, Chiarini M, Backhaus I, La Torre G. Shift work, overweight and obesity in health professionals: a systematic review and meta-analysis. Clin Ter 2018 Jul-Aug;169(4):e189–97. https://doi.org/10.7417/T.2018.2077.
[29] Sun M, Feng W, Wang F, Li P, Li Z, Li M, Tse G, Vlaanderen J, Vermeulen R, Tse LA. Meta-analysis on shift work and risks of specific obesity types. Obes Rev 2018 Jan;19(1):28–40. https://doi.org/10.1111/obr.12621.
[30] Brum MCB, Dantas Filho FF, Schnorr CC, Bertoletti OA, Bottega GB, da Costa Rodrigues T. Night shift work, short sleep and obesity. Diabetol Metab Syndrome 2020 Feb 10;12:13. https://doi.org/10.1186/s13098-020-0524-9.
[31] Cox DTC, Sánchez de Miguel A, Dzurjak SA, Bennie J, Gaston KJ. National scale spatial variation in artificial light at night. Rem Sens 2020;12(10):1591. https://doi.org/10.3390/rs12101591.
[32] Gaston KJ, Bennie J, Davies TW, Hopkins J. The ecological impacts of nighttime light pollution: a mechanistic appraisal. Biol Rev Camb Phil Soc 2013 Nov;88(4):912–27. https://doi.org/10.1111/brv.12036. Epub 2013 Apr 8.
[33] Abay KA, Amare M. Night light intensity and women's body weight: evidence from Nigeria. Econ Hum Biol 2018;31:238–48.
[34] Rybnikova NA, Haim A, Portnov BA. Does artificial light-at-night exposure contribute to the worldwide obesity pandemic? Int J Obes 2016;40(5):815–23.
[36] Obayashi K, Saeki K, Kurumatani N. Ambient light exposure and changes inobesity parameters: a longitudinal study of the HEIJO-KYO cohort. J Clin Endocrinol Metab 2016;101(9): 3539–47.
[37] Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, et al. Exposure to light at-night, nocturnal urinary melatonin excretion, and obesity/dyslipidemia in the elderly: a cross-sectional analysis of the HEIJO-KYO study. J Clin Endocrinol Metab 2013;98(1):337–44.
[38] McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. Am J Epidemiol 2014; 180(3):245–50.
[39] Lai KY, Sarkar C, Ni MY, Gallacher J, Webster C. Exposure to light at night (LAN) and risk of obesity: a systematic review and meta-analysis of observational studies. Environ Res 2020;187:109637.
[40] Heyde I, Oster H. Differentiating external zeitgeber impact on peripheral circadian clock resetting. Sci Rep 2019;9(1):20114.
[41] Pulivarthy SR, Tanaka N, Welsh DK, De Haro L, Verma IM, Panda S. Reciprocity between phase shifts and amplitude changes in the mammalian circadian clock. Proc Natl Acad Sci U S A 2007;104(51):20356–61.
[42] IARC Monographs Vol 124 group. Carcinogenicity of night shift work. Lancet Oncol 2019 Aug;20(8):1058–9.
[43] Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 2009;13(4):257–64.
[44] Hurley S, Nelson DO, Garcia E, Gunier R, Hertz A, Reynolds P. A cross-sectional analysis of light at night, neighborhood socio-demographic and urinary 6-sulfatoxymelatonin concentrations: implications for the conduct of health studies. Int J Health Geogr 2013;12:39.
[45] Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. Chronobiol Int 2008;25(1):65–81.
[46] Kim YJ, Lee E, Lee HS, Kim M, Park MS. High prevalence of breast cancer in light polluted areas in urban and rural regions of South Korea: an ecologic study on the treatment prevalence of female cancers based on National Health Insurance data. Chronobiol Int 2015;32(5):657–67.
[47] Kim KY, Lee E, Kim YJ, Kim J. The association between artificial light at night and prostate cancer in Gwangju City and South Jeolla Province of South Korea. Chronobiol Int 2017;34(2): 203–11. https://doi.org/10.1080/07420528.2016.1259241.
[48] Rybnikova N, Haim A, Portnov BA. Artificial Light at Night (ALAN) and breast cancer incidence worldwide: a revisit of

earlier findings with analysis of current trends. Chronobiol Int 2015;32(6):757–73.
[49] Al-Naggar RA, Anil S. Artificial light at night and cancer: global study. Asian Pac J Cancer Prev APJCP 2016;17(10):4661–4.
[50] Kloog I, Stevens RG, Haim A, Portnov BA. Nighttime light level co-distributes with breast cancer incidence worldwide. Cancer Causes Control 2010;21(12):2059-2068.
[51] Kloog I, Haim A, Stevens RG, Portnov BA. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. Chronobiol Int 2009;26(1):108-125.
[52] Zhang D, Jones RR, James P, Kitahara CM, Xiao Q. Associations between artificial light at night and risk for thyroid cancer: a large US cohort study. Cancer 2021;127(9):1448–58.
[53] Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE. A case-referent study: light at night and breast cancer risk in Georgia. Int J Health Geogr 2013;12:23.
[54] Kim YJ, Park MS, Lee E, Choi JW. High incidence of breast cancer in light-polluted areas with spatial effects in Korea. Asian Pac J Cancer Prev APJCP 2016;17(1):361–7.
[55] Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. Light and the city: breast cancer 639 risk factors differ between urban and rural women in Israel. Integr Cancer Ther 2017;16(2):176–87.
[56] Keshet-Sitton A, Or-Chen K, Huber E, Haim A. Illuminating a risk for breast cancer: a preliminary ecological study on the association between streetlight and breast cancer. Integr Cancer Ther 2017 Dec;16(4):451–63. https://doi.org/10.1177/1534735416678983.
[57] Rybnikova N, Stevens RG, Gregorio DI, Samociuk H, Portnov BA. Kernel density analysis reveals a halo pattern of breast cancer incidence in Connecticut. Spat Spatiotemporal Epidemiol 2018;26:143–51.
[58] Garcia-Saenz A, Sanchez de Miguel A, Espinosa A, Valentin A, Aragones N, Llorca J, et al. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain study). Environ Health Perspect 2018;126(4):047011.
[59] Rybnikova N, Portnov BA. Population-level study links short-wavelength nighttime illumination with breast cancer incidence in a major metropolitan area. Chronobiol Int 2018;35:1198–208.
[60] Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst 2001;93(20):1557–62.
[61] Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M. Light at night and breast cancer risk: results from a population-based case-control study in Connecticut, USA. Cancer Causes Control 2010;21(12):2281–5.
[62] O'Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, et al. Shift work, light at night, and breast cancer on Long Island, New York. Am J Epidemiol 2006;164(4):358–66.
[63] Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. Can avoiding light at night reduce the risk of breast cancer? Integr Cancer Ther 2016;15(2):145–52.
[64] Kloog I, Portnov BA, Rennert HS, Haim A. Does the modern urbanized sleeping habitat pose a breast cancer risk? Chronobiol Int 2011;28(1):76–80.
[65] Aubrecht TG, Jenkins R, Nelson RJ. Dim light at night increases body mass of female mice. Chronobiol Int 2015;32(4):557–60.
[66] Fonken LK, Lieberman RA, Weil ZM, Nelson RJ. Dim light at night exaggerates weight gain and inflammation associated with a high-fat diet in male mice. Endocrinology 2013;154(10):3817–38661 25.
[67] Opperhuizen AL, Stenvers DJ, Jansen RD, Foppen E, Fliers E, Kalsbeek A. Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats. Diabetologia 2017;60(7):1333–43.
[68] Borck PC, Batista TM, Vettorazzi JF, Soares GM, Lubaczeuski C, Guan D, et al. Nighttime light exposure enhances Rev-erbalpha-targeting microRNAs and contributes to hepatic steatosis. Metabolism 2018;85:250–8.
[69] Agbaria S, Haim A, Fares F, Zubidat AE. Epigenetic modification in 4T1 mouse breast cancer 669 model by artificial light at night and melatonin - the role of DNA-methyltransferase. Chronobiol Int 2019;36(5):629–43.
[70] Schwimmer H, Metzer A, Pilosof Y, Szyf M, Machnes ZM, Fares F, et al. Light at night and 672 melatonin have opposite effects on breast cancer tumors in mice assessed by growth rates and global 673 DNA methylation. Chronobiol Int 2014;31(1):144–50.
[71] Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: impact of constant light-induced nocturnal melatonin suppression. Breast Cancer Res Treat 2003;79(3):313–20.
[72] Blask DE, Dauchy RT, Brainard GC, Hanifin JP. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. Integr Cancer Ther 2009;8(4):347–53.
[73] Blask DE, Dauchy RT, Dauchy EM, Mao L, Hill SM, Greene MW, et al. Light exposure at night disrupts host/cancer circadian regulatory dynamics: impact on the Warburg effect, lipid signaling and tumor growth prevention. PLoS One 2014;9(8):e102776.
[74] Cos S, Mediavilla D, Martinez-Campa C, Gonzalez A, Alonso-Gonzalez C, Sanchez-Barcelo EJ. Exposure to light-at-night increases the growth of DMBA-induced mammary adenocarcinomas in rats. Cancer Lett 2006;235(2):266–71.
[75] Xiang S, Dauchy RT, Hauch A, Mao L, Yuan L, Wren MA, et al. Doxorubicin resistance in breast cancer is driven by light at night-induced disruption of the circadian melatonin signal. J Pineal Res 2015;59(1):60–9.
[76] Heidari MH, Zamanian Azodi M, Zali MR, Akbari Z. Light at night exposure effects on differentiation and cell cycle in the rat liver with autonomic nervous system denervation. J Laser Med Sci 2019;10(Suppl 1):S43–8.
[77] Dauchy RT, Xiang S, Mao L, Brimer S, Wren MA, Yuan L, et al. Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. Cancer Res 2014;74(15):4099–110.
[78] Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, et al. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. Int J Cancer 2004;111(4):475–9.
[79] Popovich IG, Zabezhinski MA, Panchenko AV, Piskunova TS, Semenchenko AV, Tyndyk ML, et al. Exposure to light at night accelerates aging and spontaneous uterine carcinogenesis in female 129/Sv mice. Cell Cycle 2013;12(11):1785–90.
[80] Anisimov VN, Vinogradova IA, Panchenko AV, Popovich IG, Zabezhinski MA. Light-at- night-induced circadian disruption, cancer and aging. Curr Aging Sci 2012;5(3):170–7.
[81] Vinogradova IA, Anisimov VN, Bukalev AV, Semenchenko AV, Zabezhinski MA. Circadian disruption induced by light-at-night accelerates aging and promotes tumorigenesis in rats. Aging (Albany NY) 2009;1(10):855–65.
[82] Zubidat AE, Fares B, Fares F, Haim A. Artificial light at night of different spectral compositions differentially affects tumor growth in mice: interaction with melatonin and epigenetic pathways. Cancer Control 2018;25(1). 1073274818812908.
[83] Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, et al. Chronically alternating light cycles increase breast cancer risk in mice. Curr Biol 2015;25(14):1932–7.
[84] Guerrero-Vargas NN, Navarro-Espindola R, Guzman-Ruiz MA, Basualdo MDC, Espitia-Bautista E, Lopez-Bago A, et al. Circadian disruption promotes tumor growth by anabolic host metabolism; experimental evidence in a rat model. BMC Cancer 2017;17(1):625.