
Re: Melatonin and Breast Cancer: A Prospective Study

The recent paper by Travis et al. (1) describing 24-hour urinary melatonin metabolite excretion among women in the Guernsey cohort study, who have or have not developed breast cancer since 1985, requires two specific comments. In general, this is a solid study considering the impact of most known modulators of breast cancer risk and the level of 24-hour urinary 6-sulfatoxymelatonin excretion obtained near the point of study entry. These data fail to show a predictive relationship between the level of 24-hour melatonin excretion and breast cancer risk an average of 12 years later.

First, melatonin is a primary circadian pacemaker whose chronobiologic job is to provide environmental information to each cell of the body. This information is, at least in part, transduced by light-sensitive changes in

daily timing of melatonin onset and offset and by the daily nocturnal peak. In addition, differences in the nocturnal duration of melatonin secretion and thus its distribution across the night cannot be accounted for by measuring 24-hour excretion levels. For example, in the face of no change in the circadian phase of nocturnal melatonin peaks, some individuals may experience a shorter duration and higher amplitude of nocturnal melatonin, whereas others may experience a longer duration and a lower amplitude of melatonin across the night. These events could result in identical average 24-hour melatonin levels among these individuals, even though the distribution, and, thus duration, of exposure to elevated nocturnal melatonin over the course of each night would be vastly different. The average 24-hour level of this hormone provides no timekeeping information. The question at hand is, therefore, whether cancer risk is conferred by an average 24-hour melatonin exposure or by the circadian temporal organization of melatonin availability. Those studies, which demonstrate relationships between cancer risk and melatonin excretion, find this relationship between circadian amplitude or phase (time of melatonin upswing), not the average amount of melatonin metabolite excreted in 24 hours.

Second, the authors, appropriately, take pains to point out the relationship between light at night and cancer risk and light at night and melatonin availability. Women who do shift work, which is considered a surrogate for light at night, have an elevated risk of both breast and colorectal cancers (2–4). Recent experimental evidence in animal models of cancer shows that exposure to light during the dark phase of an alternating light–dark cycle suppresses the synthesis of melatonin and increases fatty acid metabolism and the growth of transplantable murine liver tumors (5,6) and human breast cancer xenografts (7). The authors do not provide information or comment upon the relative nighttime light exposure of case patients and control subjects, which is most germane and potentially the most serious confounding factor in this study.

In summary, studies of the circadian pattern of melatonin secretion

and metabolite excretion are essential to knowing whether melatonin circadian dynamics confer cancer risk. Not determining the time of the melatonin nightly upswing, the nocturnal peak, the duration of nocturnal melatonin exposure, and the slope of its rise and fall is akin to averaging amplitude- and frequency-modulated radio signals and being surprised when no music issues from a radio receiver. Because light exposure and especially nocturnal light exposure may confer cancer risk through modulation of the melatonin circadian pattern, independent information about nocturnal light exposure of each case patient and control subject is essential for assessing the melatonin-modulated cancer risk.

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