Medical Hypotheses 75 (2010) 305–311

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Are some melanomas caused by artificial light?

Marina Kvaskoff [a,b], Philip Weinstein [c,*]

[a] Inserm, CESP Centre for Research in Epidemiology and Population Health, U1018, Nutrition, Hormones and Women's Health Team, Institut Gustave Roussy, F-94805, Villejuif, France
[b] Université Paris Sud 11, UMRS 1018, F-94805, Villejuif, France
[c] University of Queensland, School of Population Health, Herston Road, Herston, QLD 4072, Brisbane, Australia

ARTICLE INFO

Article history:
Received 2 March 2010
Accepted 7 March 2010

SUMMARY

The incidence rate of cutaneous melanoma has been increasing faster than that of any other cancer in white-skinned populations over the past decades. The main risk factors for melanoma (i.e. exposure to sunlight, naevus count, phototype, and family history of melanoma) may not wholly explain the epidemiological trends observed for this cancer. The light-at-night theory postulates that increasing use of artificial light-at-night may contribute to the increasing breast cancer incidence through suppressed secretion of melatonin (a hormone produced in the dark and inhibited by light, which regulates circadian rhythms). Here, we postulate that this theory may also apply to melanoma and that it may explain a part of this cancer burden.

Consistent with our hypothesis is evidence from experimental studies suggesting a lightening effect of melatonin on frog skin and mammal hair during seasonal changes, its antioxidant and anti-carcinogenic effects in skin melanocytes, as well as the expression of melatonin receptors in melanocytes. Also, epidemiological data suggest lower melatonin concentrations in melanoma patients compared with controls; a potential therapeutic effect of melatonin in patients with metastatic disease; a higher prevalence of melanoma in pilots and aircrews, with increased risks with higher time zones travelled; and increased melanoma risks in office workers exposed to fluorescent lighting. Moreover, melanoma incidence and seasonal patterns are consistent with a reduction of melatonin secretion with intensity of exposure to light, although it remains difficult to distinguish the effect of melatonin disruption from that of sun exposure on the basis of ecological studies. Finally, the reported associations between hormonal factors and melanoma are consistent with melatonin inhibition increasing the risk of melanoma by increasing circulating oestrogen levels.

Despite the existing suggestive evidence, the light-at-night hypothesis has never been directly tested for melanoma. Very few studies examined the potential associations between melanoma risk and shift work or melatonin concentrations, and we found no studies reporting on the relationship between melanoma and number of sleeping hours, use of melatonin supplements, blindness, night-time city light levels, bedroom light levels, or clock genes polymorphisms. Therefore, since several observations support our hypothesis and very little research has been undertaken on this subject, we strongly encourage analytic epidemiological studies to test the light-at-night theory for melanoma causation.

Introduction

Cutaneous melanoma is a potentially lethal neoplasm with an incidence rate that has been increasing considerably worldwide in white-skinned populations over the past decades [1]. This incidence rate has risen more rapidly than that of any other cancer, with several authors referring to these trends as the "melanoma epidemic" [2]. Several risk factors for melanoma have been clearly established, such as exposure to ultraviolet radiation (UVR) [3]; phenotypic factors such as naevus count, freckling, and phototype; and familial history of the disease [4,5]. However, these factors altogether may not wholly explain the epidemiological trends observed for this cancer, and it is essential to determine which other aspects may also play a role in the melanoma burden.

Melatonin is a pineal hormone with circadian production rhythm: secretion is maximal in the dark, and is inhibited by retinal exposure to light [6]. After its discovery by Lerner et al. in 1958 [7], melatonin has been shown to be involved in several biological processes, such as circadian and seasonal biorhythms, and sleep initiation. More recently, it has been shown that melatonin is also synthesized and metabolized locally at extrapineal sites, such as the skin [8]. Melatonin has also proven an efficient antioxidant and anti-carcinogenic agent in experimental studies; in the skin, this hormone was shown to exhibit anti-tumour and growth-suppressive effects, and to effectively reduce damage from exposure to UVR [8–10].

* Corresponding author. Tel.: +61 7 3365 5345.
E-mail address: p.weinstein@sph.uq.edu.au (P. Weinstein).

0306-9877/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2010.03.010

In 1978, Cohen et al. postulated that reduced function of the pineal gland might lead to the development of breast cancer, mainly on the grounds that, because of the inhibitory effect of melatonin on oestrogens, melatonin suppression could lead to increased oestrogen production and thus increased breast cancer [11].

Later, in 1987, Stevens proposed the Light-At-Night (LAN) theory, which postulates that the increasing use of artificial light-at-night, paralleling industrialization, may explain a part of the increasing breast cancer incidence by inhibiting melatonin secretion [12]. Suggestive evidence has then consistently accumulated in favour of this hypothesis: several studies reported a positive association between night-shift work and breast cancer risk; totally blind women have been shown to be at increased risk for breast cancer compared to normally sighted women; a modest inverse association has been reported between sleep duration and breast cancer risk; an increased breast cancer risk was reported in relation to increased bedroom light level at night; indigenous populations living at extreme northern latitudes were generally shown to be at decreased breast cancer risk; breast cancer incidence has been shown to be higher in communities with higher levels of night-time lighting; and rodent models confirmed antitumorigenic effects of melatonin, and its inhibition by exposure to light [13]. Recently, higher urinary melatonin levels were found to be associated with a lower risk of breast cancer in postmenopausal women [14], and particular clock genes polymorphisms were associated with breast cancer risk [15].

Recent evidence also suggests that the LAN theory may be applicable for other neoplasms such as prostate cancer [16–21], endometrial cancer [22–24], and possibly colon cancer [25]. However, while the interaction between melatonin and skin is well established, the LAN theory has never been put forward to explain epidemiological trends for cutaneous melanoma. Here, we present the hypothesis that the increase in melanoma incidence over the past decades may be explained in part by the increasing use of artificial light, and we review and discuss supporting evidence from the existing literature.

The hypothesis

Since melatonin plays significant antioxidant and anti-carcinogenic roles in melanocytes (the skin cells from which melanomas arise) and considering that melatonin secretion is inhibited by the use of artificial light-at-night through a disruption of the circadian rhythm, we speculate that use of artificial light-at-night may increase the risk of melanoma by inducing loss of the cancer-preventive effects of melatonin. Alternatively, melatonin suppression may imply an imbalance in immune or hormonal regulation of melanocytes, which may then lose some of their ability to provide efficient defence against carcinogenic agents (such as UVR). This hypothesis predicts that factors related to hampered melatonin synthesis will be associated with an increased risk of melanoma, while factors promoting melatonin synthesis should be associated with decreased melanoma risk. Fig. 1 summarises our hypothesis.

Supporting evidence

Experimental studies

Over the past 60 years, there has been increasing evidence suggesting that melatonin is synthesized not only by the pineal gland, but also at other sites such as the skin [8,26], where it plays an important role in regulation of skin function and structure in response to different threats from the environment [8,10]. Melatonin has also been shown to exhibit an important role in skin pigmentation and hair development: historically, melatonin was discovered because of its lightening effects on skin pigmentation in frogs [6], and this hormone was also shown to inhibit melanin production during seasonal coat colour changes in mammals, and to stimulate hair growth in animals as well as humans [8,9]. Indeed, melanocytes, which are the target cells involved in both melanin production (and thus skin and hair colour changes) and melanoma initiation, are controlled by melanocyte-stimulating hormones (MSH) [27], and melatonin has been suggested to reverse the skin's darkening response to α-MSH [28].

Importantly, it has been shown that melatonin receptors were expressed both in normal and malignant melanocytes, and that expression may be altered by various environmental stimuli such as UVR [29,30]. Moreover, as a potent free radical scavenger, melatonin has been demonstrated to exert an anti-oxidative role in the skin, and to exhibit anti-apoptotic and anti-carcinogenic properties [30]. Melatonin has also been shown to efficiently prevent and reduce UVR-induced skin damage [8,10].

Interestingly, several experimental studies suggested that melatonin exerts oncostatic effects on melanoma tumour cells, suggesting a slowing effect on melanoma progression. First, a link between the pineal gland and the growth and spread of melanoma has been hypothesised after the demonstration that pinealectomy resulted in increased growth of melanoma and more frequent local and distant metastases in hamsters [31–33]. Second, administration of melatonin was demonstrated to cancel melanoma growth in pinealectomized hamsters, although there was no effect of melatonin intake on tumour growth in intact animals [34]. Besides, oral administration of melatonin was associated with decreased melanoma growth and reduced gonadal and adrenal masses in athymic mice [35]. A later study provided evidence of a differential effect of melatonin in melanoma cells according to melatonin concentration: at low-concentration, physiological levels, melatonin inhibited cell proliferation, whereas at high-concentration, pharmacological levels, melatonin either had no effect or actually stimulated proliferation of melanoma cells [36]. The stimulatory effect of pharmacological levels of melatonin on melanoma cell proliferation has been confirmed in a later study, although no protective effect was observed at physiological levels [37]. However, nocturnal melatonin administration has been shown to enhance survival from melanoma in mice under light–dark conditions, whereas it increased melanoma progression in mice submitted to continuous light exposure [38], suggesting that melatonin effects may be differential according to photoperiod and time.

Epidemiological studies

Melatonin and melanoma

We found only two studies reporting on the relationship between melatonin levels and melanoma risk in humans. First, a case-control study showed that urine levels of 6-oxymelatonin decreased with age in men, and also in women who were not in the ovulatory phase of their menstrual cycle [39]; the authors also demonstrated that melanoma patients had significantly lower urine melatonin levels compared with healthy controls (except in women in the ovulatory phase of their menstrual cycle). Another study described lower 24-h urine melatonin levels in patients with skin cancer compared with controls [40], although the number of melanoma cases was very low. The results of both studies are consistent with the LAN hypothesis for melanoma, but neither paper describes LAN as a possible reason for the findings. Although experimental studies show higher tumour proliferation in melanoma cells or animals administered with pharmacological doses of melatonin [36,37], phase II studies suggest that melatonin may be effective in the treatment of melanoma. Indeed, melatonin as an

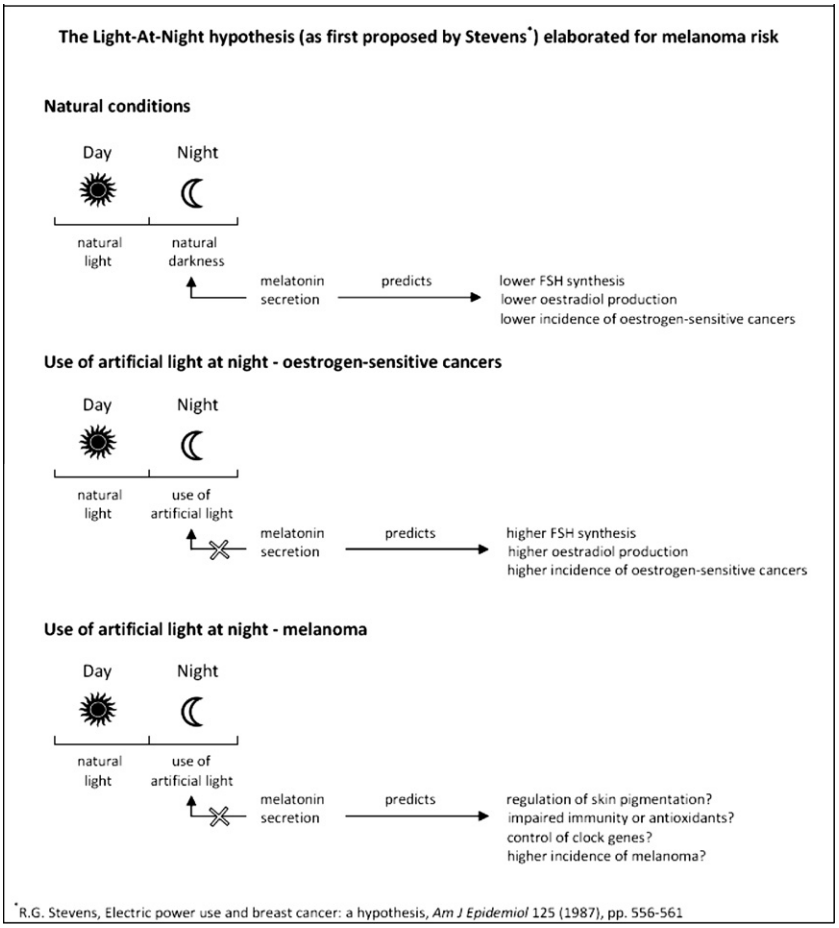

Fig. 1. Summary diagram of the light-at-night hypothesis.

adjuvant has been suggested to be an efficient therapeutic agent in the treatment of metastatic melanoma [41–44].

Melanoma and occupation

Past studies of melanoma in relation to occupation have generally suggested higher risks among professions associated with a high socio-economic status [45]. Among those, one particular occupational category is that of commercial pilots and aircrews, which has been consistently associated with higher-than-expected risks of melanoma according to a recent review [46]. UVR exposure at high altitudes during flights has been shown to be negligible and was thus excluded as a potential risk factor; instead, it has been hypothesized that these higher rates could be due to excessive sun exposure during holidays and breaks between flights. However, a retrospective cohort study showed an increased risk of melanoma in commercial airline pilots, with an even higher risk in pilots who have been travelling over five time zones [47], and the authors hinted a potential importance of shift work and circadian disrhythmia in melanoma, consistent with the LAN hypothesis. Further, a subsequent study from the same group showed no significant difference in host or sunlight-related factors between pilots/aircrew and a random sample from the general population, suggesting that the increased melanoma risk among this occupational category cannot be only explained by intense intermittent sun exposure [48]. A potential role of cosmic radiation has also been suggested; indeed, airline pilots and crews are exposed to this type of radiation, and higher risks of melanoma were found with increasing time since employment [46]. It is still unclear whether increased melanoma rates in pilots/aircrew are mostly explained through circadian rhythm disruption, exposure to cosmic radiations, or both. However, two recent reviews suggested a potentially important role of irregular sleeping hours and disturbance in circadian rhythms in melanoma through inhibition of melatonin secretion [46,49].

Because shift work has been associated with higher incidence of several cancers, it has recently been classified by the International Agency for Research on Cancer as probably carcinogenic to humans [50]. Rotating night-shift work has been demonstrated to be associated with a reduction of urinary melatonin levels, and long-term shift work has been correlated with increased oestradiol concentrations in postmenopausal women [51], which could explain the relationships previously described between shift work and breast cancer. If the LAN theory was applicable for melanoma, it would predict a positive association between melanoma and night-shift work. An exploration of this association has been largely overlooked in previous research: the only available published study reports no significant association in a Swedish retrospective cohort [52].

Interestingly, two studies reported higher melanoma risks in office workers, but not in other indoor workers [53,54], a result first attributed to intense intermittent sun exposure during leisure activities. A single study also suggested an association between fluorescent light exposure and melanoma risk in office workers compared to other indoor workers, with a dose–response relationship with intensity of fluorescent light [55]. Fluorescent lighting used in offices is typically cool-temperature, white light, which has been suggested to more strongly suppress nocturnal melatonin secretion than warm-temperature, yellowish light [56]. The

previously observed relationship between fluorescent light and melanoma would thus be consistent with deeper melatonin disruption in office workers; however, these results have not been replicated ever since, and a spurious association could not be ruled out.

Melanoma incidence worldwide

Since exposure to sunlight is a major risk factor for melanoma, and considering the combined effects of sun exposure and phototype on melanoma risk, it is particularly difficult to assess the potential associations between melanoma incidence and melatonin suppression through increased exposure to light on the basis of descriptive incidence studies.

However, it is interesting to note that the incidence of melanoma has increased considerably worldwide over the past decades [1], and has increased faster than that of any other cancer [2], paralleling both (i) increased leisure time, skimpier clothing and the pursuit of tanning, and (ii) increasing industrialization, city lights, and shift work. Fig. 2 illustrates the increase in age-adjusted melanoma incidence rates paralleling that of electric power use (as an indicator of artificial light use) in the US over the past decades.

Also, if the LAN hypothesis were true for melanoma, a higher melanoma incidence would be expected in areas of bright light, since melatonin secretion is more strongly suppressed by intense light [57]. Such an association holds true for white-skinned populations living in low-latitude areas with intense sunlight (and high ambient UVR levels), such as Australia and the US, where melanoma incidence has been shown to increase with increasing latitude [1]. Thus, it is possible that the effect of melatonin suppression on melanoma incidence parallels that of exposure to UVR, although it appears complex to assess the importance of intensity of melatonin inhibition over that of UVR exposure. The trend is less clear in Western Europe, where a parabolic relationship has been observed: melanoma incidence decreases from North to South until latitude 52°N, and then increases with decreasing latitude [58]; however, this pattern has been attributed to the wide range of skin complexion in this area, as well as a higher opportunity for recreational sun exposure during holidays overseas [59].

The corollary of the LAN hypothesis [60] would predict that melanoma incidence is minimal at high northern latitude areas involving long winter darkness periods, and thus hypersecretion of melatonin. Consistent with this prediction, lower risks of melanoma are observed in indigenous populations of the Artic circle compared to non-indigenous populations living around the same areas (Inuits over the period 1969–1988 [61,62], and in American Indians and indigenous Alaskans over 1969–1987 [63–65]). Melanoma incidence rates have also been shown to be lower in Greenland than in Denmark [66]. However, it is unclear to what extent these observations are also attributable to lower sun exposure and darker skin pigmentation in these populations.

Another interesting observation is the cyclicity of melanoma incidence rates. Some authors have indeed suggested that variations in melanoma rates were associated with heliogeophysical cycles, which could altogether interact with environmental light and melatonin disruption [67]. Also, a seasonal pattern of incidence showing a summer peak of melanoma occurrence and diagnosis was first hinted at in the 1980s [68], and has since then been consistently confirmed (most recently in Western Europe over 1978–1993 [69], in Australia over 1989–1998 [70], and in the US over 1975–1990 [71]). These patterns were hypothesized to result from easier diagnosis of melanoma in summer, and/or delayed cancer promotion effect of sun exposure. However, these incidence patterns are also consistent with the hypothesis that a reduced melatonin secretion during summer months (with increased number of daylight hours) would promote the development of melanoma.

Melanoma and reproductive and hormonal factors

Melatonin has been suggested to reduce circulating estradiol levels [72], most likely through a down regulation of follicle

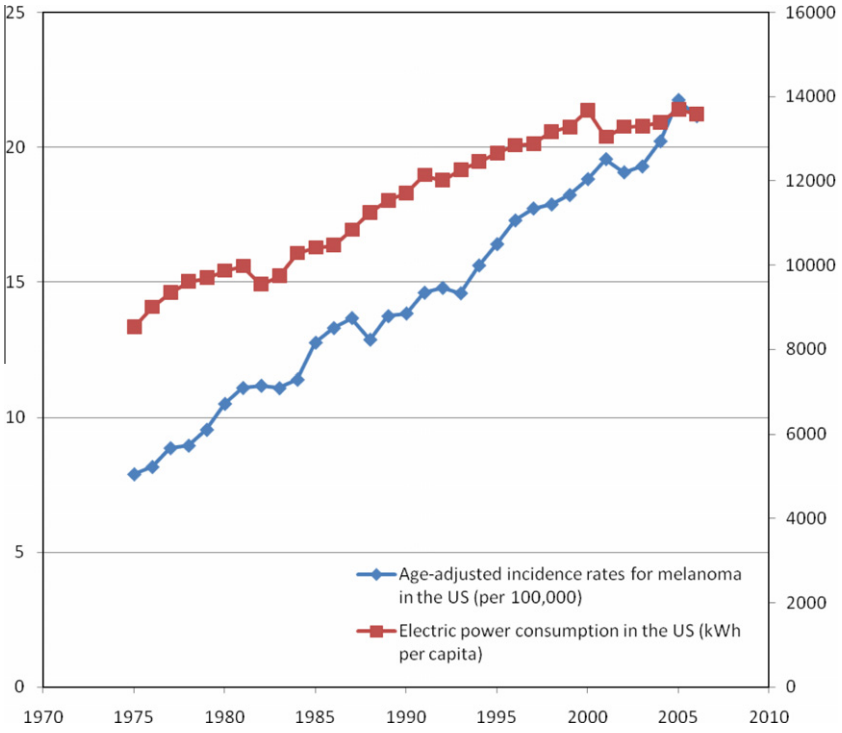

Fig. 2. Age-adjusted incidence rates for melanoma and electric power consumption (as an indicator of exposure to artificial light-at-night) in the US over 1975–2006. Sources: Surveillance, Epidemiology and End Results (SEER), Cancer Statistics Review 1975–2006, National Cancer Institute; Annual electric power consumption indicator, The World Bank.

stimulating hormone (FSH) [73]. Therefore, it has been hypothesized that melatonin inhibition may result in higher levels of endogenous hormones, thereby increasing the risk of hormone-dependent cancers such as breast cancer [74].

Several observations have led to the hypothesis of a hormonal dependence of melanoma, such as the higher prevalence of the disease in women in Europe [1], the better survival and prognosis in women worldwide [75], the occurrence of melasma subsequent to hormonal exposure [76], or colour changes of pigmented lesions during pregnancy [77]. Epidemiological studies suggested an inverse relationship between parity and melanoma risk [78–81], age at first live birth [79,80,82], and a positive relationship has been reported between melanoma and use of oral contraceptives or hormonal replacement therapy [83]. Globally however, previously published results are less clear than are those for breast cancer. Together, these findings are consistent with a decreased risk of melanoma with decreased exposure to sex hormones, and are compatible with the hypothesis that melatonin suppression increases melanoma risk through increased exposure to estradiol.

Discussion

Overall, the evidence reviewed above provides some support to the LAN hypothesis for increased melanoma risk. First, experimental studies show that melatonin is synthesised locally in the skin, where it plays important roles in skin function, structure, and the skin's response to environmental stressors such as UVR. Melatonin receptors are expressed in melanocytes, where this hormone has been shown to exert anti-cancer properties, and melatonin has also been shown to have oncostatic effects on melanoma cells. Second, epidemiological studies have suggested lower melatonin concentrations in melanoma patients compared with controls, and a potential therapeutic effect of melatonin on advanced disease. Further, studies that include occupational data report higher melanoma risks in pilots and aircrews who experience circadian rhythms disruption, as well as in office workers who are highly exposed to out-of-phase fluorescent lighting. Additionally, incidence patterns of melanoma are compatible with the LAN hypothesis: the increasing incidence over past decades parallels industrialization; consistent with greater melatonin inhibition occurring with more intense light, melanoma incidence is inversely correlated with latitude in Australia, the US and Eastern Europe; and incidence is lower in native populations in the Arctic region. The frequency of melanoma diagnosis is also maximal in summer when daylight hours are extended. Finally, published data support a potential association between hormonal factors and melanoma, consistent with an increased melanoma risk through melatonin inhibition of oestradiol.

Exposure to sunlight is one of the main risk factors for melanoma, and considering the relationship between melatonin and light intensity, it would be challenging to distinguish the carcinogenic effect of melatonin disruption from that of UVR in the skin using epidemiological tools. The LAN hypothesis for melanoma could be tested in several other ways, however. Unfortunately, too few studies assessed the potential relationships between melanoma risk and either circulating melatonin levels or shift work, so definitive testing of the LAN hypothesis for melanoma has not been possible with existing data. The LAN hypothesis also predicts other testable observations that, to our knowledge, have not yet been investigated.

First, according to the LAN hypothesis, one would expect that blind individuals would be at decreased risk of melanoma, since melatonin secretion depends upon the alternating dark–light cycle that is entrained via the retina and retino-hypothalamic pathways. Authors have shown that women with deep bilateral blindness were at decreased risk of breast cancer compared to normal sighted women [84], which was also observed, albeit less clearly, with prostate cancer in men [20]. Both findings support the LAN hypothesis for these cancers. In a Swedish cohort examining the relationship between cancer and blindness, cancer incidence was significantly lower in totally blind people, while it was marginally significantly lower in severely visually impaired people [85]. In that study, the number of skin cancer cases was too low to estimate a potential risk reduction; however, the standardized incidence ratio was 0.51. We found no published data on melanoma prevalence in the visually impaired. However, in the case of melanoma, a lower prevalence among the blind could also reflect lower levels of sun exposure in such individuals.

Other predictions of the LAN hypothesis include a decreased melanoma risk associated with longer sleep duration (and thus extended dark period), and lower bedroom light levels as well as community night-time lighting. To our knowledge, none of these factors have been studied in relation to melanoma.

Several clock genes have been identified and implicated in the regulation of circadian rhythms: *CLOCK* (circadian locomotor output cycles kaput homolog); *PER1*, *PER2* and *PER3* (period 1, 2 and 3); *CRY1* and *CRY2* (cryptochrome 1 and 2); *TIM* (timeless homolog); *CK1* (casein kinase 1); and *BMAL1* (brain and muscle Arnt-like protein-1). Mutations in these genes have been shown to disrupt circadian rhythms in animal models, and were associated with sleep timing preference as well as psychiatric, mood, and metabolic disorders in humans [86]. Mutations and polymorphisms in clock genes have been associated with lymphoma and breast, colon and prostate cancers, and overexpression of *PER1* and *PER2* has been associated with inhibition of tumour proliferation [15]. Studies have shown that *CLOCK*, *TIM*, *PER1*, *CRY1*, and *BMAL1* were expressed in human skin, and a rhythmic expression according to the time of the day has been reported for some of these genes [87,88]. However, the potential associations between melanoma and clock genes polymorphisms remain completely unstudied to date.

Another interesting potential association to be tested is that between melanoma risk and the use of melatonin supplements. These supplements are indeed available without prescription in several countries such as the US, and are usually taken in the treatment of indications such as sleep disorders and jetlag [89]. In countries like the UK, where melatonin supplements are available on prescription only and on a named patient basis [89], a data linkage could be performed between physician prescriber databases and cancer registries to assess this relationship.

In conclusion, some evidence supports our suggestion that the LAN hypothesis may apply to melanoma. The hypothesis could be further tested in future studies by exploring the relationship between melanoma risk and melatonin concentrations, use of melatonin supplements, shift work, clock genes polymorphisms, blindness, bedroom and community night-time light levels, and sleep duration. Ideally, these relationships should be analysed in prospective studies allowing for adjustment for potential confounders such as host factors. There is a need for studies assessing occupational exposures associated with biological measures for melatonin to elucidate the relationship between this hormone, use of artificial light-at-night, and the risk of melanoma. The LAN hypothesis could also be tested in relation to other cancers that have not yet been studied for such associations. If the LAN hypothesis for melanoma were confirmed, it would improve our knowledge of causation and therefore also position researchers to develop novel treatment strategies for this cancer. In the long run, if the LAN theory is confirmed for melanoma and other cancer types, it may encourage the development of strategies to prevent melatonin suppression. Such strategies may include the use of dimmer artificial light [84], or the use of amber glasses when working under electric light-at-night [90].

Conflict of interest

None declared.

Funding source

Dr. Kvaskoff is supported by a *Fondation de France* postdoctoral fellowship.

Acknowledgements

The authors wish to thank Dr David Whiteman for his useful comments during the preparation of the manuscript.

References

[1] IARC, Cancer incidence in five continents, vol. IX. IARC Sci Publ; 2008. p. 1–837.
[2] Beddingfield 3rd FC. The melanoma epidemic: res ipsa loquitur. Oncologist 2003;8:459–65.
[3] Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005;41:45–60.
[4] Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer 2005;41:28–44.
[5] Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer 2005;41:2040–59.
[6] Cohn BA. Melatonin and the skin: from frog to human. Int J Dermatol 1996;35:695–7.
[7] Lerner AB, Case JD, Takahashi Y, Lee TH. Isolation of melatonin, the pineal gland factor that lightens melanocytes. J Am Chem Soc 1958;50:2587.
[8] Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. Melatonin in the skin: synthesis, metabolism and functions. Trends Endocrinol Metab 2008;19:17–24.
[9] Fischer TW, Slominski A, Tobin DJ, Paus R. Melatonin and the hair follicle. J Pineal Res 2008;44:1–15.
[10] Fischer TW, Slominski A, Zmijewski MA, Reiter RJ, Paus R. Melatonin as a major skin protectant: from free radical scavenging to DNA damage repair. Exp Dermatol 2008;17:713–30.
[11] Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. Lancet 1978;2:814–6.
[12] Stevens RG. Electric power use and breast cancer: a hypothesis. Am J Epidemiol 1987;125:556–61.
[13] Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. Int J Epidemiol 2009;38:963–70.
[14] Schernhammer ES, Hankinson SE. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. Cancer Epidemiol Biomarkers Prev 2009;18:74–9.
[15] Wood PA, Yang X, Hrushesky WJ. Clock genes and cancer. Integr Cancer Ther 2009;8:303–8.
[16] Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology 2007;18:182–3.
[17] Kakizaki M, Inoue K, Kuriyama S, Sone T, Matsuda-Ohmori K, Nakaya N, et al. Sleep duration and the risk of prostate cancer: the Ohsaki Cohort Study. Br J Cancer 2008;99:176–8.
[18] 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;26:108–25.
[19] Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. Am J Epidemiol 2006;164:549–55.
[20] Pukkala E, Ojamo M, Rudanko SL, Stevens RG, Verkasalo PK. Does incidence of breast cancer and prostate cancer decrease with increasing degree of visual impairment. Cancer Causes Control 2006;17:573–6.
[21] Zhu Y, Zheng T, Stevens RG, Zhang Y, Boyle P. Does "clock" matter in prostate cancer? Cancer Epidemiol Biomarkers Prev 2006;15:3–5.
[22] Grin W, Grunberger W. A significant correlation between melatonin deficiency and endometrial cancer. Gynecol Obstet Invest 1998;45:62–5.
[23] Viswanathan AN, Hankinson SE, Schernhammer ES. Night shift work and the risk of endometrial cancer. Cancer Res 2007;67:10618–22.
[24] Viswanathan AN, Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. Cancer Lett 2009;281:1–7.
[25] Schernhammer ES, Laden F, Speizer FE, Willett WC, Hunter DJ, Kawachi I, et al. Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst 2003;95:825–8.
[26] Slominski A, Fischer TW, Zmijewski MA, Wortsman J, Semak I, Zbytek B, et al. On the role of melatonin in skin physiology and pathology. Endocrine 2005;27:137–48.
[27] Fitzpatrick TB, Wolff K. Fitzpatrick's dermatology in general medicine. New York: McGraw-Hill; 2008.
[28] Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev 2004;84:1155–228.
[29] Pandi-Perumal SR, Trakht I, Srinivasan V, Spence DW, Maestroni GJ, Zisapel N, et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol 2008;85:335–53.
[30] Slominski A, Wortsman J, Tobin DJ. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. FASEB J 2005;19:176–94.
[31] Aubert C, Prade M, Bohuon C. Effect of pinealectomy on the melanic tumours of the golden hamster induced by administration (per os) of a single dose of 9,10-dimethyl-1,2-benzanthracene. C R Acad Sci Hebd Seances Acad Sci D 1970;271:2465–8.
[32] Das Gupta TK. Influence of the pineal gland on the growth and spread of malignant tumors. Surg Forum 1968;19:83–4.
[33] Das Gupta TK, Terz J. Influence of pineal gland on the growth and spread of melanoma in the hamster. Cancer Res 1967;27:1306–11.
[34] El-Domeiri AA, Das Gupta TK. The influence of pineal ablation and administration of melatonin on growth and spread of hamster melanoma. J Surg Oncol 1976;8:197–205.
[35] Narita T, Kudo H. Effect of melatonin on B16 melanoma growth in athymic mice. Cancer Res 1985;45:4175–7.
[36] Slominski A, Pruski D. Melatonin inhibits proliferation and melanogenesis in rodent melanoma cells. Exp Cell Res 1993;206:189–94.
[37] Izykowska I, Gebarowska E, Cegielski M, Podhorska-Okolow M, Piotrowska A, Zabel M, et al. Effect of melatonin on melanoma cells subjected to UVA and UVB radiation in in vitro studies. In Vivo 2009;23:733–8.
[38] Otalora BB, Madrid JA, Alvarez N, Vicente V, Rol MA. Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. J Pineal Res 2008;44:307–15.
[39] Grinevich YA, Labunetz IF. Melatonin, thymic serum factor, and cortisol levels in healthy subjects of different age and patients with skin melanoma. J Pineal Res 1986;3:263–75.
[40] Ghaderi R, Sehatbakhsh S, Zardast M, Sharifzade G, Amini A. The relationship between skin cancers and 24-hour urine melatonin level. J Invest Dermatol 2009;129:#455.
[41] Gonzalez R, Sanchez A, Ferguson JA, Balmer C, Daniel C, Cohn A, et al. Melatonin therapy of advanced human malignant melanoma. Melanoma Res 1991;1:237–43.
[42] Lissoni P, Brivio O, Brivio F, Barni S, Tancini G, Crippa D, et al. Adjuvant therapy with the pineal hormone melatonin in patients with lymph node relapse due to malignant melanoma. J Pineal Res 1996;21:239–42.
[43] Lissoni P, Paolorossi F, Tancini G, Ardizzoia A, Barni S, Brivio F, et al. A phase II study of tamoxifen plus melatonin in metastatic solid tumour patients. Br J Cancer 1996;74:1466–8.
[44] Lissoni P, Vaghi M, Ardizzoia A, Malugani F, Fumagalli E, Bordin V, et al. A phase II study of chemoneuroimmunotherapy with platinum, subcutaneous low-dose interleukin-2 and the pineal neurohormone melatonin (P.I.M.) as a second-line therapy in metastatic melanoma patients progressing on dacarbazine plus interferon-alpha. In Vivo 2002;16:93–6.
[45] MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol 2009;20(Suppl. 6):vi1–7.
[46] Ramirez CC, Federman DG, Kirsner RS. Skin cancer as an occupational disease: the effect of ultraviolet and other forms of radiation. Int J Dermatol 2005;44:95–100.
[47] Rafnsson V, Hrafnkelsson J, Tulinius H. Incidence of cancer among commercial airline pilots. Occup Environ Med 2000;57:175–9.
[48] Rafnsson V, Hrafnkelsson J, Tulinius H, Sigurgeirsson B, Olafsson JH. Risk factors for cutaneous malignant melanoma among aircrews and a random sample of the population. Occup Environ Med 2003;60:815–20.
[49] Buja A, Lange JH, Perissinotto E, Rausa G, Grigoletto F, Canova C, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. Toxicol Ind Health 2005;21:273–82.
[50] Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol 2007;8:1065–6.
[51] Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. Cancer Epidemiol Biomarkers Prev 2004;13:936–43.
[52] Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work Environ Health 2007;33:336–43.
[53] Beral V, Robinson N. The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. Br J Cancer 1981;44:886–91.
[54] Vagero D, Ringback G, Kiviranta H. Melanoma and other tumors of the skin among office, other indoor and outdoor workers in Sweden 1961–1979. Br J Cancer 1986;53:507–12.
[55] Beral V, Evans S, Shaw H, Milton G. Malignant melanoma and exposure to fluorescent lighting at work. Lancet 1982;2:290–3.
[56] Morita T, Tokura H. Effects of lights of different color temperature on the nocturnal changes in core temperature and melatonin in humans. Appl Human Sci 1996;15:243–6.
[57] Trinder J, Armstrong SM, O'Brien C, Luke D, Martin MJ. Inhibition of melatonin secretion onset by low levels of illumination. J Sleep Res 1996;5:77–82.

[58] Armstrong BK. Melanoma of the skin. Br Med Bull 1984;40:346–50.
[59] de Vries E, Boniol M, Dore JF, Coebergh JW. Lower incidence rates but thicker melanomas in Eastern Europe before 1992: a comparison with Western Europe. Eur J Cancer 2004;40:1045–52.
[60] Erren TC, Piekarski C. Does winter darkness in the Artic protect against cancer? The melatonin hypothesis revisited. Med Hypotheses 1999;53:1–5.
[61] Miller AB, Gaudette LA. Cancers of skin, bone, connective tissues, brain, eye, thyroid and other specified and unspecified sites in Inuit. Acta Oncol 1996;35:607–16.
[62] Nielsen NH, Storm HH, Gaudette LA, Lanier AP. Cancer in Circumpolar Inuit 1969–1988, a summary. Acta Oncol 1996;35:621–8.
[63] Lanier AP, Blot WJ, Bender TR, Fraumeni Jr JF. Cancer in Alaskan Indians, Eskimos, and Aleuts. J Natl Cancer Inst 1980;65:1157–9.
[64] Lanier AP, Bulkow LR, Ireland B. Cancer in Alaskan Indians, Eskimos, and Aleuts, 1969–1983: implications for etiology and control. Public Health Rep 1989;104:658–64.
[65] Nutting PA, Freeman WL, Risser DR, Helgerson SD, Paisano R, Hisnanick J, et al. Cancer incidence among American Indians and Alaska Natives, 1980 through 1987. Am J Public Health 1993;83:1589–98.
[66] Kromann NP, Nielsen NH, Hansen JP. Skin cancer in Greenland 1955–1974. J Cancer Res Clin Oncol 1983;105:76–8.
[67] Dimitrov BD, Rachkova MI, Atanassova PA. Cyclic patterns of incidence rate for skin malignant melanoma: association with heliogeophysical activity. J Zhejiang Univ Sci B 2008;9:489–95.
[68] Scotto J, Nam JM. Skin melanoma and seasonal patterns. Am J Epidemiol 1980;111:309–14.
[69] Boniol M, De Vries E, Coebergh JW, Dore JF. Seasonal variation in the occurrence of cutaneous melanoma in Europe: influence of latitude, an analysis using the EUROCARE group of registries. Eur J Cancer 2005;41:126–32.
[70] Boniol M, Armstrong BK, Dore JF. Variation in incidence and fatality of melanoma by season of diagnosis in New South Wales, Australia. Cancer Epidemiol Biomarkers Prev 2006;15:524–6.
[71] Braun MM, Tucker MA, Devesa SS, Hoover RN. Seasonal variation in frequency of diagnosis of cutaneous malignant melanoma. Melanoma Res 1994;4:235–41.
[72] Sanchez-Barcelo EJ, Cos S, Mediavilla D, Martinez-Campa C, Gonzalez A, Alonso-Gonzalez C. Melatonin-estrogen interactions in breast cancer. J Pineal Res 2005;38:217–22.
[73] Damian E, Ianas O, Badescu I, Oprescu M. Anti-LH and FSH activity of melatonin-free pineal extract. Neuroendocrinology 1978;26:325–32.
[74] Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? Br J Cancer 2004;90:941–3.
[75] Scoggins CR, Ross MI, Reintgen DS, Noyes RD, Goydos JS, Beitsch PD, et al. Gender-related differences in outcome for melanoma patients. Ann Surg 2006;243:693–8 (discussion 698–700).
[76] Resnik S. Melasma induced by oral contraceptive drugs. JAMA 1967;199:601–5.
[77] Driscoll MS, Grant-Kels JM. Hormones, nevi, and melanoma: an approach to the patient. J Am Acad Dermatol 2007;57:919–31 (quiz 932–916).
[78] Kvale G, Heuch I, Nilssen S. Parity in relation to mortality and cancer incidence: a prospective study of Norwegian women. Int J Epidemiol 1994;23:691–9.
[79] Lambe M, Thorn M, Sparen P, Bergstrom R, Adami HO. Malignant melanoma: reduced risk associated with early childbearing and multiparity. Melanoma Res 1996;6:147–53.
[80] Neale RE, Darlington S, Murphy MF, Silcocks PB, Purdie DM, Talback M. The effects of twins, parity and age at first birth on cancer risk in Swedish women. Twin Res Hum Genet 2005;8:156–62.
[81] Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Risk of malignant melanoma in relation to drug intake, alcohol smoking and hormonal factors. Br J Cancer 1996;73:1126–31.
[82] Naldi L, Altieri A, Imberti GL, Giordano L, Gallus S, La Vecchia C. Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure and hormonal factors: a case-control study from Italy. Ann Epidemiol 2005;15:545–50.
[83] Koomen ER, Joosse A, Herings RM, Casparie MK, Guchelaar HJ, Nijsten T. Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study. Ann Oncol 2009;20:358–64.
[84] Jasser SA, Blask DE, Brainard GC. Light during darkness and cancer: relationships in circadian photoreception and tumor biology. Cancer Causes Control 2006;17:515–23.
[85] Feychting M, Osterlund B, Ahlbom A. Reduced cancer incidence among the blind. Epidemiology 1998;9:490–4.
[86] Cermakian N, Boivin DB. The regulation of central and peripheral circadian clocks in humans. Obes Rev 2009;10(Suppl. 2):25–36.
[87] Bjarnason GA, Jordan RC, Wood PA, Li Q, Lincoln DW, Sothern RB, et al. Circadian expression of clock genes in human oral mucosa and skin: association with specific cell-cycle phases. Am J Pathol 2001;158:1793–801.
[88] Zanello SB, Jackson DM, Holick MF. Expression of the circadian clock genes clock and period 1 in human skin. J Invest Dermatol 2000;115:757–60.
[89] Arendt J. Melatonin. BMJ 1996;312:1242–3.
[90] Alpert M, Carome E, Kubulins V, Hansler R. Nighttime use of special spectacles or light bulbs that block blue light may reduce the risk of cancer. Med Hypotheses 2009;73:324–5.