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Chapter 2

Light Exposure Associated Hormonal Equilibrium is Protective against Cancer Risk

Zsuzsanna Suba*

National Institute of Oncology, Surgical and Molecular Tumor Pathology Center, Budapest, Hungary

Abstract

Pineal hormone melatonin is the mediator of physiological adaptation to external light, and to the day and night rhythms of activity and rest. It seems to be a natural hormone to facilitate sleep as melatonin secretion is physiologically increased in darkness at night being associated with decreased hormonal and metabolic activities.

Immigrants from low cancer incidence regions to northern high-incidence areas might exhibit similarly higher or excessive cancer risk as compared with the inhabitants of their adoptive country. Additional cancer risk may be conferred by incongruence between their dark pigmentation and the poor light exposure of foreign environment. Many studies established the racial/ethnic disparities in the risk and biology of female breast cancer in United States between African-American and Caucasian women. Mammary tumors in black women are diagnosed at earlier age, and are associated with higher rate of mortality as compared with cancers of white cases. Poor light exposure associated melatonin overproduction may explain the deleterious metabolic and hormonal alterations; such as insulin-resistance, deficiencies of estrogen, thyroxin and vitamin-D conferring excessive cancer risk. The more northern the location of an adoptive country the higher the cancer risk for dark skinned immigrants.

Recognition of the pivotal role of ideal light exposure in human health may supply new insight into the process of carcinogenesis. Deficient light exposure and increased melatonin level exhibit thorough interplay with systemic cancer risk factors and these correlations illuminate many apparently controversial associations between cancer incidence and hormonal disorders. Moreover, correlations between darkness associated

* Correspondent author: Prof. Zsuzsanna Suba, National Institute of Oncology, Surgical and Molecular Tumor Pathology Centre, Address: 1122 Ráth György str. 7-9, Budapest, Hungary, e-mail: subazdr@gmail.com.

hormonal imbalance and human malignancies supply effective new strategies for primary cancer prevention.

Introduction

Examinations on overall cancer morbidity and mortality data in European countries revealed conspicuous geographic differences between male and female cases. Countries with highest male cancer incidence and mortality do not exhibit accumulation in special geographic locations, while among countries with highest female overall cancer morbidity and mortality, northern regions are conspicuously highly represented, such as; Denmark, Iceland, Norway and Sweden [1]. Common risk factors may affect both sexes but women have peculiar susceptibility to certain cancerogenic agents in northern regions owing to their special hormonal and metabolic features [2].

In the middle of past century, high incidence of oral cancer among Swedish women as compared with Americans was established but no causal explanation could be found for this special cancer risk in northern region [3]. Risk for breast cancer is significantly high in the northern regions of America and Europe, whereas in Asia and Africa it is conspicuously low. Incidence and mortality rates of breast cancer are five times higher in the United States than in Japan [4].

Source of differences in the incidence and mortality rates of breast cancer among countries seem to be both genetic and environmental. Genetic adaptation to a given geographic environment may be a long lasting process and biologic selection can have a great role in it. Migration of people shows a typical trend from Southern, low cancer incidence regions to Northern, high incidence areas, which are economically highly developed. Immigrants tend to acquire the cancer incidence rates of their adoptive country, which may mainly be attributed to environmental factors [4]. The acquired excessive cancer incidence and mortality rates of dark skinned immigrants might be explained by the incongruence between their dark pigmentation and the light deficient environment.

Many studies established the racial/ethnic disparities in the risk and nature of female breast cancer in United States between African-American and Caucasian women [5]. Mammary cancers in black skinned women are diagnosed at an earlier age, their tumors are more aggressive, showing a lower grade of differentiation and the disease exhibits a higher rate of mortality as compared with white cases. Studies suggesting socioeconomic, nutritional, anthropometric, and inherited genetic differences between African-American and Caucasian women were unable to supply confirmatory results [6].

The present study compiles data on differences in breast cancer risk and tumor progression between Afro-American and Caucasian American women based on the results of case-control, prospective and meta-analytic investigations. High acquired cancer risk of dark skinned immigrants in northern countries and Afro-American cases was compared and seemed to exhibit close parallelism.

Dysparities between African-American and White American Women in Breast Cancer Incidence and Mortality

Among African-American (AA) women, breast cancers exhibit a higher prevalence and are more often diagnosed at an earlier age as compared with white American (WA) cases [5]. There are well-known disparities in tumor biology as well. In AA women mammary tumors are strongly progressive, exhibit lower differentiation and a higher incidence rate of triple negativity as compared with white cases [7]. Tumor recurrence rate, metastatic spread and mortality are all disadvantageous in AA women as compared with either Caucasian or Asian groups in America [5, 8, 9]. In a review of twenty-six research articles, the effect of nutrition, lifestyle and socioeconomic factors were examined in AA and WA cases in correlation with breast cancer incidence. In AA women these parameters were not definitely distinct from those observed in white women [6].

Identification of differentially expressed genes in breast tumors from AA women was compared with those of Caucasian cases. Despite similar pathological characteristics of tumors, molecular profiles exhibited differentially expressed genes in the two ethnic groups of patients, including CRYBB2, PSPHL and SOS1. These genes are involved in cellular growth, differentiation, tumor invasion, metastasis and immune response, thus may presumably contribute to the poor outcome of mammary cancer in AA women [10].

Further studies tried to explain the race and ethnicity disparities in breast cancer cases with the delayed treatment of tumors in black cases [11]. There were differences between black and white women in receiving adjuvant chemotherapy and radiotherapy following tumor removal. Higher risk of mortality in black women as compared to whites was found only in those receiving no chemotherapy [12], but these treatment differences might be sporadic and don't explain the disadvantageous morbidity and mortality data of AA women.

Excessive Cancer Risk of African-Americans and Dark Skinned Immigrants in Northern Geographic Regions

Poor light exposure in northern regions means a presumable cancer risk factor for their inhabitants, particularly for women [13]. Predominance of blond, blue eyed, white skinned people in northern regions seems to be a compensatory biological selection as the low level of pigmentation permits more light to pass with higher intensity in case of low exposure to environmental light.

Overall cancer morbidity and mortality in Europe exhibited a conspicuously high rate in northern countries among female cases, but not among men [1]. In Northern countries the excessive cancer risk of women as compared with men suggests that the hormonal system of female cases is more sensitive to northern specific risk factors, such as darkness. In Northern Sweden, studies on correlations between obesity and overall cancer risk showed that obese women had a 29.5% excess of risk for developing any malignancy, whereas in obese men there was no significant association between BMI and overall cancer risk [14]. Breast cancer

mortality rates were historically lower in the South as compared with the Northeast of United States [15].

Immigrants from southern, low cancer incidence regions to high-incidence northern areas might exhibit similarly increased risk as compared with the inhabitants of their adoptive country, which may be explained by their common environmental factors [4]. By contrast, dark skinned immigrants have markedly higher cancer risk as compared with the natives of northern countries [16, 17]. This excessive risk may be conferred by incongruence between their strong pigmentation and the low environmental light exposure.

Studies on dark skinned immigrants may provide valuable insight into the environmental etiology of cancer. In Sweden median age at the diagnosis of nasopharyngeal carcinoma (NC) was 63 years among Swedes and 55 years among immigrants from South showing a higher risk of the latter group. In black skinned immigrants from North Africa, male cases exhibited highly increased risk (12.4) for NC, whereas women showed extremely high risk (34.7). Among brown skinned Asian Arabic male cases, there was an excessive risk for NC (4.9) and the risk was more than double (10.9) in women [16]. This valuable study reveals that the darker the skin of immigrants the higher their cancer risk in Sweden. Moreover, women exhibit much higher cancer risk as compared with men in each skin color category.

Correlations between ethnicity and age at the time of breast cancer diagnosis were studied on immigrants in Sweden as well. The results showed that in many immigrant groups from South the diagnostic age is earlier (<50) than in natives of Sweden (>50 years) suggesting that true biological factors underlie the differences [17].

Cancer initiation requires a long term exposition to carcinogenic agents. When the patient is debilitated by diverse endocrine defects; such as in cases of black skinned people living in northern regions, the defense mechanisms are weaker and tumor initiation may come earlier. In cases of clinically diagnosed malignancies the imbalance of hormonal mechanisms will disadvantageously affect both the tumor progression and the outcome of the disease.

Interaction between poor light exposure and excessive defense against light and sunshine by high pigmentation appears to be strong cancer risk factor both among African-Americans and other dark-skinned immigrants in northern countries. This strong correlation seems to be controversial to the wide-spread concept that excessive light exposure leads to an endocrine disruption and increased breast cancer risk via impaired pineal secretion of melatonin [18].

Correlations between Excessive Melatonin Level, Other Endocrine Alterations and Cancer Risk

Pineal hormone melatonin is the mediator of physiological adaptation to external light, as well as to the day and night rhythms of activity and rest [19]. It seems to be a natural hormone that facilitates sleep as melatonin secretion is physiologically increased in darkness at night being associated with decreased hormonal and metabolic activities. Melatonin administration reduces serum estradiol and thyroxin levels, suggesting that pineal gland is a common neural site that modulates both neuroendocrine-gonadal and neuroendocrine-thyroid axes [20].

Excessive melatonin synthesis has important role in the inhibition of reproductive capacity. Melatonin administration may have contraceptive impact in case of female cats by suppression of gonadotropin releasing hormone (GnRH) production [21]. Conversely, in male

cases, hypogonadism mediated by acquired GnRH deficiency is associated with melatonin hypersecretion [22]. In humans, melatonin synthesis is intense during the overnight fasting period, and insulin release is decreased by the inhibiting action of excessive melatonin levels [23]. This suggests that light deficiency associated high melatonin activity may be causally linked to an elevated risk of type 2 diabetes.

Correlations between Melatonin Overproduction and Insulin Resistance

Involvement of melatonin in the development of *insulin resistance and diabetes* is poorly understood, whereas there are evidences for its important role in the regulation of glucose uptake [24]. In postmenopausal women melatonin administration reduced their glucose tolerance and provoked insulin resistance [25]. These observations correctly reflect the decreased insulin sensitivity in correlation with melatonin excess, which means an increased cancer risk particularly for female breast. By contrast, experimental results on rodents suggested antidiabetogenic effects of melatonin treatment [26, 27], improved glucose tolerance and insulin sensitivity in obese diabetic mice [26, 27, 28]. On the other hand, pinealectomy or a removal of melatonin receptors provoked insulin resistance in mice [29, 30].

Melatonin may inversely regulate the day and night changes of glucose uptake and insulin sensitivity in rodents and humans [24]. In a daily active phase (for rodents at night) melatonin level is low resulting in increased insulin secretion and glucose uptake as well as higher estrogen and thyroxin levels. During inactivity at night (for rodents daytime) higher melatonin level may be associated with decreased glucose uptake, lower insulin secretion and decreased circulating estrogen and thyroxin levels.

Melatonin has important impact on diabetes-related metabolic and hormonal disorders [23]. Insulin resistant states, such as metabolic syndrome and type-2 diabetes are in close correlation with carcinogenesis [31-36], and breast cancer risk is particularly closely associated with these hormonal and metabolic disorders [37-45].

Higher prevalence of metabolic syndrome and type-2 diabetes was observed among African-American women with diagnosed breast cancer as compared with Caucasian cancer cases [41,46-48]. High plasma insulin concentrations in insulin resistance are associated with alterations in sexual steroid hormone levels as well. There was a significant direct correlation between hyperinsulinism and excessive free testosterone level in young African-American women [47]. Increased prevalence of hyperinsulinemia and the associated relative androgen excess in premenopausal African-American women may have a great role in their excessive breast cancer risk [33, 34, 49].

Visceral obesity is in close correlation with insulin resistance. Obesity and especially the fat deposition on the upper body is more frequent among African-American women and it can partly explain the higher risk and worse prognosis of breast cancer as compared with Caucasian cases [46, 50]. In a study in Los Angeles, associations between BMI defined obesity and breast cancer proved to be significant only among African-American women and was especially significant among postmenopausal cases [51]. These data suggest that obesity and ageing mean higher breast cancer risk for black skinned women as compared with whites in America.

Melatonin Excess Suppresses the Synthesis and Signaling Pathways of Estrogen

Estrogen and its signal transduction pathways are the chief regulators of cell proliferation. Embryonic development well demonstrates the omnipotent actions of estrogen [33]. High estrogen levels in pregnant women might ensure the safety of explosion-like cell proliferation in the developing embryonic tissues due to the predominance of estrogen receptor alpha (ERα) signaling pathways. When growth should be stopped, the cessation of mitotic activity results in a dynamic equilibrium of cell number conducted by a concomitant activation of both receptor isoforms (ERα and ERβ). Conversely, by the predominance of ERβ activity, a stimulation of apoptotic cell death may induce involution in embryonic structures, which have lost their function. Estrogen deficiency or disorders in estrogen-signaling pathways may elicit a breakdown of the exquisite surveillance of gene regulation and results in cancer initiation [52, 53].

Presumed oncostatic actions of melatonin are predominantly based on the suppression of estrogen-signaling by several pathways [54, 55, 56, 57]. Melatonin down-regulates the hypothalamic-pituitary reproductive axis by an indirect neuroendocrine mechanism resulting in reduction of circulating gonadal estrogens [20, 54]. Melatonin interacts with both membrane associated and nuclear estrogen receptors (ERs) and blocks preferentially the ERα isoform [58]. In tumor cell culture, membrane-bound melatonin receptors confer antiestrogenic effects by suppression of ER expression [59]. In case of mammary tumor cells, melatonin interferes with the 3 of nuclear ERs as well, thus behaving as a selective estrogen receptor inhibitor [60-63]. Melatonin may also inhibit the expression and activity of aromatases, the enzymes responsible for the local tissular synthesis of estrogens, thus behaving as a selective enzyme inhibitor [57].

In hamsters, daily melatonin injections significantly reduced the circulatory serum level of estradiol, rendered female animals acyclic and suppressed their reproductive capacity [20]. Melatonin administration in rats resulted in significant reduction in the number of uterine estrogen receptors, which justifies further counteraction with estrogen effect [64]. On the other hand, estrogen administration exhibited an inhibitory effect on nocturnal melatonin synthesis in peripubertal female rats [65].

Clinical investigations support the finding that in women suffering from highly hormone associated tumors; such as breast or endometrial cancer, melatonin levels are depressed [66, 67]. These findings are strongly influenced by the fact that melatonin secretion is continuously decreasing with aging to about half of the values seen in young people [68, 69]. Decreased melatonin level in women with breast and endometrial cancers may be a defensive contraregulatory effect, since such women generally exhibit insulin resistance and/or defective estrogen signaling [52]. The reactively decreased melatonin level in these metabolically and hormonally challenged women may improve the hormonal imbalance, while exogenous melatonin supplementation would further suppress the circulating level and signaling pathways of estrogens.

All clinical and experimental results support the physiologic counteraction between melatonin and estrogen effects but do not justify protection of the strong antiestrogenic impact of melatonin against hormone related cancers. In both healthy and pathologic states the majority of hormones are at levels that closely adapt to day/night changes through melatonin dependent synchronization [23].

Breast cancer risk is increasing with age. In the United States 75% of women with breast cancer are older than age 50 [4]. Recent clinical and epidemiological results suggest that healthy hormonal equilibrium and fertility are protective against breast cancer in premenopausal women [33, 70]. In estrogen deficient postmenopausal cases, hormone replacement therapy improves metabolic and hormonal equilibrium and may decrease the risk of breast cancer [33, 49, 70], while exogenous melatonin administration may deepen the imbalance of hormonal functions.

In dark skinned American women, hyperinsulinism and defective estrogen signaling are associated with excessive melatonin synthesis, which are high cancer risks for female breast. These hormonal alterations might contribute to their increased breast cancer risk [47, 49].

Excessive Melatonin Synthesis and Suppressed Thyroid Function

Melatonin administration induces the suppression of *thyroid function* in animal experiments and in clinical examinations [20]. In melatonin administered hamsters serum thyroxin level was reduced to near half that of untreated control animals. Prolonged melatonin treatment in the perimenopausal and early postmenopausal period of women produced a decrease in luteinizing hormone, depressed estradiol level and hypothyroidism [69]. Among patients with hypothyroidism, higher serum melatonin levels, total nocturnal melatonin secretion and urinary melatonin excretion were found as compared with normal control individuals [71].

In a population based study, patients without clinical evidence of thyroid disease were examined to determine whether race or age may influence the serum levels of TSH and free thyroxin (fT4). Mean fT4 value was significantly lower in blacks than in whites, which reveals the wide-spread subclinical hypothyroidism in African-American women [72].

Coincidence of thyroid disorders and breast cancer has long been a subject of debate. Although no convincing evidence exists regarding the causal role for overt thyroid disease in breast cancer, the preponderance of published works favors an association with hypothyroidism [73]. Incidences of thyroid diseases were investigated in patients with breast cancer and age-matched tumor free control individuals. The results indicated an increased prevalence of both autoimmune and non-autoimmune thyroid diseases in breast cancer patients [74]. In a prospective study, hypothyroidism and low serum FT4 values exhibited direct correlation with increased breast cancer risk in postmenopausal women [75]. In animal experiments hypothyroidism enhanced the invasiveness of breast cancer xenografts and accelerated the development of metastases as well [76]. Even subclinical hypothyroidism may increase the expression of thyroid hormone receptor by means of feed back mechanism. High receptor concentration in mammary tissue samples proved to be an early indicator of high risk for breast cancer [77]. These associations suggest that low free thyroxin level in black skinned American women may be an additional factor resulting in their excessive breast cancer risk.

Hypothyroidism has a statistically significant relationship with recurrent pregnancy loss in the first trimester [78], suggesting that insufficient thyroid function exhibits correlation with defective estrogen signaling pathway. This association may be a newly revealed link between hypothyroidism and breast cancer risk.

Melatonin Excess Related Vitamin D Deficiency

Melatonin production is enhanced in the darkness at night, whereas vitamin D synthesis is associated with the UV-B spectrum of sunshine. These correlations suggest at least partially opposite actions of these bioactive compounds.

Vitamin D has *beneficial musculoskeletal effects* and crucial extraskeletal ones as well [79]. Vitamin D generates antimicrobial peptide synthesis within epithelial layers of barrier sites, i.e. the respiratory tract, the gastrointestinal tract and skin [80]. Recent prospective studies have shown inverse correlations between serum vitamin D levels and all-cause mortality [81]. In Nordic countries increasing serum vitamin D levels from oral supplementation or ultraviolet-B irradiance mean a marked health benefit [82].

Vitamin D *improves insulin sensitivity*, and its deficiency has been associated with the onset and progression of type-2 diabetes mellitus. Vitamin D3 supplementation might provide a public health measure in preventing or delaying the manifestation of diabetes [83]. Overweight and obese people are insulin resistant and they exhibit lower circulating vitamin D level as compared with cases with normal weight [84]. Vitamin D deficiency is common in children in the United States and is significantly more prevalent in obese children [85].

Vitamin D has important roles in the *reproductive health of women*. Recently, there are literary evidences that vitamin D status influences female fertility and pregnancy outcomes. Low levels of circulatory vitamin D are associated with impaired fertility, polycystic ovarian syndrome, preterm birth and gestational diabetes in women suggesting a defective estrogen signaling pathway in the background. Vitamin D supplementation improves fertility in anovulatory women [86].

Vitamin D was shown to induce *antiproliferative effects* on tumors. In normal and malignant epithelial mammary cells vitamin D has been shown to inhibit pathologic cell proliferation and promote differentiation and apoptosis. Vitamin D deficiency means an increased risk for many cancer types such as; the malignancies of breast, colon, prostate, and pancreas [87, 88]. In cancer patients vitamin D deficiency is associated with a worsening of the prognosis [89]. Vitamin D supplementation was associated with decreased breast cancer incidence, particularly among older postmenopausal women having higher breast cancer risk [90].

Correlations between the *epidemiology of vitamin D supply*, cancer incidence and mortality were studied in the United States [84]. Higher rates of total cancer mortality were observed in regions with less UV-B radiation and among dark-skinned African-American people. A possible role of serum vitamin D3 level emerged in health disparities in black and white cases in United States. Significantly higher ratios of mortality rates for African-Americans to Caucasians were observed for female breast cancer, colorectal cancer, cardiovascular disease and all-cause mortality rate [90].

African-American population exhibits a widespread vitamin D deficiency, which suggests that adequate replacement may be an important public health measure for reduction of race-related disparities in breast cancer incidence [48, 91].

Correlations among Light Exposure, Melatonin Level and Breast Cancer Risk

In *metropolitan inhabitants* "excessive electric light" exposure at night was supposed to impair the pineal secretion of melatonin [18, 92]. The "endocrine disruption" hypothesis presumed exposure to artificial light at night as a carcinogenic impact by means of defective melatonin synthesis and high circulatory estrogen levels [19, 92]. The hypothesis seemed to be one of the explanations for increased breast cancer risk in highly industrialized regions [93]. However, this concept disregards that electric light at night maybe only a tiny fragment of daylight and sunshine. Moreover, people, staying up the whole night must sleep during the day, resulting in a severe loss of light exposure rather than an excess. This may be the real explanation for their increased cancer risk. Nevertheless, spread of "western lifestyle" and increased prevalence of insulin resistance and obesity in highly developed countries might be additional high risk for the cancers of breast and other hormone-related sites.

Among *female night shift workers* an increased breast cancer risk has been observed by several studies [94-97]. This excessive risk was mistakenly attributed to high artificial light exposure at night, presumed defective melatonin secretion and the associated high circulatory estrogen level [98]. However, artificial light at night is negligible in comparison with daylight and female night shift workers sleep during the day. They have a serious deficit of natural light exposure and might suffer of excessive melatonin production with associated hormonal alterations. These systemic disorders really justify their highly increased risk for breast cancer [13].

Several studies suggest that *visual impairment and blindness* in women should exhibit lower risk for breast cancer in correlation with their increased melatonin and decreased estrogen levels [19, 99-102]. These results suggest a shocking association that blindness would be advantageous for women to avoid hormone-related cancers. However, the predominance of blond, white skinned and blue eyed persons in northern regions seems to be a compensatory biological selection in case of low exposure to environmental light. This fact justifies that daylight and sunshine are necessary physiological stimuli for human beings and blindness or visual disability may not be associated with beneficial anticancer capacity.

Taken together, pineal hormone, melatonin seems to be a very important regulator, which harmonizes the diurnal cycles of metabolic and hormonal equilibrium depending on the light exposure and physical activity of living creatures. Darkness and excessive melatonin synthesis results in low estrogen and vitamin D levels, insulin resistance and hypothyroidism, which all seem to be systemic risk factors for cancer.

Review of Melatonin Use As Nutritional Supplement

Discovery of melatonin was published in 1960 by American physician Aaron B. Lerner and his colleagues at Yale University of Medicine [103]. Melatonin is a hormone synthesized naturally by the pineal gland in response to darkness. Diurnal changes in melatonin level mediate physiological adaptation to the changes in environmental light, as well as to the day

and night rhythms of activity and rest [19]. Effects of melatonin have been studied since its discovery, and in the 1990s synthetic melatonin became available as a nutritional supplement.

Melatonin supplements are frequently recommended for *sleep disorders*, involving disturbed sleep cycles caused by irregular night shift work. People who have sleeping troubles frequently exhibit low melatonin levels and in such cases melatonin treatment is a top choice [104]. There is a high demand for sleep aids in the U.S. The National Health Interview Survey found 1.6 million US adults, who were using sleep aids for insomnia in 2007. According to certain studies melatonin may be recommended for children as well who suffer from insomnia related to autism, mental retardation and disorders of the central nervous system [105]. Nevertheless, children and adolescents should not use long term melatonin supplementation as it may suppress the function of other hormones and interfere with development at young age.

Preliminary research has shown that melatonin supplements may help the insomnia in older adults and elderly people who are stopping benzodiazepine administration [106]. Physiologic, age-related decrease in melatonin synthesis exhibits strong parallelism with decline in sexual steroid and thyroxin production in case of older patients [107, 108] exhibiting decreased sexual and physical activities. In elderly cases, long term exogenous melatonin supplementation may result in further decrease in levels of antagonistic hormones and may induce stronger alteration in hormonal equilibrium instead of restoration.

Melatonin treatment seems to be ineffective in changing sleep schedules among night shift workers. Considering the relatively weak associations between light at night and decrease in melatonin levels, multiple factors may be operating along the pathway between night shift work and adverse health consequences [109].

Melatonin has pivotal role in the *regulation of hormonal equilibrium*, particularly in women. Melatonin administration may postpone the start of menstruation, influences the length of ovulatory cycles and the onset of menopause [110]. All these activities of melatonin supplements are in close correlation with their strong antagonistic effects on estrogen signaling. Melatonin supplements should be avoided in pregnancy, during breastfeeding, and when women are trying to conceive. Exogenous hormone use, such as birth control pills increases circulating melatonin levels until achieving a new hormonal equilibrium.

Melatonin suppresses the synthesis of thyroid hormones. Under conditions of constant darkness, reduced plasma T_4 concentrations were observed, accompanied by lower thyroid weight in squirrels. Conversely, an enhanced thyroid function was found after pinealectomy [111]. In middle aged or older patients with symptom-free subclinical hypothyroidism, melatonin supplements may provoke the manifestation of overt disease.

Melatonin treatment decreases insulin secretion and insulin sensitivity. In middle aged women, melatonin administration reduced their glucose tolerance and increased blood sugar levels [25]. In patients with type 2 diabetes, melatonin supplements may counteract the effectiveness of diabetes medication. Since melatonin provokes insulin resistance and may also cause blood vessel constriction, its administration could be dangerous for hypertensive people or those suffering from cardiovascular disease.

Recently, melatonin administration is increasingly suggested for *breast cancer therapy* because of its strong antiestrogenic impact [112]. Clinical investigations support that in women with hormone dependent tumors; such as breast or endometrial cancers, melatonin levels are typically decreased [66, 67]. Similarly, men with prostate cancer usually exhibit lower melatonin levels than tumor free male control cases. Decreased melatonin level in

patients with hormone dependent tumors may be attributed to adaptive synchronization with the defective synthesis of insulin, estrogen and thyroxin, which alterations are frequent is women with breast cancer [113]. Exogenous melatonin administration may cause further imbalance in all hormonal activities of patients with tumors instead of improvement.

Conclusion

Literary data on geographic differences in cancer incidence suggest that darkness in northern countries is a gender-related risk for malignancies, particularly among women. Increased cancer morbidity and mortality in northern regions strongly suggest that light and sunshine exposition have important beneficial role in the maintenance of metabolic and endocrine equilibrium. By contrast, literary data suggest an endocrine disruption caused by high estrogen level in light and a beneficial anticancer capacity of long-term darkness. These assumptions are based on the concept that estrogen has carcinogenic capacity, especially on highly hormone responsive organs.

Results of experimental and epidemiological studies exhibit strong correlations between melatonin secretion and the equilibrium of circulatory hormone levels. Health and longevity require a balance and harmony among hormonal signals. Complexity of the endocrine system supplies the high regulation of the proliferative activity of different cell types depending on the nature of temporary intra- and extracellular stimuli.

Literary data on correlations between hormonal disorders and cancer risk are fairly controversial. Overproduction of peptide hormones, such as growth hormone, insulin and insulin-like growth factors, interacting simply with cell membrane receptors, has proven tumor inducing capacity. Another group of hormones, including estrogens, thyroids and vitamin D, has both genomic intranuclear and non-genomic membrane-associated receptor signals, thus they have complex roles in all basic cellular functions. Recent results suggest that defective synthesis of these latter hormones or alterations in their signal transduction pathways may equally disturb metabolic processes, reproduction and the regulation of cell proliferation.

Recognition of the pivotal role of ideal light exposure in human health may supply new insight into the process of carcinogenesis. Deficient light exposure associated high melatonin level exhibits thorough interplay with hormonal cancer risk factors. These correlations illuminate many apparently controversial associations between cancer incidence and hormonal disorders. Moreover, correlations between darkness associated hormonal imbalance and human malignancies supply effective new strategies for primary cancer prevention.

References

[1] Otto Sz. Cancer epidemiology in Hungary and the Béla Johan National Program for the Decade of Health. *Pathol Oncol Res*. 9:126-130, 2003.

[2] Suba Z. Common soil of smoking-associated and hormone-related cancers: estrogen deficiency. *Oncol Rev*. 4:73-87, 2010.

[3] Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. *Cancer*. 10:1300-1323, 1957.
[4] Montag A, Kumar V. The female genital system and breast. Chapter 19. In: Kumar V, Abbas AK, Fausto N, Mitchell RN. Eds. *Robbins basic pathology, 8th Ed*. Philadelphia, Saunders Elsevier, pp. 711-50, 2007.
[5] Amend K, Hicks D, Ambrosone CB. Breast cancer in African-American women: differences in tumor biology from European-American women. *Cancer Res.* 66:8327-30, 2006.
[6] Chandran U, Hirshfield KM, Bandera EV. The role of anthropometric and nutritional factors on breast cancer risk in African-American women. *Public Health Nutr*. 15:738-48, 2012.
[7] Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women: Implications for breast cancer screening recommendations. *Cancer*. 117:2747-53, 2011.
[8] Stark A, Stapp R, Raghunathan A, Yan X, Kirchner HL, Griggs J et al. Disease-free probability after the first primary ductal carcinoma in situ of the breast: a comparison between African-American and White-American women. *Breast Cancer Res Treat*. 131:561-70, 2012.
[9] Holmes L Jr, Opara F, Hossain J. A five-year breast cancer-specific survival disadvantage of African American women. *Afr J Reprod Health.* 14:195-200, 2010.
[10] Field LA, Love B, Deyarmin B, Hooke JA, Shriver CD, Ellsworth RE. Identification of differentially expressed genes in breast tumors from African-American compared with Caucasian women. *Cancer*. 118:1334-44, 2012.
[11] Fedewa SA, Edge SB, Stewart AK, Halpern MT, Marlow NM, Ward EM. Race and ethnicity are associated with delays in breast cancer treatment (2003-2006). *J Health Care Poor Underserved*. 22:128-41, 2011.
[12] Sail K, Franzini L, Lairson D, Du X. Differences in treatment and survival among African-American and Caucasian women with early stage operable breast cancer. *Ethn Health 2011*; Nov 9 [Epub ahead of print].
[13] Suba Z. Insulin resistance, hyperinsulinemia and cancer risk. Chapter 2. In: Ed. Suba Z. *Estrogen versus Cancer*. New York, Nova Science Publishers Inc. pp. 19-40, 2009.
[14] Lukanova A, Björ O, Kaaks R, Lenner P, Lindahl B, Hallmans G et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer*. 118:458-66, 2006.
[15] Sturgeon SR, Potischman N, Malone KE, Dorgan JF, Daling J, Schairer C et al. Serum levels of sex hormones and breast cancer risk in premenopausal women: a case-control study (USA). *Cancer Causes and Control*. 15:45-53, 2004.
[16] Mousavi SM, Sundquist J, Hemminki K. Nasopharyngeal and hypopharyngeal carcinoma risk among immigrants in Sweden. *Int J Cancer*. 127:2888-92, 2010.
[17] Hemminki K, Mousavi SM, Sundquist J, Brandt A. Does the breast cancer age at diagnosis differ by ethnicity? A study on immigrants to Sweden. *Oncologist*. 16:146-54, 2011.
[18] Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol.* 125:556-561, 1987.
[19] Rohr UD, Herold J. Melatonin deficiencies in women. Maturitas. 41:S85-S104, 2002.

[20] Vriend J, Bertalanffy FD, Ralcewicz TA. The effects of melatonin and hypothyroidism on estradiol and gonadotropin levels in female Syrian hamsters. *Biology of Reproduction.* 36:719-728, 1987.

[21] Goericke-Pesch S. Reproduction control in cats: new developments in non-surgical methods. *J Feline Med Surg.* 12:539-46, 2010.

[22] Luboshitzky R, Shen-Orr Z, Ishai A, Lavie P. Melatonin hypersecretion in male patients with adult-onset idiopathic hypogonadotropic hypogonadism. *Exp Clin Endocrinol Diabetes.* 108:142-5, 2000.

[23] Espino J, Pariente JA, Rodriguez AB. Role of melatonin on diabetes-related metabolic disorders. *World J Diabetes*. 2:82-91, 2011.

[24] Peschke E, Mühlbauer E. New evidence for a role of melatonin in glucose regulation. *Best Pract Res Clin Endocrinol Metab*. 24:829-41, 2010.

[25] Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol*. 54:339-46, 2001.

[26] Shieh JM, Wu HT, Cheng KC, Cheng JT. Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCzeta-Akt-GSK3beta pathway in hepatic cells. *J Pineal Res*. 47:339-44, 2009.

[27] Nishida S, Segawa T, Murai I, Nakagawa S. Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of Delta-5 desaturase activity. *J Pineal Res*. 32:26-33, 2002.

[28] Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, Nicod P. Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology*. 150:5311-7, 2009.

[29] Contreras-Alcantara S, Baba K, Tosini G. Removal of melatonin receptor type 1 induces insulin resistance in the mouse. *Obesity* (Silver Spring). 18:1861-3, 2010.

[30] Mühlbauer E, Gross E, Labucay K, Wolgast S, Peschke E. Loss of melatonin signaling and its impact on circadian rhythms in mouse organs regulating blood glucose. *Eur J Pharmacol.* 606:61-71, 2009.

[31] Bloomgarden ZT. Second World Congress on the Insulin Resistance Syndrome: Mediators, pediatric insulin resistance, the polycystic ovary syndrome, and malignancy. *Diabetes Care*. 28:1821-1830, 2005.

[32] Suba Z**.** Insulin resistance and oral cancer risk. *Cancer Res J.* 3:1-22, 2009.

[33] Suba Z. Interplay between insulin resistance and estrogen deficiency as co-activators in carcinogenesis. *Pathol Oncol Res.* 18:123-133, 2011.

[34] Suba Z. Insulin resistance, estrogen deficiency and cancer risk. In: Suba Z Ed. *Estrogen versus Cancer*. Chapter 7. New York, Nova Science Publishers Inc, pp. 127-146, 2009.

[35] Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. *Proc Nutr Soc*. 71:181-9, 2012.

[36] Grote VA, Becker S, Kaaks R. Diabetes mellitus type 2 – an independent risk factor for cancer? *Exp Clin Endocrinol Diabetes*. 118:4-8, 2010.

[37] Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A et al. Metabolic syndrome and the risk of breast cancer in postmenopausal women. *Ann Oncol.* 22:2687-92, 2011.

[38] Sieri S, Muti P, Claudia A, Berrino F, Pala V, Grioni S et al. Prospective study on the role of glucose metabolism in breast cancer occurrence. *Int J Cancer*. 130:921-9, 2012.

[39] Abbasi M, Tarafdari A, Esteghamati A, Vejdani K, Nakhiavani M. Insulin resistance and breast carcinogenesis: a cross-sectional study among Iranian women with breast mass. *Metab Syndr Relat Disord*. 8:411-416, 2010.

[40] Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 101:48-60, 2009.

[41] Colonna SV, Douglas Case L, Lawrence JA. A retrospective review of the metabolic syndrome in women diagnosed with breast cancer and correlation with estrogen receptor. *Breast Cancer Res Treat.* 131:325-31, 2012.

[42] Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type-2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev*. 8:395-408, 2007.

[43] Arif JM, Al-SaifAM, Al-Karrawi MA, Al-Sagair OA. Causative relationship between diabetes mellitus and breast cancer in various regions of Saudi Arabia: an overview. *Asian Pac J Cancer Prev*. 12:589-92, 2011.

[44] Kalla Singh S, Brito C, Tan QW, De León M, De León D. Differential expression and signaling activation of insulin receptor isoforms A and B: A link between breast cancer and diabetes. *Growth Factors*. 29:278-89, 2011.

[45] Suba Z. Insulin resistance and oral cancer risk. Chapter 4. In: Watanabe HS. Ed. *Horizons in Cancer Research Vol. 43*. New York, Nova Science Publishers Inc, pp. 77-97, 2011.

[46] Rose DP, Haffner SM, Baillargeon J. Adiposity, the metabolic syndrome, and breast cancer in African-American and white American women. *Endocr Rev.* 28:763-77, 2007.

[47] Falkner B, Sherif K, Sumner A, Kushner H. Hyperinsulinism and sex hormones in young adult African Americans. *Metabolism*. 48:107-12, 1999.

[48] Harris SS. Does vitamin D deficiency contribute to increased rates of cardiovascular disease and type 2 diabetes in African Americans? *Am J Clin Nutr*. 93:1175S-78S, 2011.

[49] Suba Z, Kásler M. Interactions of insulin and estrogen in the regulation of cell proliferation and carcinogenesis. *Orv Hetil* (in Hungarian). 153:47-58, 2012.

[50] Conroy SM, Maskarinec G,Wilkens LR, White KK, Henderson BE, Kolonel LN. Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. *Breast Cancer Res Treat.* 129:565-74, 2011.

[51] Sarkissyan M, Wu Y, Vadgama JV. Obesity is associated with breast cancer in African-American women but not Hispanic women in South Los Angeles. *Cancer*. 117:3814-23, 2011.

[52] Suba Z. Low estrogen exposure and/or defective estrogen signaling induces disturbances in glucose uptake and energy expenditure. *J Diabet Metab*. 2013, 272, doi.4172/2155-6156.1000272.

[53] Suba Z. Diverse pathomechanism leading to the breakdown of cellular estrogen surveillance and breast cancer development. New therapeutic strategies. Drug Design, Development and Therapy. Under pre-press. 2014.

[54] Cos S. González A. Martínez-Campa C. Mediavilla MD. Alonso-González C. Sánchez-Barceló EJ. Melatonin as a selective estrogen enzyme modulator. *Current Cancer Drug Targets*. 8:691-702, 2008.

[55] Sandyk R, Anastasiadis PG, Anninos PA, Tsagas N. Is the pineal gland involved in the pathogenesis of endometrial carcinoma. *Int J Neurosci*. 62:89-96, 1992.

[56] Grant SG, Melan MA, Latimer JJ, Witt-Enderby PA. Melatonin and breast cancer: cellular mechanisms, clinical studies and future perspectives. *Expert Rev Mol*. 11:e5, 2009.

[57] Gonzalez A, Cos S, Martinez-Campa C, Alonso-Gonzalez C, Sanchez-Mateos S, Mediavilla MD. Selective estrogen enzyme modulator actions of melatonin in human breast cancer cells. *J Pineal Res*. 45:86-92, 2008.

[58] Viswanathan AN, Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. *Cancer Lett.* 281:1-7, 2009.

[59] Girgert R, Hanf V, Emons G, Gründker C. Membrane-bound melatonin receptor MT1 down-regulates estrogen responsive genes in breast cancer cells. *J Pineal Res*. 47:23-31, 2009.

[60] Cos S, Gonzalez A, Martínez-Campa C, Mediavilla MD, Alonso-González C, Sanchez Barceló EJ. Estrogen signaling pathway: a link between breast cancer and melatonin oncostatic actions. *Cancer Detect Prev*. 30:118-28, 2006.

[61] Hill SM, Frasch T, Xiang S, Yuan L, Duplessis T, Mao L. Molecular mechanisms of melatonin anticancer effects. *Integr Cancer Ther*. 8:337-46, 2009.

[62] Martínez-Campa C, Alonso-González C, Mediavilla MD, Cos S, González A, Ramos S et al. Melatonin inhibits both ER alpha activation and breast cancer cell proliferation induced by a metallo-estrogen, cadmium. *J Pineal Res*. 40:291-6, 2006.

[63] Watanabe M, Kobayashi Y, Takahashi N, Kiguchi K, Ishizuka B. Expression of melatonin receptor (MT1) and interaction between melatonin and estrogen in endometrial cancer cell line. *J Obstet Gynaecol Res*. 34:567-73, 2008.

[64] Abd-Allah AR, El-Sayed el SM, Abdel-Wahab MH, Hamada FM. Effect of melatonin on estrogen and progesterone receptors in relation to uterine contraction in rats. *Pharmacol Res*. 47:349-354, 2003.

[65] Hayashi K, Okatani Y. Mechanisms underlying the effects of estrogen on nocturnal melatonin synthesis in peripubertal female rats: relation to norepinephrine and adenylatecyclase. *J Pineal Res*. 26:178:83, 1999.

[66] Grin W, Grünberger W. A significant correlation between melatonin deficiency and endometrium cancer. Gynecol Obstet Invest. 45:62-5, 1998.

[67] Bartsch C, Bartsch H, Blask DE, Cardinali DP, Hrushewsky WJM, Mecke D. *The pineal gland and cancer*. Springer: Berlin 2001.

[68] Ohashi Y, Okamoto N, Uchida K, Iyo M, Mori N, Morita Y. Differential pattern of the circadian rhythm *Biol Signals*. 6:301-6, 1997.

[69] Bellipani G, Bianchi P, Pierpaoli W, Bulian D, Ilyia E. Effects of melatonin in perimenopausal women and menopausal women: a randomized and placebo controlled study. *Exp Gerontol*. 36:297-310, 2001.

[70] Suba Z. Triple negative breast cancer risk in women is defined by the defect of estrogen signaling: preventive and therapeutic implications. *Onco Targets Ther*. 7:147-164, 2014.

[71] Röjdmark S, Berg A, Rössner S, Wetterberg L. Nocturnal melatonin secretion in thyroid disease and in obesity. *Clin Endocrinol*. 35:61-65, 1991.
[72] Boucai L, Surks MI. Reference limits of serum TSH and free T4 are significantly influenced by race and age in an urban outpatient medical practice. *Clin Endocrinol* (Oxf). 70:788-93, 2009.
[73] Smyth PP. The thyroid and breast cancer: a significant association? *Ann Med*. 29:189-91, 1997.
[74] Turken O, Narin Y, Demirbas S, Onde ME, Sayan O, Kandemir EG et al. Breast cancer in association with thyroid disorders. *Breast Cancer Res.* 5:R110-113, 2003.
[75] Kuijpens JL, Nyklictek I, Louwman MW, Weetman TA, Pop VJ, Coebergh JW. Hypothyroidism might be related to breast cancer in post-menopausal women. *Thyroid*. 15:1253-9, 2005.
[76] Martinez-Inglesias O, Garcia-Silva S, Regadera J, Aranda A. Hypothyroidism enhances tumor invasiveness and metastasis development. *PLoS One.* 4:e6428, 2009.
[77] Jeschke U, Ditsch N, Mayr D. Thyroid hormone receptor expression for the diagnosis and prognosis on breast cancer and ovarian cancer. WO2011135091A1, **2011**
[78] Rao VR, Lakshmi A, Sadhnani MD. Prevalence of hypothyroidism in recurrent pregnancy loss in first trimester. *Indian J Med Sci.* 62:357-61, 2008.
[79] Dobnig H. A review of the health consequences of the vitamin D deficiency pandemic. *J Neurol Sci*. 311:15-18, 2011.
[80] White JH. Vitamin D as an inducer of cathelicidin antimicrobial peptide expression: past, present and future. *J Steroid Biochem Mol Biol*. 121:234-8, 2010.
[81] Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med.* 168:1629-37, 2008.
[82] Grant WB, Juzeninene A, Moan JE. Review article: Health benefit of increased serum 25 (OH)D levels from oral intake and ultraviolet-B irradiance in the Nordic countries. *Scand J Public Health*. 39:70-78, 2011.
[83] Nazarian S, St Peter JV, Boston RC, Jones SA, Mariash CN. Vitamin D3 supplementation improves insulin sensitivity in subjects with impaired fasting glucose. *Transl Res.* 158:276-81, 2011.
[84] Giovanucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control.* 16:83-95, 2005.
[85] Olson ML, Maalouf NM, Oden JD, White PC, Hutchinson MR. Vitamin D deficiency in obese children and its relationship to glucose homeostasis. *J Clin Endocrinol Metab*. 97:279-85, 2012.
[86] Grundmann M, von Versen-Höynck F. Vitamin D – roles in women's reproductive health? *Reprod Biol Endocrinol*. 9:146-55, 2011.
[87] Mitchell D. The relationship between vitamin D and cancer. *Clin J Oncol Nurs*. 15:557-60, 2011.
[88] Pilz S, Tomaschitz A, Obermayer-Pietsch B, Dobnig H, Pieber TR. Epidemiology of vitamin D insufficiency and cancer mortality. *Anicancer Res.* 29:3699-704, 2009.
[89] Arends J. *Vitamin D in oncology*. Forsch Komplementmed. 18:176-84, 2011.
[90] Crew KD, Gammon MD, Steck SE, Hershman DL, Cremers S, Dworakowski E et al. Association between plasma 25-hydroxyvitamin D and breast cancer risk. *Cancer Prev Res* (Phila). 2:598-604, 2009.

[91] Grant WB, Peiris AN. Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. *J Am Med Dir Assoc*. 11:617-28, 2010.

[92] Stevens RG. Working against our endogenous circadian clock: Breast cancer and electric lighting in the modern world. *Mutat Res.* 680:106-108, 2009.

[93] Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet*. 2:814-6, 1978.

[94] Bonde JP, Hansen J, Kolstad HA,Mikkelsen S, Olsen JH, Blask DEet al. Work at night and breast cancer – report on evidence-based options for preventive actions. *Scand J Work Environ Health* 2012; Feb 20 [Epub ahead of print]

[95] Langley AR, Graham CH, Grundy AL, Tranmer JE, Richardson H, Aronson KJ. A cross sectional study of breast cancer biomarkers among shift working nurses. *BMJ Open;* 2:e000532, 2012.

[96] Grundy A, Tranmer J, Richardson H, Graham CH, Aronson KL. The influence of light and night exposure on melatonin levels among Canadian rotating shift nurses. *Cancer Epidemiol Biomarkers Prev*. 20:2404-12, 2011.

[97] Brudnowska J, Peplonska B. Night shift work and cancer risk: a literature review (Polish). *Med Pr.* 62:323-38, 2011.

[98] Blask DE, Brainard GC, Dauchy RT, Hanifin JP, Davidson LK, Krause JA et al. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res.* 65:11174-11184, 2005.

[99] Kliukiene J, Tynes T, Andersen A. A risk of breast cancer among women with visual impairment. *Br J Cancer*. 84:397-9, 2001.

[100] Hahn RA. Profound bilateral blindness and incidence of breast cancer. *Epidemiology*. 2:208-10, 1991.

[101] Feychting M, Osterlund B, Ahlbom A. Reduced cancer incidence among the blind. *Epidemiology*. 9:490-4, 1998.

[102] Verkasalo PK, Pukkala E, Stevens RG, Ojamo M, Rudanko SL. Inverse association between breast cancer incidence and degree of visual impairment in Finland. *Br J Cancer.* 80:1459-60, 1999.

[103] Lerner AB, Case JD, Takahashi Y. Isolation of melatonin and 5-methoxyindole-3-acetic acid from bovine pineal glands. *J Biol Chem.* 235:1992-7, 1960.

[104] Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One.* 17;8(5):e63773, 2013.

[105] Smits MG, van Stel HF, van der Heijden K, Meijer AM, Coenen AM, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2003 Nov;42(11):1286-93.

[106] Garzon C, Guerrero JM, Aramburu O, Guzman T. Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. Aging Clin Exp Res 21: 38–42, 2009.

[107] The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: Reanalyis of nine prospective studies. *J Natl Cancer Inst.* 94:606-16, 2002.

[108] Brown-Borg HM: Endocrine regulation of longevity. *Ageing Research Reviews*. 6:28-45, 2007.

[109] Fritschi L, Glass DC, Heyworth JS, Aronson K, Girschik J, Boyle T, Grundy A, Erren TC. Hypotheses for mechanisms linking shiftwork and cancer. *Med Hypotheses.*77:430-6, 2011.

[110] Shechter A, Boivin DB. Sleep hormones, and circadian rhythms throughout the menstrual cycle in healthy women and women with premenstrual dysphoric disorder. *Int J Endocrinol.* 2010:259345. doi: 10.1155/2010/259345.

[111] Shavali SS, Haldar C. Effects of continuous light, continuous darkness and pinealectomy on pineal-thyroid-gonadal axis of the female indian palm squirrel, Funambulus Pennanti. *J Neural Transm.* 105:407-13, 1998

[112] Sanchez-Barcelo EJ, Mediavilla MD, Alonso-Gonzalez C, Rueda N. Breast cancer therapy based on melatonin. *Recent Pat Endocr Metab Immune Drug Discov.* 6:108-16, 2012.

[113] Suba Z. Light deficiency confers breast cancer risk by endocrine disorders. *Recent Pat Anticancer Drug Discov.* 7:337-44, 2012.