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Association between Artificial Light at Night Exposure and breast and prostate cancer risk – the review

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Summary:

Introduction and purpose: Light is one of the defining features of life on the Earth, allowing certain biological processes to be subordinated to its presence and absence. With the introduction of artificial light, the human natural biological clock was dysregulated. Apart from that, the studies showed a connection between exposure to artificial light at night (ALAN) and carcinogenesis. The aim of this review was to present currently available knowledge in the online database PubMed about Association Between Artificial Light at Night and Breast and Prostate Cancer Risk.

Brief description of the state of knowledge: The article covers clinical and population-based control studies which indicate to ALAN exposure can lead to increased incidence of breast and prostate cancer by disruption of circadian rhythms in several mechanisms involving

suppression of melatonin production, dysregulation of sleep–activity pattern and disruption of circadian genes.

Conclusions: The review support an assumption that breast and prostate cancer incidence is a consequence of ALAN exposure. Further studies should clarify the relationship between ALAN exposure and other types of cancer. Besides, ALAN exposure levels should be measured more precisely than by satellite pictures analysis to reliably conduct studies proving the relation between ALAN exposure and risk of cancer development.

Key words: circadian rhythm; artificial light; breast cancer; prostate cancer

1. Introduction

Light has extensively influenced the evolution of life on the Earth. For 4 billion years, before electric light was invented, life on Earth evolved under the defined sequence of light during the day and darkness at night. Throughout this time, nearly all species, including humans, internalized the Earth's 24-hour cycle and eventually developed self-sustained biological clocks that align behavioral and physiological activities to approximate the light-dark cycle in nature. Basically, all biological processes display rhythms of function that approximate 24 hours [1]. These biological clocks called circadian rhythms are self-sustaining, endogenous rhythms of optimal function that are set to precisely 24 hours each day. Well-known examples of mammalian circadian rhythms are the sleep-wake cycle, body temperature and patterns of hormone secretion. In the past century, natural light-dark cycles have been highly disrupted by the increasing light pollution caused by artificial light at night (ALAN), emerging from a diversity of sources, such as streetlamps, illuminated buildings, lit advertisements, domestic lights and lights from vehicles [2][3]. ALAN contains light with different spectra and intensities than sunlight. Therefore, it affects natural daily rhythms. Over 80% of the world population (99% of the population from Europe and the US) and almost one-fifth of the globe is under light-polluted skies that suffer from an excessive, inappropriate, or obtrusive artificial (usually outdoor) light [4].

The biological clock consist of the central oscillator suprachiasmatic nucleus, a region of the brain in the hypothalamus, situated directly above the optic chiasm [5][6]. It receives dark/light signals via photoreceptors of the eye's retina called non–image forming photoreceptors (NIFPs) which contain the photopigment called melanopsin [7][8].

Furthermore, it results in an output of the neurohormone melatonin (N-acetyl-5-methoxytryptamine - MLT) produced and secreted by the pineal gland, which among others, transmits environmental signals to organs, tissues, and cells, as well as suprachiasmatic nucleus cells. The illumination at the range of ~440 to 520 nm may efficiently suppress the synthesis of the pineal neurohormone MLT.

Importantly, some of the key processes involved in carcinogenesis are related to circadian rhythms. To give an example, cell cycle and the circadian clock represent major cellular rhythms that appear to be coupled [9]. Therefore, regulation of circadian rhythms greatly influences cell division and can cause cancer development. On the other hand, malignant transformation disrupts circadian rhythm organization [10].

Recently, artificial light at night (ALAN) has been revealed to cause breast and prostate cancer [11][12][13]. These two are the most common invasive cancers in women and men, respectively. Several mechanisms related to the circadian system, exposure to light at night and potential carcinogenesis were examined by IARC (International Agency for Research on Cancer) involving suppression of melatonin production, dysregulation of sleep–activity pattern and disruption of circadian genes [13].

2. State of knowledge

2.1 Clock genes, Circadian rhythm and Cancer

Circadian rhythms are guarded by circadian pathway genes. The molecular circadian clock is originated by a transcriptional/translational loop of circadian clock genes with autoregulatory feedback. The primary loop implicates the genes CLOCK (Clock Circadian Regulator), ARNTL (Aryl Hydrocarbon Receptor Nuclear Translocator Like) also known as BMAL1 (Brain and Muscle ARNT-like), PER1–3 (Period Circadian Clock 1-3) and CRY1-2 (Cryptochrome Circadian Clock 1-2) [14] There are also other core circadian genes, such as CSNK1E (Casein Kinase I Epsilon) [15] , NR1D1 (Nuclear Receptor Subfamily 1 Group D Member 1 also called Rev-Erb Alpha) [16] NR1D2 (Nuclear Receptor Subfamily 1 Group D Member 2 also referred to Rev-Erb Beta) [17],), NPAS2 (Neuronal PAS Domain Protein 2) [18], RORA (RAR Related Orphan Receptor A) [19] and TIMELESS (Timeless Circadian Clock) [20].

Numerous studies have proven correlation between clock genes polymorphisms and human endocrine related cancers such as ovarian, pancreatic, prostate and breast cancer. This mainly applies to genes BMAL1, CLOCK, CSNK1E, CRY1-2, NPAS2, and PER1-3 [21].

Worldwide, breast cancer is the most common cancer affecting women, and its incidence and mortality rates are expected to increase significantly in next year's [22].

Studies show that gens PER1, PER2, and PER3 exhibited changes associated with the tumor suppressor activity [23]. Breast cancer patients frequently demonstrate elevated methylation and mutations of the gene promoters in PER 1 and 2 [24][25]. Further studies confirmed that circadian genes CRY2 and PER1-3 were down-regulated, additionally CLOCK and TIMELESS were over-expressed [26]. Studies showed that increased TIMELESS expression in breast cancer patients is linked with reduced metastasis-free survival. On the other hand, increased expression of NPAS2 or CLOCK prolonged metastasis-free survival in breast cancer patients [27].

A German population-based case-control study supported the association between seven polymorphisms in circadian genes (CLOCK, NPAS2, ARTNL, PER2 and CRY2), genes of melatonin biosynthesis and signaling (AANAT and MTNR1B) and development of breast cancer in which detailed information about shift work was documented from 857 breast cancer cases and 892 controls. In the participants with the rs8150 polymorphism from AANAT gene, as well as for the rs10462028 polymorphism from the CLOCK gene, an increased frequency of breast cancer was observed, while a lower risk was observed for the rs3816358 from ARNTL gene. In a two-way interaction analysis, interactions between shift work and CLOCK genes were observed. Furthermore, gene shift interactions for MTNR1B with NPAS2 and ARNTL were detected [28].

French scientists found 577 SNPs (Single Nucleotide Polymorphisms) in 23 circadian clock genes associated with breast cancer risk in a French population of 1232 women with breast cancer, in comparison to 1317 subject controls. The results of the study showed that among postmenopausal women, breast cancer was associated with CLOCK and RORA, but only the association with CLOCK gene remained statistically significant. The strongest associations with postmenopausal breast cancer were observed for rs11932595 in CLOCK and rs1482057 in RORA. When it comes to premenopausal breast cancer, no such associations were observed [29].

When it comes to BMAL1, studies have shown that this circadian gene has a cancer-promoting effect in breast cancer [30]. Further study found more about the molecular

mechanism of BMAL1. Overexpression of this circadian gene significantly increased the mRNA and protein level of matrix metalloproteinase9 (MMP9) and improved its overall activity, that led to increased metastasis and migration of breast cancer cells [31].

According to IARC prostate cancer is the second most common cancer and leading cause of cancer death in men, worldwide.

Numerous studies have proven that circadian clock genes can regulate, modify and suppress tumor growth by controlling DNA replication, repair mechanisms, cell proliferation and apoptosis [32]. Contrastingly, mutations of these genes can lead to disruption of circadian rhythm and result in accelerated neoplastic growth.

A limited number of existing studies have showed association between several circadian genes and prostate cancer regulation; BMAL1, CLOCK, CRY1-2, CSNK1e, MTNR1A and MTNR1B, NPAS2, NR1D1, PER1-3, RORA, RORB, and TIMELESS [33][34][35][36].

One of the earliest epidemiological studies evaluating the link between prostate cancer and clock genes' SNPs was carried out by Chu et al. [37] Authors examined the relationships between five variants of five circadian genes and prostate cancer risk in a based case–control study in China. The study was conducted on 187 cases and 242 control subjects The SNPs included CRY2 rs1401417, CSNK1E rs1005473, NPAS2 rs2305160, and PER1 rs2585405 and PER3 54-bp. They found that men with the CRY2-variant C allele had a significant 1.7-fold increased risk for prostate cancer as compared with those with the GG genotype, this risk was also more substantial for men who also had a greater IR. The men with greater IR and with the variant alleles of PER3 or CSNK1E likewise had higher prostate cancer risk in comparison to those with reduced IR. Moreover, the A allele from NPAS2 polymorphism was associated with reduced prostate cancer risk among men with less IR compared to GG genotype.

Another study evaluated the link between circadian clock related genes with prostate tumors in Caucasian men population included 1,308 cases and 1,266 control subjects. In this study, 41 variants in 10 genes related with circadian clock were genotyped. Three of the investigated genes: ARNTL, CSNK1E, and NPAS2, were significantly associated with higher prostate cancer risk. They also observed that the estimate risk for variants rs885747 and rs2289591 in PER1, rs1012477 in PER3, and rs11133373 in CLOCK notably changed dependence on cancer aggressiveness [34].

The studies carried out in two populations from Seattle and Sweden, respectively, examined 937 polymorphisms in 156 genes in 1,309 men with prostate cancer in a Seattle cohort. 22

variants associated with prostate cancer-specific mortality (PCSM) were identified and validated with the Swedish cohort, which included 2,875 patients. The results showed that five polymorphisms, out of the 22 SNPs identified in the Seattle cohort, were found to be significantly associated with lethal prostate cancer. One each in the LEPR, CRY1, RNASEL, IL4, and ARVCF genes. With a statistical significance variant in the CRY1 gene (rs10778534) [38].

Markt et al. [39] tested 96 variants in 12 circadian-related genes using 3 patient cohorts (24, 40, and 105 cases/respectively). The relevance with lower levels of melatonin was also analyzed by measuring the level of 6-sulfatoxymelatonin. The results showed that none of the individual polymorphism were consistently associated with fatal prostate cancer across the three cohorts. However, within the individual cohorts, significant association between two SNPs in CRY1, rs7297614 and rs1921126 and risk of fatal disease were found. Authors also found thirteen different individual SNPs in four genes (TIMELESS, PER3, NPAS2, CSNK1E), which were associated with 6-sulfatoxymelatonin.

Recent study performed an analysis to detect association of the diversity in circadian clock genes and risk of prostate cancer [33]. The authors used previously published meta-analysis/data regarding prostate cancer [40] and found a highly significant statistical association between circadian pathway genetic variation and susceptibility to prostate cancer. The 17 SNPs located in seven genes were analyzed. The most significant gene and its SNP were ARNTL and ARNTL rs142435152, respectively. The analysis of subgroups showed the risk of aggressive prostate cancer was also highly associated with circadian clock genes variation. Where the most significant gene was RORA with the rs17191414 SNP, among the 28 SNP's found/ located on seven genes.

Together, these findings emphasize the significant role of clock genes in breast and prostate cancer pathogenesis.

2.2 Disrupted Circadian Rhythms and Cancer

Disrupted circadian rhythms have been documented to be a potential risk factor for cancer development in a great amount of scientific literature. Among all modern disruptors of circadian rhythms, artificial light at night (ALAN) and its influence on carcinogenesis have been of popular interest because of its rapidly growing worldwide presence [41][42][43]. Due to different light intensity and wavelength, exposure to ALAN may affect human health by

reducing the production and secretion of pineal melatonin, which is a hormone normally produced in the dark phase of the 24-hour cycle [8] [44].

Shift work is a cause of numerous circadian rhythm disturbances such as sleep deprivation, social jet lag, meal skipping and ALAN exposure. This makes it difficult to analyze the disruptive aspects of shiftwork that lead to increased cancer incidence. However, the results of these studies can provide data on how cancer risk may grow because of the circadian rhythm disruption, which is a result of shiftwork and the consequence of exposure to artificial light at night.

One of the first studies investigating breast cancer incidence and shiftwork was carried out in the female telegraph workers population from Norway. The authors observed an increased odds ratio, but after correction for the duration of employment, it did not remain statistically significant [45]. Another study conducted on Norway population revealed a significantly increased risk of breast cancer in women who worked mainly (>60%) night-shift jobs for more than half of the year [46] Furthermore, a US case-control study on female-shift workers reported that any earlier history of shift work was associated with increased risk for breast cancer, and with increased years of shift work this risk worsened. The researchers also suggested that among subjects who reported not sleeping during the period of the night, when nocturnal melatonin levels are typically at their highest, had an increased risk of breast cancer [47].

MCC-Spain Study is a population based multi-case–control study which assessed five types of cancer (colorectal, stomach, chronic lymphocytic leukemia, prostate, and breast). The study was conducted on 1708 incident breast cancer cases and 1778 population controls [48]. Having ever performed night work, either in a permanent or rotating schedule, in a variety of occupations, was associated with an insignificant increase of breast cancer risk. Nevertheless, authors found an indication of a possible connection between night shiftwork and hormone related parameters. The risk of breast cancer was higher in the presence of estrogen and progesterone receptors (ER and PR), especially among premenopausal women. Also, the risk for invasive, lobular, and anaplastic tumors was found to be higher among examined women.

Several satellite imaging studies have revealed an association between breast cancer and ALAN exposure. Two studies carried out in Israel reported that urban environmental ALAN was associated with an increased breast cancer risk development [49][50].

Further study showed that Georgian women exposed to high levels of LAN (>41 watts per steradian cm2) have an increased risk of breast cancer in comparison to women exposed to low levels of ALAN (0–20 watts per steradian cm2). What is more, ALAN exposure was

associated with increased breast cancer risk among white women, but not among black [51]. Also, the study conducted on Californian teachers showed increased risk of breast cancer in areas with the highest quintile of outdoor light-at-night exposure [12] In 2010 Kloog et al. [52] using the GLOBOCAN 2002 database conducted a significant relationship between environmental ALAN levels and risk of breast cancer. Another group conducted a follow-up study 5 years later that identified a non-significant and weakened relationship between ALAN and breast cancer [53].

The latest meta-analysis examined 14 studies, comprising four cohorts, nine case-control and one case-referent study of female subjects across seven countries, indicating that outdoor and indoor ALAN exposure was consistently associated with higher breast cancer risk [54].

The majority of studies are analyzing the association between ALAN and risk of cancer development, focusing mainly on breast cancer but the incidence rates of other cancers have also been examined. One previously discussed study did not observe an association between ALAN levels and risk of lung cancer among women [50]. Using global satellite ALAN analysis, another group found a correlation between ALAN and increased prostate, but not lung or colon, cancer risk in male population [55].

Moreover, the analysis of ALAN levels in 164 countries yielded a risk of prostate cancer in the highest ALAN-exposed countries 110% higher than in the lowest ALAN-exposed countries.

Papantoniou et al. [56] carried out a study on Spanish men population which included 1,095 prostate cancer cases and 1,388 randomly selected population controls. Detailed information on shift schedules, consisting of permanent vs. rotating, time schedules, duration, frequency was collected. The results showed that men who had been working for at least one year in night shift work had a slightly higher prostate cancer risk, compared with those who had never worked at night. That possibility increased with longer exposure. Furthermore, the risk was more pronounced for high-risk tumors, especially among subjects with longer duration of exposure to ALAN.

Another Spanish study, which registered 1,219 breast cancer cases, 1,385 female controls, 623 prostate cancer cases, and 879 male controls, analyzed satellite ALAN data and reported a significant correlation between outdoor blue light spectrum at night and breast and prostate cancer incidence. What is more, the study showed an association between bedroom lightening levels and risk of cancer. Women, who slept in “quite illuminated” bedrooms had slightly lower risk of breast cancer; contrastingly men who slept in bedrooms with higher levels of light had higher risk of prostate cancer [13].

Conclusions:

Together, these findings support an assumption that breast and prostate cancer incidence is a consequence of ALAN exposure and other circadian rhythm disruptors. Further studies should clarify the relationship between ALAN exposure and other types of cancer. Besides, ALAN exposure levels should be measured more precisely than by satellite pictures analysis to reliably conduct studies proving relation between ALAN exposure and risk of cancer development.

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