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Update on the role of melatonin in the prevention of cancer tumorigenesis and in the management of cancer correlates, such as sleep-wake and mood disturbances: review and remarks

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Abstract

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The aim of this article was to perform a systematic review on the role of melatonin in the prevention of cancer tumorigenesis—in vivo and in vitro—as well as in the management of cancer correlates, such as sleep-wake and mood disturbances. The International Agency for Research on Cancer recently classified "shift-work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A) based on "limited evidence in humans for the carcinogenicity of shift-work that involves night-work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)". The clinical implications and the potential uses of melatonin in terms of biologic clock influence (e.g. sleep and mood), immune function, cancer initiation and growth, as well as the correlation between melatonin levels and cancer risk, are hereinafter recorded and summarized. Additionally, this paper includes a description of the newly discovered effects that melatonin has on the management of sleep-wake and mood disturbances as well as with regard to cancer patients' life quality. In cancer patients depression and insomnia are frequent and serious comorbid conditions which definitely require a special attention. The data presented in this review encourage the performance of new clinical trials to investigate the possible use of melatonin in cancer patients suffering from sleep-wake and mood disturbances, also considering that melatonin registered a low toxicity in cancer patients.

Keywords: Cancer, Melatonin, Mood, Sleep

Methods

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Melatonin treatment not only improved total sleep time, but also reduced depressive symptoms [20, 26–28], thus indicating a correlation between sleep disturbance and depression.

Melatonin secretion in cancer patients: what happens?

This research has been carried out based on the keywords: "melatonin" AND "secretion" AND "cancer"; 248 articles were sourced. Among them, the most significant epidemiological and retrospective, case–control studies have been selected and discussed.

In patients suffering from breast, endometrial, or colorectal cancer [29] melatonin secretion is impaired. The increased incidence of breast and colorectal cancer observed in nurses and other night-shift workers suggests a possible correlation between the reduced melatonin secretion and their increased light exposure at night [30, 31]. The physiological surge of melatonin at night is thus considered a "natural restraint" on tumor initiation, promotion, and progression.

The International Agency for Research on Cancer (IARC) recently classified "shift work that involves circadian disruption" as "probably carcinogenic to humans" (Group 2A) on the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" [32].

The epidemiologic evidence of a relationship between shift and night work and breast cancer in women is based upon nine different studies, six of which suggest a moderately increased risk to develop breast cancer after prolonged exposure to shift and night work [33]. The possible physio-pathological mechanisms actually relate to the internal disruption of biological circadian rhythms and clock genes, melatonin suppression through light by night, sleep deprivation.

Among the above-mentioned retrospective case–control studies, several of them registered in the blood and/or urine of patients suffering from breast cancer a lower melatonin or melatonin metabolite concentrations compared with breast cancer–free women [34–37]. In particular, a study [36] on the correlation between main melatonin metabolite excretion and plasma melatonin suggested that the lower levels registered in breast cancer patients were due to the lower pineal gland hormone secretion, rather than to an increase in peripheral metabolism. One of the earlier studies considered [38] also found nighttime plasma melatonin levels to be lower in estrogen receptor–positive breast cancer patients compared with estrogen receptor–negative breast cancer patients as well as healthy control women. However, other case–control studies registered a higher daytime serum melatonin concentration in breast cancer patients compared with healthy control subjects [39, 40], thus assuming that there is no correlation between breast cancer risk and the mean daytime nadir and night-time peak plasma concentrations [41]; in addition, the amount of 6-sulfatoxymelatonin excreted in 24-hour urine samples turned to be similar both in women suffering from malignant tumors and in women suffering from benign breast disease [42]. It is difficult to relate such findings to both breast cancer patients and breast cancer–free control subjects, since a series of factors—such as the disease itself, treatment, and/or behavioral changes—which might occur after the diagnosis or before surgery/treatment may actually affect melatonin blood levels. Indeed, several studies found melatonin secretion to be positively or negatively associated with the severity of the disease in terms of tumor size [37], depending on whether the cancer has metastasized [43], as well as whether the patients suffered from primary or secondary tumors or not [36]. It is to be said, however, that such studies were performed on a rather limited sample, and some of them did not even include adequate steps to exclude potential confounding effects relating to age, parity, medication use, or body mass index.

Melatonin levels and cancer risk

This research has been carried out based on the keywords: "melatonin" AND "secretion" AND "cancer"; 45 articles were sourced. Among them, the most significant epidemiological and retrospective, case–control studies have been selected and discussed.

Epidemiological studies investigated the role of circadian disruption and cancer risk—breast cancer risk in particular—based upon both direct (urinary melatonin levels) and indirect measurements, including sleep duration and shift work. Melatonin production may be closely related to sleep duration, whereas night-shift work is expected to disrupt sleep pattern and thus decrease melatonin levels [44, 45]. To date, epidemiological studies based on direct and indirect melatonin measurements have been carried out upon Western and Asian populations [46] with suggestive results [47, 48]. Breast cancer risk was significantly and inversely associated with urinary melatonin levels (6-sulfatoxymelatonin) in the Nurses' Health Study II [49], but not in the United Kingdom Guernsey Cohort [50]. Breast cancer risk also resulted to be significantly reduced in association with long sleep duration in Finnish women [51], but not in US women [52, 53]. Results from three different cohort studies [54–56] as well as from two [30, 57] out of three case–control studies [30, 58] also show higher breast cancer risk in women who usually work at evening or in overnight-shifts.

An Italian case–control study nested within the ORDET cohort assessed the concentration of melatonin's major metabolite, 6-sulfatoxymelatonin (aMT6s), in 178 postmenopausal women with incident invasive breast cancer as well as in 710 matched controls. The multivariate relative risk for women in the highest quartile of total overnight aMT6s output, compared with the lowest, was 0.56 (95 % CI, 0.33–0.97). In this report, overnight urinary aMT6s level and breast cancer risk resulted to be more strongly associated in women who were diagnosed with invasive breast cancer more than 4 years after urine collection (OR 0.34 highest versus lowest quartile, 95 % CI, 0.15–0.75) [59]. In a recent study, the same authors observed a positive correlation between aMT6s and breast cancer risk [60].

Overall, present studies a correlation between night-shift work and breast cancer development in Western countries, as reported by Leonardi et al. [61] in her recent review. Table 1 summarizes the studies investigating the correlation between melatonin levels and cancer risk. Further studies are, however, needed to confirm such a correlation as well as to detect the biomolecular mechanisms which may be involved in the pathogenesis of cancer diagnosed in with night-shift workers.

Table 1
Melatonin level and cancer risk

Melatonin, sleep-wake, and mood disturbances in cancer

This research has been carried out based on the keywords: "melatonin" AND "cancer" AND "insomnia" OR "sleep"; 99 articles were sourced. Between these, studies with the greatest number of patients has been selected and discussed.

In cancer patients, depression and its correlated disorders stand for a frequent and severe comorbid condition which may require a special attention [62]. In such patients the prevalence of major depression ranges from 6 to 42 %, whereas based on the 31 reports available, the estimated prevalence rate of depression is 10.8 % [63]. This depends on various cancer-related variables, such as pain and low-performance status, as well as risks for major depression. To avoid the risk of under-diagnosing

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depression, cancer patients should undergo an accurate psychological assessment, combined with a careful analysis of concomitant physical symptoms, such as anxiety, fatigue, cognitive dysfunction, and sleep disturbances [64–69].

When depression complicates medical conditions, this is usually associated with a substantially reduced quality of life (QOL) [70]. Patients also experience increased symptom burden and greater disability and are less likely to adhere to medical treatments [71].

Although depression is common in cancer patients, this is frequently undetected and untreated, so despite high prevalence of depression, studies on effective pharmacotherapy are relatively scarce and in particular are burdened by a high number of dropouts, due to the side-effects relatingto the use of antidepressants vs placebo [72–75]. The evidence for the efficacy of conventional medication in the treatment of depression, such as tricyclics antidepressants and selective serotonin reuptake inhibitors, is very limited. This could be a consequence of their late onset of action. The use of psychostimulants, which on the contrary grant for a rather rapid onset of action might, therefore, deserve more attention [63].

It is thus rather difficult to clearly determine as to what is the best treatment for major depression disorders (MDD) in cancer patients. It has been assumed that conventional evidence-based treatments for depression in noncancer patients can be applicable [76], although further research is anyway required. Additional studies on how to treat depression are also needed to better understand the role of depression treatments in the improvement of life quality, as it has been proved they may lead to a higher completion of adjuvant therapy and can actually extend lifetime [72, 77, 78].

Literature does not include recent double-blind placebo-controlled studies on the use of melatonin in the treatment of cancer patients' depression. However, numerous studies actually prove that melatonin is effective in the treatment of major depression in adult [79–81] and elderly patients [21]. In addition the scientific community shows a rising interest on this topic: in April 2012, a protocol article was published in the British Medical Journal to present a clinical trial which should shortly be started. Such a double-blind placebo-controlled trial is to investigate the effect that melatonin performs on breast cancer patients' depression, anxiety, sleep, and cognitive function disorders [82].

With regard to sleep, the risk of insomnia is usually high in cancer patients [83, 84], yet no large study on the prevalence and nature of cancer patients' sleep disturbance is available to date. The most interesting study on this topic is that of Davidson et al. [83]. This cross-sectional survey study examined (a) the prevalence of reported sleep problems in the patients registered by six clinics at a regional cancer center, (b) sleep problem prevalence in relation to cancer treatment, and (c) the nature of reported insomnia (type, duration, and associated factors). The most prevalent problems seem to be excessive fatigue (44 % of patients), leg restlessness (41 %), insomnia (31 %), and excessive sleepiness (28 %). The breast clinic registered a high prevalence of insomnia and fatigue. Recent cancer treatment was associated with excessive fatigue and hypersomnolence. Insomnia commonly involved multiple awakenings (76 % of cases) and duration $\geq$ 6 months (75 % of cases). In most cases (48 %), insomnia onset was reported to coincide with time at which cancer was actually diagnosed (from 6 months pre-diagnosis to 18 months post-diagnosis).

The causes of cancer patients' sleep disturbance are various, numerous, and pre-existing sleep difficulties often seem to be aggravated by cancer [68].

Cancer itself, including tumors responsible for steroid production and symptoms of tumor invasion

(pain, dyspnoea, fatigue, nausea, and pruritus) can also contribute to poor sleep. As a result of chemotherapy, corticosteroid treatment and hormonal fluctuations also affect patients' sleep and so do medications (narcotics, chemotherapy, neuroleptics, sympathomimetics, sedative/hypnotics, steroids, caffeine/nicotine, antidepressants, and diet supplements) and environmental factors (disturbing light and noise and/or extreme temperature in bedrooms). In addition, the correlation between insomnia and an increased psychological distress due to cancer diagnosis, as well as increased hot flashes caused by menopause, which is often induced by breast cancer treatment, must also be investigated [85]. In cancer patients insomnia may lead to fatigue, mood disturbances, contribute to immunosuppression, affect life quality, and to some extent, may also impact on the course of disease [86] too. The most probable hypothesis about the phenomenology of sleep in breast cancer patients is that the challenges they face may contribute to or cause insomnia, which in turn may exacerbate cancer-associated medical conditions such as pain, psychiatric comorbidities, fatigue, use of opioids (which could contribute to daytime sedation and sleep disorder breathing), stimulating or alerting drugs, napping, and preexisting sleep disturbance [87], thus enhancing a negative feedback loop.

Few pharmacological studies investigating the effect of sleeping pills on cancer patients' insomnia and other symptoms did not register any significant relevance with respect to the full symptom cluster. Although numerous drugs are currently approved for the treatment of insomnia, to date none of them has been tested for safety or efficacy in cancer patients [84]. No pharmacological treatment has been thus specifically validated for the treatment of cancer cluster symptoms. In a cross-sectional survey carried out in Israel on more than 900 cancer patients, the use of a sleeping pill or a tranquilizer was reported by 25 % and was associated with poorer QOL as well as with increased severity of symptoms like insomnia, fatigue, pain, dyspnoea, and constipation. As a conclusion, authors outlined causal inference is not possible given the cross-sectional design [88]. This reinforces the need for well-controlled clinical trials aiming at detecting the best pharmacological sleep treatments for targeted patients.

With regard to drugs treating insomnia in cancer patients, a study by Casault et al. [89] recently assessed the type and frequency of hypnotic medication among a large sample of randomly selected patients who had been previously treated for cancer. Overall, hypnotic medication resulted to be used by 22.6 % out of the patients's sample. Factors associated with a larger use of hypnotic medication were older age, greater difficulty to fall asleep, more stressful life events experienced over the past 6 months, higher levels of anxiety, past or current psychological difficulties, poorer role functioning, less severe urinary symptoms, larger use of opioids as well as past or current chemotherapy treatments. In spite of the precautions taken to ensure that the medication was specifically prescribed for sleep disturbance, the registered rate of current use (22.6 %) was very similar to those reported by Davidson et al. [83] (21.5 %) as well as by Paltiel et al. [88] (25.7 %), who had not made any distinction between the use of medication for sleep and the use of anxiolytic medication or tranquilizers for more general purposes. Also to be mentioned, the prevalence rate of hypnotic consumption since the cancer diagnosis was 37 % (for both current and past users). In this study, nearly 80 % out of the participants who were to take drugs were prescribed benzodiazepine (mainly lorazepam and oxazepam), followed by zoplicone (9 %), a non-benzodiazepine hypnotic. Overall, 12.7 % out of the total sample currently used a drug different from the prescribed medication to control sleep disturbance. Moreover, this study showed that three out of four times hypnotics had been prescribed by general practitioners. Based on this, it might be concluded that cancer patients are more inclined to discuss about their sleeping difficulties with their general practitioner, rather than with oncologists, maybe because they feel more at ease, due either to a consolidated relationship of confidence or to the fact that, compared with

oncologists, practioners normally perform longer and more informal visits. Such a result is similar to those reported in the epidemiological study by Morin et al. [90], according to which over the previous year 15 % out of the sample (2001 participants from Quebec) had been opting for natural products, 3.8 % had been using over-the-counter medications, whereas 4.1 % of them had been turning to alcohol to treat insomnia. Among cancer patients it might be thus assumed that the consumption rate for substances other than hypnotics appears to be equivalent to the rate generally observed among Quebec's population. Although sleep experts recommend patients to limit the use of hypnotics to a period of 2–4 weeks, in this study the average duration turned to be close to 5 years. Moreover, a large proportion (78 %) of the sample used it every day. With such an extended and regular usage, tolerance is very likely; this means that for many patients medications had a lower effect over the time, thus leaving them with unrelieved or only partially treated sleep disturbances (e.g., fatigue and mood disturbances).

To date no double-blind placebo-controlled study has been performed to investigate the use of melatonin in the tratment of cancer patients' sleep disorders.

Melatonin and anticancer effects

This research has been carried out based on the keywords "melatonin" AND "anticancer" OR "oncostatic"; 59 articles were sourced: 13 about in vitro studies, 28 about animal model studies and 18 about clinical studies. With respect to mood disturbance, the research has been carried out based on the keywords: "melatonin" AND "cancer" AND "depression" OR "mood disturbances"; 99 articles were sourced. Between these, studies with the greatest number of patients has been selected and discussed.

Clinical studies in cancer patients show that [91]:

1. melatonin lowers the toxicity of various chemotherapeutic agents including cisplatin, etoposide, anthracyclines, and 5-fluorouracil;
2. in addition, studies registered a statistically significant reduction in treatment-related adverse events, such as myelosuppression, neurotoxicity, nephrotoxicity, cardiotoxicity and asthenia, which overall result in a decreased mortality rate.

A significantly larger interest for the use of melatonin in cancer treatment was recently raised by the Journal of Pineal Research, publishing the meta-analysis performed by a research group led by Mills et al. [92]. The authors studied 643 cancer patients that did not respond to conventional therapy between 1992 and 2002. Such patients were given melatonin as sole treatment for a variety of different solid tumors including lung, brain, skin, renal, and breast. The effect of large doses of melatonin (10–40 mg/day) was assessed on survival rates after 1 year. The risk of death at 1 year was reduced by 34 %. Effects were consistent depending on melatonin dosage as well as on cancer type. No severe adverse events were reported and the study concluded that substantial reduction in death risk, low side effects, and low costs can actually forecast a larger potential use of melatonin in cancer treatment.

The role of melatonin as an oncostatic drug has been widely documented in in vivo and in vitro experimental investigations, covering a large number of different neoplasias including breast, prostate, colorectal cancer, glioblastoma, leukemia, etc. [93–99]. This definitely clashes with the very limited number of clinical trials aiming at possibly transferring such basic findings into proper clinical protocols [91]. An exhaustive review on anticancer drugs is provided by Grant et al. [18].

In vitro and in animal model studies

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Studies proved melatonin plays a role in the prevention of tumor initiation, promotion, and progression. Melatonin's oncostatic properties relate to

a. its antiproliferative effects [93, 97];
b. direct inducing of natural killer cell activity, which enhances immunosurveillance and stimulates cytokine production, such as interleukin 2,6, 12, and interferon gamma [17];
c. its ability to increase protein 53, a tumor suppressor protein [100];
d. inhibiting linoleic acid uptake via activation of MT1 and MT2 receptors, thereby preventing the formation of the mitogenetic metabolite 1,3-hydroxyoctadecadienoic acid [101];
e. its capacity to induce cell differentiation [102];
f. its antimetastatic effects [103];
g. its anti-angiogenic activity [104];
h. its ability to modulate gene expression [105];
i. its interaction with estrogen receptors, down-regulating their expression, binding to DNA and transactivation [97, 106, 107];
j. its anti aromatase actions [108, 109];
k. its modulation of the immune response [110, 111];
l. its capacity to decrease telomerase activity [112, 113]; and
m. its function as a free radical scavenger [114].

Studies in animal models generally support the hypothesis according to which melatonin can influence the frequency and growth of spontaneous and induced tumors: a pinealectomy can increase tumorigenesis and shorten survival time, whereas administration of melatonin reverses these trends and inhibits tumor growth [115].

Clinical studies

Melatonin is transmitted through receptors as well as through distinct second-messenger pathways to reduce cellular proliferation and induce cellular differentiation. In addition, independently from receptors, melatonin can also modulate estrogen-dependent pathways and reduce free-radical formation, thus preventing mutation and cellular toxicity. Since melatonin works through a myriad of cell-protecting signaling cascades, this hormone can be suitable for clinical cancer prevention and/or treatment [91].

Wang et al. [116] recent meta-analysis of randomized controlled trials indicates a consistent effect on tumor remission, 1-year survival, and radiochemotherapy-related side effects of adjunct melatonin in a variety of advanced stage cancers. As an adjuvant therapy melatonin led to significantly higher tumor remission, better survival at 1 year, and less radiochemotherapy-related side effects, including thrombocytopenia, neurotoxicity, and fatigue. In many cases cancer had previously resulted to be refractory to standard therapy and thus more suitable for the adjunct use of an untested and unproven therapy like melatonin. The large efficacy as well as the limited number of serious adverse events should actually be of interest to both clinicians and patients. The main limitation is that most [6] trials were performed in the same center [117–122], while only two other studies were performed in different centers [123, 124]. Although the sample size of eight different trials has been enlarged, it is still relatively limited. Since such items may to some extent affect the reliability of the results assessed, authors pointed out international multicentre RCTs with larger sample size are still needed. In the eight studies performed, a once-a-day 20-mg melatonin oral dosage was prescribed. Table 2 summarizes the main studies in which melatonin was administered to cancer patients.

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Table 2
Clinical studies in which melatonin has been administered to cancer patients

Toxicity studies of melatonin

The vast majority of studies document the very low toxicity of melatonin over a wide range of doses, even in up to 20-mg dosages, as reported by Sánchez-Barceló et al. [91], where a number of clinical trials have been reviewed to assess the therapeutic usefulness of melatonin in different medical fields.

Conflict of interest

Go to:

The authors declare that there is no conflict of interest. As this paper is meant for review, this is to certify there is no conflict of interest relating to the control of all primary data.

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