# The Melatonin Hypothesis: Electric Power and Breast Cancer

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Breast cancer is a disease of modern life. As societies industrialize, risk increases, yet it is unclear which of the myriad changes coming with industrialization drives this increase. One important hallmark of modern life is the pervasive use of electric power. Electric power produces light at night (LAN) and electric and magnetic fields (EMF), either or both of which may alter pineal function and its primary hormone melatonin, thereby, perhaps increasing the risk of breast cancer. This hypothesis, stated a decade ago, is now receiving considerable experimental and epidemiological attention. The circumstantial case for the hypothesis has three aspects: light effects on melatonin, EMF effects on melatonin, and melatonin effects on breast cancer. The strongest of these aspects is the effects of light on melatonin. It is clear that the normal nocturnal melatonin rise in humans can be suppressed by light of sufficient intensity. The evidence for an effect of melatonin on breast cancer in experimental animals is strong, but the evidence in humans is scant and difficult to gather. The weakest aspect of the circumstantial case is EMF effects on melatonin. Whereas a half dozen independent laboratories have published findings of suppression in animals, there are inconsistencies, and there are no published data on humans. The direct evidence bearing on the hypothesis is sparse but provocative. Two laboratories have published data showing substantial increases in chemically induced breast cancer in rats by a weak AC (alternating current) magnetic field. The epidemiological evidence is very limited but has offered some support as well. An effect of electric power on breast cancer would have profound implications, and this possibility deserves continued investigation. — Environ Health Perspect 104(Suppl 1):135–140 (1996)

Key words: breast cancer, EMF, electric power, epidemiology

## Introduction

Breast cancer is the leading cause of cancer death in women in industrialized countries. Incidence rates, and to some extent mortality, are increasing worldwide (1,2). The assumption that the cause of these increases is the change from indigenous diets to the high-fat western diet has been challenged by recent evidence showing no relationship between adult fat consumption and breast cancer risk (3). Given the conflicting evidence, the role of adult consumption of dietary fat in breast cancer etiology, if any, is unclear. High energy intake in childhood may be important (4) but is difficult to study epidemiologically. Recent enthusiasm for estrogenic chemicals in the environment as an important determinant of risk (5) has also been tempered by recent studies (6) and biological considerations (7).

Something about industrialization seems to increase risk of breast cancer. But which of the changes brought by industrialization is responsible? The generation, distribution, and use of electric power is a hallmark of modern life. Electric power results in human exposure to light at night (LAN) and anthropogenic (including 50/60 Hz) electric and magnetic fields (EMF). These are relatively new exposures in the human environment and, in modern society, virtually everyone is exposed to some extent. Could electric power be implicated in the high rates of breast cancer in industrialized nations? The reason to consider this suggestion is the possible reduction of melatonin by LAN and/or EMF (8–10). Melatonin, in turn, has a strong inhibitory effect on breast cancer in animals (11). The relative importance of melatonin disruption in the etiology of breast cancer in humans is not yet clear.

## The Circumstantial Case

There are three aspects to the circumstantial case: the effect of light on production of melatonin, the effect of EMF on production of melatonin, and the role of melatonin in breast cancer.

### Light Effects on Melatonin

The effect of light on pineal function in humans has been extensively studied (12). Several features of light's effect are relevant to the melatonin hypothesis for a connection between electric power and breast cancer: a) the effect is qualitatively similar to the effect in other mammals in that sufficient intensity of nocturnal illumination suppresses melatonin production to daytime levels (13,14); b) some people are much more sensitive than others (15); c) blue–green light is most effective in reducing melatonin production, whereas red light has little or no effect (16,17); d) there appears to be a dose–response relationship with light (18) from minimal suppression at 200 lux to maximal suppression at 3,000 lux (the brighter the light the greater the reduction in circulating melatonin); and e) the effect of light at night can be seen in humans within 15 min (14,18).

The normal melatonin rhythm in humans has characteristics that may be relevant to breast cancer risk (19). The rise of melatonin at night is not dependent on the sleep/wake state; if the light level is dim, a person will maintain a normal rhythm even if he or she is awake all night. There are large interindividual differences in total 24-hr melatonin production, although each person's rhythm is quite stable from night to night. A person's usual 24-hr melatonin production is not dependent on his/her usual sleep length per night. Usual sleep length per night is, however, positively correlated with the percent of the 24-hr melatonin production that occurs at night. An interesting question that has not so far been answered is whether individual sensitivity is related to usual melatonin rhythm,

e.g., do those who are most sensitive to the suppressive effects of nocturnal illumination also have a low (or high) normal melatonin peak at night or a total production over 24 hr?

It is not clear whether the intensity of night-time light typically found in bedroom environments at night (several lux or less) has any effect on melatonin production. The ambient nocturnal illumination may be inadequate to affect pineal function at all, particularly during sleep when the eyelids are shut, further reducing retinal illumination from bedroom light intensity. In animals, very brief light exposure (minutes or even seconds) at night can suppress melatonin production (20); however, extension of illumination by use of electric lighting into the night before sleep and brief exposure to bright light during the night may or may not have chronic effects on melatonin that are relevant to breast cancer risk in humans. Effects will depend on the intensity of light and the sensitivity of the individual.

## Effects of Electric and Magnetic Fields on Melatonin

The first reports that the pineal body might respond to an artificial EMF appeared in the early 1980s. Semm et al. (21) measured electrical activity of pineal cells in anesthetized male guinea pigs. They found that some pineal cells showed a drop in activity upon application of a static magnetic field generated by two Helmholtz coils positioned around the head to provide an addition or subtraction to the vertical component of the geomagnetic field. Wilson et al. (22) reported that exposure of rats to a 60-Hz electric field suppressed the normal nocturnal rise in pineal melatonin production in male Sprague-Dawley-derived rats.

Since the Semm et al. (21) and Wilson et al. (22) publications, there have been additional reports that melatonin can be suppressed by AC electric fields (23), rapid changes in a static magnetic field (24–27), and AC magnetic fields (28–30). There have also been reports that such fields have little or no effect (31–33). AC magnetic fields as low as 10 mG have been reported to suppress melatonin in rats (29,30). The differences among experimental reports may result from real differences in the effectiveness of the fields employed in each experiment, from artifacts associated with the EMF exposures, such as noise or other stress that account for a reduction of melatonin production in those experiments claiming to show effects of EMF; or from

real effects on melatonin that are sometimes masked by natural biological variability. Because the various laboratories reporting effects are experienced in melatonin research and have experience or expert assistance in EMF dosimetry, the possibility that artifact accounts for all of the positive effects seems unlikely.

It is unclear whether EMF can affect melatonin in humans, and several laboratories are currently pursuing the question. Typical ambient AC magnetic fields away from appliances in people's homes are in the 1 to 2 mG range (34). The weight of evidence supports the position that an artificial EMF can lower melatonin in some animal species under some exposure conditions.

## Melatonin and Breast Cancer

Manipulation of melatonin levels has been found to affect development of several different cancer types in animals including breast cancer, prostate cancer, and melanoma (11). In particular, melatonin injection has been reported to inhibit chemically induced mammary tumor development in rats, and pinealectomy enhances it in both the DMBA model (35) and the N-nitroso-N-methylurea (NMU) model (36). There are several mechanistic interpretations of these observations (37). Two of these interpretations—that melatonin may slow development and turnover of the normal mammary cells at risk of malignant transformation and that melatonin may be directly oncostatic—act at opposite ends of the carcinogenic process. For epidemiological studies, the oncostatic capability of melatonin is far more tractable because recent exposures that lower melatonin level would be relevant; if melatonin slows development of normal cells that are at risk, exposures in the very distant past would be relevant and correspondingly much more difficult to estimate.

Night-time plasma melatonin levels have been reported to be lower in women with estrogen receptor positive (ER+) breast cancer than in ER negative (−) breast cancer and in healthy control women (38) and lower in cases of primary breast cancer than in women with benign breast disease (39). In contrast, daytime melatonin was found to be higher in breast cancer patients in one report (40). It is difficult to assess the meaning of these findings due to the presence of disease and its possible effect on melatonin levels. It is difficult to determine whether low nocturnal melatonin predisposes to increased risk of breast cancer in women. Clarifying

the role of melatonin in normal and malignant growth of breast tissue may provide a better understanding of the roles of estrogen and prolactin in the etiology of breast cancer.

## The Direct Evidence

### Experimental Evidence

Shah et al. (41) reported that constant light increased DMBA-induced mammary tumorigenesis in rats. Constant light effectively suppresses melatonin production by the pineal gland. At 55 days of age, rats exposed to constant light from birth showed a greater concentration of terminal end buds and alveolar buds in mammary tissue than did rats raised on a 10-hr light:14-hr dark regimen. Animals exposed to constant light also showed greater DNA synthesis activity in the mammary tissue and higher levels of circulating prolactin. A suggested mechanism for these results is that reduced melatonin resulted in increased circulating estrogen and prolactin and, consequently, increased turnover of the breast epithelial stem cells at risk of malignant transformation (41,42).

The first report of an EMF-mammary cancer experiment to appear in the peer-reviewed literature was published in late 1991 by Beniashvili et al. (43). Magnetic field exposure increased mammary cancer incidence in rats treated with NMU compared to NMU-treated rats not exposed to the field (controls). There were 50 female rats in each of five groups treated with NMU at 55 days of age. The first four groups were exposed to either a 50-Hz magnetic field or a static field for 30 min/day or 3 hr/day. The rats were followed for 2 years. All exposed groups developed more mammary tumors than the unexposed group 5, and the mean time to appearance of first tumor was shorter. The group exposed to a 50-Hz magnetic field for 3 hr/day developed mammary tumors in 43 of its members, whereas in the control group only 27 developed tumors; there were 75 total tumors in the exposed group and 31 in the unexposed group (p<0.05). Five more groups of rats were studied in which no NMU was used. No tumors developed in 50 control rats over the 2-year study period, whereas seven tumors appeared in 25 rats exposed to the 50-Hz magnetic field for 3 hr/day. The results of Beniashvili et al. (43) are striking; this is the first publication, positive or negative, describing the direct influence of EMF on mammary tumor induction in an animal model.

Löscher et al. (44) performed a similar experiment using a 1-G 50-Hz magnetic field and 20 mg of DMBA. These authors also reported a significant increase in mammary tumor induction in rats exposed to the field. Given the high 20-mg dose, 35 of 99 control animals developed palpable mammary tumors within 13 weeks of treatment. Among 99 exposed rats, 53 developed tumors (p<0.05). The size of tumors was also significantly larger in the exposed animals. Löscher's laboratory has repeated these experiments and has also published a series of papers (30,45–48).

Among the mechanisms that have been proposed for an EMF effect on mammary tumor development (37), the one with the shortest expected latency period is an EMF-induced disruption of melatonin's oncostatic action. Liburdy et al. (49) reported that a 12-mG 60-Hz magnetic field could reverse the growth inhibition of MCF-7 mammary cancer cells by melatonin in vitro. This is the only report thus far on this potential mechanism and deserves to be pursued in additional independent laboratories.

The direct laboratory evidence is still quite limited but is clearly provocative and important to pursue. This experimental evidence provides direct support for the biological rationale for examining a possible influence of EMF exposure on risk of breast cancer in women.

### Epidemiological Evidence

If LAN increases risk of breast cancer in sighted women, Hahn (50) reasoned that profoundly blind women, who do not perceive LAN, would be at reduced risk. He analyzed over 100,000 hospital discharge records published by the National Hospital Discharge Survey to determine how frequently there was a diagnosis of profound bilateral blindness in women also diagnosed with breast cancer compared to control women with diagnoses of stroke or cardiovascular disease. Among the control women, 0.26% were also blind, which is approximately the percentage expected on the basis of national surveys of nonhospitalized women. Among the women with breast cancer, however, only 0.15% were also blind; this was consistent with Hahn's prediction. Hahn adjusted for diabetes and marital status, but the adjustment depended on complete data in the medical records. The effect of blindness was strongest in young women.

The first epidemiological studies to address the EMF and breast cancer hypothesis were of occupational exposure in men.

In a large study of telephone workers in New York State, Matanoski et al. (51) found two cases of breast cancer among men in one of four occupations defined as having probable high EMF exposure; none were expected (a small fraction of a case was expected). This report was followed by a case–control study from the United States (52) and a cohort study that used the entire working population of Norway (53). Both of these studies also reported an excess of breast cancer among men in occupations thought to entail high EMF exposure; however, other studies have seen no relationship of occupational exposure and risk in men (54,55).

Guénel et al. (56) in Denmark and Vågerö and Olin (57) in Sweden both reported no association of EMF occupation and breast cancer risk in women. However, there may have been extensive exposure misclassification. The definitions of EMF exposure occupations for women were broad. Vågerö and Olin (57) classified about 2.6% of men and 2% of women in Sweden as being in exposed occupations. This was broadly defined as the electronics or electrical manufacturing industry. Guénel et al. (56) classified about 1.7% of men and 0.61% of women as continuously exposed and 14.5% of men and 12.6% of women as intermittently exposed.

Loomis et al. (58) conducted an occupational study of breast cancer death in women in the United States. There was a significant excess of breast cancer deaths in women working in electrical occupations in contrast to Guénel et al. (56) and Vågerö and Olin (57). There are differences in the studies. In the U.S. study, women were classified as exposed if they worked in jobs that had been previously used to classify men in exposed occupations of leukemia and brain cancer studies. In the Loomis et al. (58) study population, 0.18% of women were in those occupations, whereas 2.6% of the U.S. male workforce are in those same occupations. It is this group of women that showed the significant elevation. An additional group of possible exposed occupations made up only 2% of women, and among these there was not a significant elevation of breast cancer risk.

It is difficult to determine if an occupational study of a ubiquitous exposure and common disease is strong evidence because even those people in occupations defined as unexposed are certainly not unexposed to anthropogenic EMF. In addition, the background risk of breast cancer in women is high, and any real effect of EMF that

may exist in the population may not respond to the additional exposures entailed in occupations with higher than average exposure.

In 1991, Vena et al. (59) reported that use of electric blankets was not associated with risk of breast cancer in postmenopausal women. In 1994, they reported no association in premenopausal women from the same case–control study of women in western New York State (60). These studies have been cited as unbiased tests of the EMF hypothesis, although they do not support it (55). In both publications, however, the risk for women who reported using electric blankets throughout the night was approximately 1.4 (1.43 for premenopausal women and 1.46 for postmenopausal women). In response to a request by Stevens (61), Vena et al. (62) have presented a combined analysis of all women in the study. The odds ratio is 1.45 (p< 0.01; 95% CI of 1.08–1.94) for women using electric blankets throughout the night after adjustment by logistic regression for age, education, age at first pregnancy, number of pregnancies, age at menarche, relative with breast cancer, Quetelet index, history of benign breast disease, and menopausal status.

There are at least three possible interpretations of the modest odds ratio and highly statistically significant results of Vena et al. (62): this is a spurious finding never to be seen again, a real association that is explained by confounding, or a real association explained by magnetic field exposure. If the elevated risk ratio results from EMF, then it may be an underestimate of the true effect of exposure because the "never user" comparison group is not unexposed to anthropogenic EMF. In any event, the Vena et al. study (62) is not strong evidence either way.

### Plausibility

The melatonin hypothesis for electric power and breast cancer stands on a three-legged stool: light effects on melatonin production, EMF effects on melatonin production, and the role of melatonin in breast cancer etiology. There is as yet very little direct evidence, either experimental or epidemiological (as described above). Table 1 shows the strength of the evidence at the date of this writing.

The strongest leg of the stool is the effects of light on melatonin. It is clear from the published evidence that light of sufficient intensity suppresses the normal nocturnal melatonin peak in all people so far tested, that there are large differences

**Table 1.** Strength of the direct evidence and of each aspect of the circumstantial case for the electric power and breast cancer hypothesis.

| Question | Evidence |
|---|---|
| Direct evidence | Sparse |
| Light effect on melatonin | |
|   In animals | Solid |
|   In humans | Strong |
| EMF effect on melatonin | |
|   In animals | Mounting |
|   In humans | Very little |
| Melatonin effect on breast cancer | |
|   In animals | Strong |
|   In humans | Unclear |

among people in their light sensitivity at night, and that there appears to be a dose response to light. It remains unclear whether ambient night-time light levels or brief exposure to bright lights at night affect melatonin in any significant proportion of the population at large; this is the subject of current research.

The effect of melatonin on breast cancer can be strong in experimental animals but is quite unclear in humans. Melatonin inhibits the development of both DMBA- and NMU-induced breast cancer in rats, whereas pinealectomy enhances tumor development. This observation does not define the mechanism by which melatonin affects breast cancer at the cellular or tissue level. Other evidence has shown melatonin to be oncostatic to certain subclones of MCF-7 cell lines and to affect estrogen and prolactin levels and the development of the breast epithelial tissue at risk. Whatever the mechanism of action may be, melatonin can have a strong influence on breast cancer in rats. For humans, however, the evidence is sparse and exceedingly difficult to gather. Stored serum banks are often used to test etiologic hypotheses for hormones or micronutrients but are virtually useless for studies of melatonin because the blood was drawn

during the day when melatonin is at its lowest. Use of stored prediagnosis morning-urine samples may make epidemiological studies of melatonin and breast cancer possible. There is evidence that the level of 6-hydroxy-melatonin sulphate, the primary metabolite of melatonin, in the morning void reflects the total nocturnal production of melatonin very well (63). There is evidence that women with ER+ breast cancer have lower night-time melatonin than control women or women with ER- breast cancer, but the disease may well affect melatonin production.

The weakest leg is EMF effects on melatonin. In animals, at least six independent laboratories have published results wherein a low intensity electric or magnetic field suppresses melatonin. Few of the experiments are directly comparable in that some labs have used 50- or 60-Hz magnetic fields, some have used rapid changes in earth-strength static magnetic fields, and some have used 60-Hz electric fields. There have been conflicting reports and some carefully executed experiments have shown no effects. To date, reported experiments have either shown suppression or no effect; there are no reports to our knowledge of a stimulation of melatonin by a low-intensity EMF exposure. The weight of evidence is that, under some circumstances in certain experimental settings, EMF can suppress melatonin. There are no published data on humans. Three laboratories have performed experiments in humans with inconsistent results. If effects are found in the laboratory, this does not necessarily mean there are effects in the typical home and work environment of people. Several studies are currently addressing that possibility by the use of portable meters and assessment of melatonin by assay of the primary urinary metabolite.

Direct evidence is also being generated; this includes epidemiological studies

designed to test the electric power hypothesis and laboratory experiments to replicate the Löscher results. If the direct evidence accumulates to the point of strongly supporting a LAN- or EMF-induced elevation of risk of breast cancer in women, then understanding the mechanism would offer possible mitigation strategies. Melatonin would be an appealing mechanism but would not rule out some other as yet unsuspected mechanism as being responsible.

## Conclusion and Future Directions

At present, the hypothesis that LAN or EMF from the use of electric power increases risk of breast cancer remains quite speculative. Although the indirect evidence provides a rationale, the direct evidence is inadequate to draw a conclusion on the subject. Direct evidence is being gathered at a rapid pace and might well lead to resolution within 5 years; because breast cancer is so common in the industrialized world, many large studies can be conducted simultaneously.

Future directions include an investigation of prostate cancer (64) in men based on a similar, though more speculative, line of reasoning (37).

The generation and distribution of electric power has made our modern life and building environments possible. Among the most profound environmental consequences of electrification is exposure to light at night and to light of a different character than sunlight during the day. Since the vast majority of people in industrialized societies work in buildings and virtually all people sleep in buildings, the long-term health effect of the indoor-lighted environment deserves attention, particularly in terms of chronic disruption of melatonin rhythms (65,66).

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