Melatonin in Breast Cancer Prevention and Adjunctive Breast Cancer Treatment

James Meschino DC, MS, ROHP

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

The published paper appearing in *Supportive Care in Cancer* in 2004*,* by Dr. P. Lissoni M.D. (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). 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 that the findings were significant and reproducible in a significant number of patients. Dr. Lissoni's 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)

Breast Cancer Prevention with Melatonin

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 multi-modal mechanisms through which melatonin may be associate with reduced risk of breast cancer development.

These include:

- **Reduces Estrogen and Progesterone Levels -** MLT affects the hypothalamic-pituitary-ovarian (HP) axis, which results in lower circulating levels of estrogen and progesterone. Over stimulation 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 to slow down cellular replication of breast cancer cells. MLT may provide a non-toxic 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 over-stimulation, 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 are 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. These include:

- **Preserves Adhesion Molecules** – MLT decreases motility and invasive capabilities of breast cancer cells (MCF-7) cells in vitro (MCF-1 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 β1-integrin**,** which allow for attachment of the cells within the extracellular matrix as well as to each other. These adhesion molecules are down-regulated 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 each 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 or 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 (RZR/RORα steroidal region of DNA)** 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. As well 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 that (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 (e.g. drug - Proleukin). A number of clinical trials have shown a potentiation of the cancer fighting effect of conventional cancer therapies when IL-2 was administered concurrently.

- **Suppress 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 that 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) .

As well, several prospective studies have shown that lower morning melatonin metabolite levels in the urine (6-sulphatoxy melatonin) is 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 that it may be prudent to take a low-dose melatonin supplement (0.5 mg – 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 etc.). (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 anti-cancer benefits and clinical studies involving melatonin can be found in the published article by Eileen M. Lynch PhD in Life Extension Magazine, January 2004 issue. (3)

References:

1. Lissoni P. Is there a role for melatonin in supportive care? Review Article. Supportive Care in Cancer. 2002. 10;2:110-116.

2. Kaczor T. An overview of melatonin and breast cancer. Natural Medicine Journal. 2010. (vol 2, issue 2): http://www.naturalmedicinejournal.com/journal/2010-02/overview-melatonin-and-breast-cancer

3. http://www.lifeextension.com/Magazine/2004/1/report_melatonin/Page-01?p=1