**Melatonin as new therapy of ovarian Cancer (review)**

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**Abstract**

One of the main reasons of loss of life amongst women with reproductive tract problems is ovarian cancers. Despite the fact that many surgical strategies and chemotherapy had been carried out to deal with ovarian cancer, the diagnosis remains weak. In latest years, a few researches have pronounced the anticancer impact of melatonin on ovarian cancer. The melatonin impact groups become studied for ovarian cancer the usage of the desired mouse model of ethanol. The left ovarian was fertilized with the ovarian tumor and the right ovary was used as a manage in sham surgical operation. They observed that melatonin can lessen ovarian tumor mass and decrease adenomas in mice. In the end, they investigated the impact of improved apoptosis in melatonin on ovarian cancer. The outcomes confirmed that absolute and relative tumor masses had been considerably decreased after melatonin therapy, regardless of ethanol intake. Together, melatonin has proven an anticancer impact on ovarian cancer. The underlying mechanisms encompass apoptosis, cellular cycle arrest, and immune regulation (receptors similar to numbers). In the end, a observe of women with ovarian cancer confirmed serum serum melatonin levels had been considerably lower in women with ovarian cancer than in healthful women (P <0.05).

**Melatonin secretion**

Response to darkness the pineal gland of mammals and human secreted melatonin (N-acetyl-5-methoxytryptamine, Figure 1)[1].

In addition, synthesis of melatonin is found in other organs, such as skin, lymphocytes, bone marrow, gastrointestinal tract, retina[2].

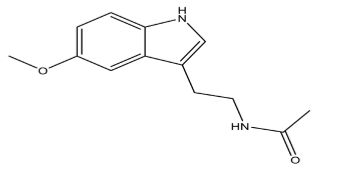
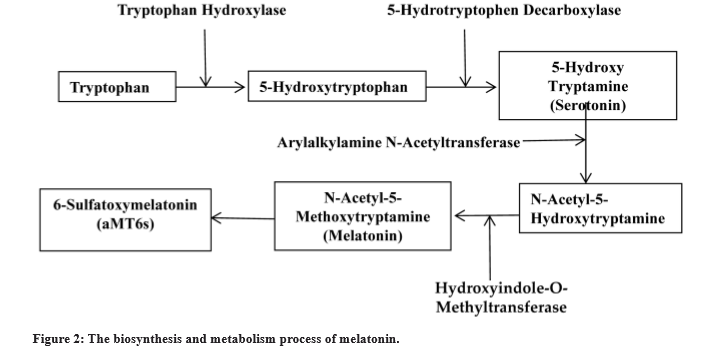


Figure (2) show the process of metabolism and biosynthesis of melatonin. The primary metabolite 6-sulphatoxymelatonin (aMT6s) only is involved. Commonly, it is used as the maker of the daily level of melatonin [3-5].



The level of melatonin is decreases throughout the day and elevates at night.

Some studies demonstrated that when the level of melatonin increase in the blood at night time can refer to the organs and body’s cells that it is night time. Furthermore, this will help organ systems into suitable homeostatic metabolic rhythms[8].

Consequently, the daily rhythm and the melatonin formation could disrupt by light at night (LAN) [9], which lead to development of cancers such as ovarian cancer (OC) [10].

The advance of various cancers counting gynecological cancers is related to the deficiency of melatonin[11, 12].

The effects of antiangiogenic activity, antioxidant and the immune system of melatonin supplementation has an important role in inhibition cancer [13].

**Is melatonin involved in the development of ovarian cancer?**

The most common gynaecological cancer in worldwide is Ovarian cancer. Typically it is lead to death.

Several studies suggested that shift work night is connected with the increased danger of gynecological cancers such as endometrial cancer [15] and breast cancer [14]. Even though the pathogenesis of ovarian cancer is not clear. One of the mechanisms of this association may be the lower melatonin production by pineal gland. At night, the darkness length is the important factor to secrete the melatonin circadian. Wherefore, melatonin secretion reduces when exposure to light at night. Decreased levels of serum melatonin were observed in a female with endometrial cancer [16].

The relationship between the danger of increasing ovarian cancer and melatonin has been recommended. While, the danger of increasing ovarian cancer does not seem to be associated with the night shift work [17].

This led us to study whether the circulating levels of melatonin are related to cancer of ovarian. In present study, the data demonstrations that the melatonin levels were significantly higher in healthy women compared to women have ovarian cancer, irrespective the organization of ovarian cancer. Melatonin is also formed by ovaries that regulate the function of the ovaries, in addition to the pineal gland [18, 19], and the decrease levels of melatonin influences ovary morphology [20] .

The studies show that the melatonin Supplementation decrease occurrence of ovarian cancer in ethanol-deprived rats [21]. Also, melatonin treatment found to have an additive influence on chemotherapy in a metastatic breast cancer case [22]. Consequently, the study data recommend that melatonin play an important role in the development of ovarian cancer. The action of melatonin such as anti-angiogenic activities and anti-oxidative stress which contributes to cancer prevention was suggested by some recent research[13].

The melatonin’s anti-oxidative effects have been recommended to be pronounced in hormone-dependent cancers for example ovarian cancer and breast [11]. The cell of cancer become more active when the melatonin secretion is blocked. These research recommended that melatonin is a modifier of developing cancer, especially in hormone-related cancers such as cancer of ovarian. However, the present result shows that there is no significant difference in levels of melatonin in patients with peritoneal metastasis compared to patients without peritoneal metastasis. Melatonin affects the secretion of estrogen, in addition, its anti-angiogenic and anti-oxidative stress. The level of estrogen is involved in the development of hormone-related cancer such as ovarian cancer [23].

Exposure to night light interrupts the natural estrogen- melatonin balance. Therefore, the decreeing secretion of melatonin than normal levels cause more estrogen release. The breast cancer and ovarian cancer have high sensitivity for estrogen.The research recommended that the decreasing of serum melatonin levels is an association with endometrial cancer regardless of the menopause status [24].

**In vitro studies**

Some researches in vitro proved that the growth of many cancer cells can be inhibit via an anti-proliferative effect of melatonin, such as ovarian cancer, breast cancer and cervical cancer. Also, melatonin has influence on controlling cell death [25].In recent studies, they investigated that the melatonin has an anticancer effect on cancer of ovarian. Melatonin-induced ovarian cancer cells collect OVCAR-429 and PA-1 in phase G1 by regulating CDK 2 and 4 [26]. In addition, although melatonin alone showed no apparent cytotoxicity against human ovarian cancer cells SK-OV-3, melatonin can support apoptosis of cisplatin apoptosis. Inhibition of Caspase 3 and encouraging inhibition of cisplatin for extracellular kinase regulation (ERK) and 90 kDa ribosomal S6 kinase (p90RSK) and 27 thermal shock protein (HSP27) phosphorylation occurs by stimulating melatonin for apoptosis

**In vivo studies**

Several studies in vivo observed that the production of melatonin is reduce when the body exposure to the light at night time and consequently the rats with breast cancer become unresponsive to chemotherapy [28].The researchers have not completely studied the relationship between ovarian cancer and melatonin.The ovary morphology effect when the level of melatonin decrease [29]. In addition, the researchers in vivo found that the melatonin supplementation reductions the ovaries weight in the rat [30] portentous the metabolism of melatonin have a direct influence on the women generative system through effect the ovaries function [31]. From the vitro and vivo studies might suggest that there is a relationship between the danger of increasing ovarian cancer and melatonin levels. Researchers used an ethanol-preferring rat model to study the melatonin effect of oncostatic on cancer of ovarian. They have vaccinated the left ovary with a tumor of ovarian, while the right ovary was used as control of sham-surgery [32-34]. They demonstrated that the tumor masses of ovarian can be reduce and decrease the rate of adenocarcinoma in rats by the melatonin. Further, they study melatonin effect of the apoptosis-promoting on cancer of ovarian.

Irrespective of ethanol consumption, the studies proved that significantly reduced of complete and relative masses of tumor after melatonin therapy. Melatonin therapy encouraged apoptosis as considered by upregulation of cleaved caspase-3, p53, and BAX, also an improvement of DNA fragmentation [32]. Moreover, the researchers observe that in rats with ovarian cancer the melatonin reduced the TLR4-induced MyD88- and TRIF-dependent signaling pathways [33].The growth factor receptors of epidermal 2 (Her-2) and 4 (Her-4) were strongly associated with the development of the ovarian cancer metastasis [35]. In the ethanol-preferring rat model, the research proved that the melatonin might reduce the Her-2-signaling pathway. Through significantly suppress the expression of Her2, p38 MAPK, and p-Akt. Communally, melatonin has shown anticancer consequence on cancer of ovarian. Also, the fundamental mechanisms contain cell cycle arrest and apoptosis, and immunoregulation (toll-like receptors)[36].

**Conclusion**

We demonstrate that there is a strong association between ovarian cancer in women and the decreasing melatonin levels. There is no relation between the level of melatonin and the occurrence of cancer of ovarian through the birth season in women with cancer of ovarian. Therefore, it is not subject to diagnosis in these patients. these findings need further studies to confirm.

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