Dynamic Chiropractic

WOMEN'S HEALTH

The Value of Melatonin in Breast Cancer Prevention and Adjunctive Treatment

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Although melatonin (MLT) is best known for its sleep-aid properties and as a natural remedy to prevent jet lag, extensive experimental studies suggest it possesses anticancer activity through several biological mechanisms: anti-proliferative action, stimulation of anticancer immunity, modulation of oncogene expression, and anti-inflammatory, antioxidant and anti-angiogenic effects. Several experimental studies have shown MLT may inhibit cancer cell growth, and preliminary clinical studies have shown its anticancer property in human cancer patients.

In 2004, Dr. P. Lissoni (Milan, Italy), provided ground-breaking clinical evidence that therapeutic doses of MLT (given orally at 20 mg/day during the dark period of the day) could be used by patients with advanced solid tumors to improve survival, quality of life outcomes, and in some cases, achieve stable disease; as well as reducing many side effects of chemotherapy (asthenia, thrombocytopenia, stomatitis, cardiotoxicity and neurotoxicity).[1] Regarding supportive care, the frequency of cachexia, asthenia, thrombocytopenia and lymphocytopenia was significantly lower in patients treated with MLT than in those who received supportive care alone.

A striking feature of these studies was the large sample size, suggesting the findings were significant and reproducible in a significant number of patients. Dr. Lissoni studied 1,440 patients in his cancer supportive care study and 200 patients in his study involving patients undergoing chemotherapy for the treatment of metastatic tumors.[1]

Melatonin for Breast Cancer Prevention

In regard to melatonin and breast cancer, a brilliant review paper appeared in *Natural Medicine Journal* in 2010, authored by T. Kaczor. In her review, she highlights the multimodal mechanisms through which melatonin may be associated with reduced risk of breast cancer development:

Reduces Estrogen and Progesterone Levels: MLT affects the hypothalamic-pituitary-ovarian (HP) axis, which results in lower circulating levels of estrogen and progesterone. Overstimulation of estrogen is linked to breast cancer development, as well as breast cancer progression, in patients with estrogen-receptor-positive breast cancer.

SERM Effects: On a cellular level, MLT acts as a selective estrogen receptor modulator (SERM) through decreased expression of estrogen receptor-alpha and reduction in the ability of estrogen-estrogen receptor alpha (ERα) complex to bind to the estrogen response element (ERE) on DNA. The net result is slowing down of cellular replication, which is linked to breast cancer prevention.

In patients with estrogen-receptor-positive breast cancer, these patients are often given SERM drugs (e.g., tamoxifen, raloxifen) to help slow down cellular replication of breast cancer cells. MLT may provide a nontoxic adjunctive treatment in this regard, working synergistically with other SERM drugs.

Aromatase Inhibitor: MLT inhibits the aromatase enzyme that converts certain androgens (androstenedione, testosterone) into estrone and estradiol hormones, both of which are linked to breast cancer in cases of overstimulation, as well as the progression of estrogen-receptor-positive breast cancer. Other natural aromatase inhibitors include indole-3 carbinol (found in cruciferous vegetables) soy isoflavones, and enterolactone and enterodiol (derived from the ingestion of ground flaxseed). Each of these aromatase inhibitors is associated with decreased breast cancer risk in various peer-reviewed, published studies.

Anti-Proliferative via Calmodulin Binding: MLT has demonstrated antagonist effects on estradiol-induced ERα-mediated transcription of proliferative genes through its binding to calmodulin in the cytosol. Calmodulin is a common intermediate signal transduction messenger in many cells. In breast cells, when the ERα-calmodulin complex is bound by melatonin, it is incapable of binding to the promoter regions or the ERE of DNA. This reduces the transcription of many downstream

genes that increase proliferation. The result is a slowing down of cellular replication, which is associated with decreased cancer risk.[2]

Melatonin as an Adjunctive Treatment in Breast Cancer

In her review, T. Kaczor also identifies the mechanisms through which MLT may reduce the invasiveness of breast cancer when used as an adjunctive treatment:

Preserves Adhesion Molecules: MLT decreases motility and invasive capabilities of breast cancer cells (MCF-7) cells *in vitro.* (MCF-7 cells are human breast cancer cells that are estrogen-receptor positive, progesterone-receptor positive and Her-2-receptor negative.) This is partly due to melatonin stimulating expression of cell surface adhesion molecules, such as E-cadherin and ß1-integrin, which allow for attachment of the cells within the extracellular matrix, as well as to each other.

These adhesion molecules are downregulated by estrogen, increasing the invasive potential of the cell. MLT has been shown to increase the expression of these adhesion molecules in MCF-7 cells.

Telomerase Inhibitor: Many tumor cells switch on their telomerase gene to produce the enzyme telomerase, which essentially makes cancer cells immortal and able to divide endlessly, by re-lengthening the telomere DNA at the end of the chromosomal chain. MLT has been shown to prevent cancer cells from preserving telomere length with each cell division by inhibiting the effects of telomerase enzyme.

As such, telomere shortening occurs in cancer cells with each cell division, which eventually leads to cells that can no longer divide. This reduces the tumor growth and prevents cancer cell immortality.

Inhibits 15 Lipoxygenase, Thus Reducing 13 HODE Synthesis: Melatonin binds to membrane receptors, ML1 and/or ML2, leading to a decrease in cellular uptake of the essential fatty acid linoleic acid. As such, cancer cells have less access to linoleic acid, which it otherwise converts to an eicosanoid known as 13-hydroxyoctadecadienoic acid (13-HODE) via the 15-lipoxygenase enzyme.

Cancer cells use 13-HODE to foster their own proliferation via several mechanisms (energy source and growth-signaling molecule via epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) pathway). By inhibiting access to linoleic acid and inhibiting the 15-lipoxygenase enzyme, MLT reduces cellar levels of 13-HODE, thereby reducing the proliferation rate of cancer cells.

Binds to Retinoid Receptors: MLT also binds within cells to retinoid receptors (RZR/RORα steroidal region of DNA), which leads to altered transcription of several genes involved in cellular proliferation, such as tumor suppressor gene p21 and pro-inflammatory 5-LOX. Additionally, melatonin has been shown to potentiate the pro-apoptotic effect of retinoic acid, thereby promoting programmed cell death by cancer cells.

Immune Modulation: One study showed MLT enhances the release of interleukin-2 (IL-2) and IL-2 receptor system, which is known to provide significant immune boost in fighting cancer. A number of clinical trials have shown a potentiation of the cancer-fighting effect of conventional cancer therapies when IL-2 was administered concurrently.

Suppresses Inflammatory Cytokine Release: MLT has been shown to exert systemic anti-

inflammatory effects, as demonstrated in lower circulating levels of IL-6 and erythrocyte sedimentation rate (ESR) in patients taking melatonin. Less inflammation is likely to affect both tumorogenesis and proliferative and metastatic pathways that are otherwise stimulated by inflammatory cytokines.[2]

Melatonin Declines with Age and in Night-Shift Workers

It is well-known that the decline in melatonin secretion by the pineal gland begins shortly after the onset of puberty and that by age 50, melatonin levels are significantly lower than in one's early teen years. Curiously, 50 years of age is approximately the time when breast cancer rates tend to escalate. Although breast cancer development is linked to various etiological factors, low melatonin may be one of them.

On a daily basis, the pineal production of melatonin follows a diurnal rhythm, with peak production at about 2 a.m. What is noteworthy is that a number of studies have shown circadian disruption of melatonin secretion, specifically in night-shift workers, is correlated with an increased risk of developing breast cancer.

"Since excessive exposure to estrogen is a well-established risk factor for breast cancer development, some researchers hypothesize that the increased risk in night shift workers is due to a relative increase in estrogenic stimulation when melatonin production is disrupted."[2]

Several prospective studies also have shown that lower morning melatonin metabolite levels in the urine (6-sulphatoxy melatonin) are associated with an increased risk of breast cancer development. In addition, some studies show that melatonin levels are lower in female breast cancer patients.[2]

Melatonin Supplementation

Although still speculative, a considerable amount of research suggests it may be prudent to take a low-dose melatonin supplement (0.5-3.0 mg) an hour before bedtime to help prevent breast cancer once one reaches middle-age (e.g., beginning between ages 40-50). Oral supplementation has been shown to have important physiological effects and therapeutic benefits in various health challenges (e.g., insomnia, jet lag, adjunctive treatment of prostate and breast cancer, reduced side effects of chemotherapy).[1] This practice may enable your body to capitalize on the breast cancer prevention mechanisms outlined in this article.

In regard to using high-dose melatonin supplementation (above 3 mg per day) in the adjunctive treatment of breast cancer, this should only be done under the supervision of the attending medical physician, who needs to monitor liver enzymes, kidney function, blood counts and other important parameters critical to cancer management. Additional research pertaining to the anticancer benefits and clinical studies involving melatonin can be found in an article by Eileen M. Lynch, PhD, published in *Life Extension* magazine.[3]

References

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3. Lynch EM. "Melatonin and Cancer Treatment." *Life Extension*, January 2004.