cessed, Prepared. Data set 8-1-1. Washington, D.C., Agricultural Research Service, 1972.
16. Science and Technology Agency. *Table on Components of Japanese Foods.* Tokyo; Ishiyaku Publishing Co., 1985.
17. Pennington JAT, Church HN. *Bowes and Church's Food Values of Portions Commonly Used.* 14th ed. New York, Harper and Row, 1985.
18. Paul AA, Southgate DAT. *McCance and Widdowson's The Composition of Foods.* 4th ed. New York, Elsevier, 1978.
19. WuLeung WT, Butrum RR,Chang FH. *Food Composition Table For Use in East Asia.* Rome, FAO, 1972.
20. Food and Nutrition Board, National Research Council, National Academy of Sciences. *Recommended Dietary Allowances.* 9th ed. Washington, DC, Natl Acad Press, 1980.
21. Lee ET. *Statistical Methods in Survival Data.* Belmont, California, Lifetime Learning Publications 1980, 298–337.
22. Goodman MT, Kolonel LN, Wilkens LR, *et al.* Smoking history and survival among lung cancer patients. *Cancer Causes Control* 1990, **1**, 155–163.
23. Ziegler RG, Mason TJ, Stemhagen A, *et al.* Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am J Epidemiol* 1986, **123**, 1080–1093.
24. Byers T, Vena J, Mettlin C, *et al.* Dietary vitamin A and lung cancer: An analysis by histologic subtypes. *Am J Epidemiol* 1984, **120**, 769–776.
25. Stryker WS, Kaplan LA, Stein EA, *et al.* The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *Am J Epidemiol* 1988, **127**, 283–296.
26. Schectman G, Byrd JC, Gruchow HW, *et al.* The influence of smoking on vitamin C status in adults. *Am J Pub Hlth* 1989, **79**, 158–163.
27. Bendich A. Carotenoids and the immune response. *J Nutr* 1989, **119**, 112–115.
28. Block G. A review of valiations of dietary assessment methods. *Am J Epidemiol* 1982, **115**, 492–505.

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Breast Cancer, Blindness and Melatonin

Michel P. Coleman and Russel J. Reiter

The hypothesis is advanced that blindness from an early age may lead to a reduced risk of breast cancer through altered patterns of melatonin secretion by the pineal gland. The available experimental evidence in animals and *in vitro* is consistent with this hypothesis. The hypothesis can be tested in humans by a simple observational study in which the breast cancer risk in blind women is compared with that of all women. The effect of age at onset, duration and degree of blindness could also be assessed, after adjustment for known risk factors for breast cancer. Melatonin might prove to be a natural oncostatic agent of practical value in cancer prevention.
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INTRODUCTION

WE ADVANCE the hypothesis that blind women, particularly those blind since childhood, may have a low risk of breast cancer due to increased melatonin secretion from the pineal gland. The rôle of melatonin in human cancer remains controversial, but this hypothesis can be tested in a simple observational study.

Melatonin is a hormone produced by the pineal gland in response to diurnal variations in light exposure. Visual perception of the light–dark cycle (the photoperiod) is required for control of pineal melatonin synthesis. The pineal thus acts as a neuroendocrine transducer, translating stimulation of the retina by light into hormonal signals. Neural pathways run from the retina via the retinohypothalamic tract to the suprachiasmatic nuclei, and thence, via descending axons to spinal nuclei in the upper thoracic cord, to pre- and eventually postganglionic fibres which innervate the pineal gland [1]. Light suppresses melatonin secretion, and the diurnal secretion cycle peaks during darkness, around 0200–0400 h [2]. Melatonin alters the firing rate of the gonadotropin-releasing hormone (GnRH) pulse frequency generator in the hypothalamus, thus reducing pituitary secretion of gonadotropins and of prolactin and, indirectly, the secretion of oestrogen by the gonads [3]. In mammals, melatonin has been shown to delay puberty, suppress ovulation and reduce gonadal steroidogenesis [4].

Light suppresses the nocturnal peak of melatonin secretion in humans [5], too, although a higher light intensity is required than for some mammals [6]. Seasonal variation in the photoperiod and in the diurnal rhythm of melatonin secretion may produce endocrine effects in humans which are similar to those in animals. Thus, in Oulu, northern Finland (65°N), where there is 20–22 h of daylight in May–June but only 3–4 h of daylight in November–January, melatonin secretion in women increases and ovarian activity decreases in the dark season [7], and reduced conception rates during the dark season have been

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reported from the northern parts of Finland, Sweden and Norway. Seasonality of breast cancer incidence has been reported in several populations, all with an increased frequency during the summer months: however, although melatonin secretion would tend to be lowest at this point, attribution of seasonality to melatonin would suggest a surprisingly short-term effect. In the UK, the summer increase was observed for breast cancer in premenopausal women (aged <55), but not in older women nor for benign breast disease at any age [8].

Two small cross-sectional studies suggest that there is an abrupt fall of serum melatonin during pubertal development in both boys and girls [9, 10]. Pineal calcification increases with age; the prevalence of radiologically detected pineal calcification in adults varies widely (5–50%), and Cohen *et al.* [11] have suggested that it is correlated with breast cancer incidence, being high in Europe and North America, and low in Japan, although the evidence that calcification is a marker for reduced pineal function appears to be weak [12].

Cohen *et al.* [11] suggested that "persons with *low* blood levels of melatonin ... would be at increased risk of developing breast cancer, and persons developing this tumour should have lower levels of melatonin in blood and urine than unaffected persons of similar sex, age and race" (our emphasis). They also suggested that "melatonin, by suppression of oestrogen secretion, or by direct inhibitory effects on breast tissue, might suppress induction of breast cancer". More recently, Stevens [13] has pointed out that extremely low-frequency electric and magnetic fields can reduce pineal melatonin secretion, at least in animals, and that the use of electric power might increase breast cancer risk, either directly via this effect on the pineal, or indirectly via the retina and the sympathetic innervation of the pineal, since electric power is often used to provide light at night, which would also reduce melatonin secretion.

Experimental evidence is consistent with the concept of melatonin as an oncostatic agent. In rats, the development of mammary tumours induced by the chemical carcinogen dimethylbenzanthracene (DMBA) is enhanced by pinealectomy [14] and inhibited by melatonin administration [15]. This effect is only seen if melatonin is given during the promotional phase of tumour growth, following administration of a known carcinogen, and is absent if melatonin is restricted to the period when the carcinogen is given (initiation phase) [16]. Melatonin also inhibited the growth of transplanted breast tumours in the rat [17]. Exposure of rats to constant light for 24 h a day from birth (described as a functional pinealectomy) increased the incidence of mammary tumours induced by DMBA, an effect which was sharply attenuated by daily administration of melatonin [18]. Melatonin may also be immunologically active in animals and humans. It appears to protect mice against encephalomyocarditis virus and to enhance the T-cytotoxic response to immunisation with sheep red blood cells [19], and it alters the activity of human natural killer cells [20].

It has recently been suggested that in humans, depressed pineal melatonin secretion might be a risk factor for both breast cancer and melanoma [21]. Melatonin transiently increases oestrogen-receptor (ER) binding activity in a human breast cancer cell-line (MCF-7) in concentrations similar to the human nocturnal peak level [22], but the long-term effect is to inhibit oestrogen-stimulated growth [23]. Inhibition by melatonin of the growth *in vitro* of ER-positive human breast cancer cells is specific, reversible and concentration-dependent: melatonin did not inhibit the growth of an ER-positive cell line of human endometrial cancer, and the inhibition of breast cancer cells observed at physiological concentrations of melatonin was absent at both higher and lower concentrations [24]. In women with early breast cancer, particularly in those with ER-positive tumours, the nocturnal peak of melatonin secretion was lower than that of control women [25], in line with the prediction of Cohen *et al.* [11].

Melatonin may thus be a natural antagonist to the development of some human breast cancers, particularly those that are ER-positive. The various possible mechanisms for this include suppression of pituitary prolactin and ovarian oestrogen, delay of puberty and the menarche, reduction of the number of oestrogen receptors, and attenuation of the effect of oestrogen on breast cell growth. In direct contrast to the effect of constant light exposure, which represents a functional pinealectomy (at least for melatonin secretion), long-term blindness may be associated both with longer or higher daily pulses of melatonin and with altered periodicity of melatonin secretion. Blind women, and especially those blind since childhood, may therefore have a relatively low incidence of breast cancer.

There is evidence for this proposition from animal studies. Light deprivation reduces the incidence of DMBA-induced mammary tumours in rats [26], while either constant light exposure or surgical pinealectomy increase it [15]. Blinding reduces the incidence of mammary tumours, and pinealectomy also reverses this effect [18, 27].

The limited human data on melatonin in the blind also suggest altered patterns of secretion. Disturbance of sleep–wake cycles [28] and of circadian melatonin secretion [29] have been reported. Melatonin partially corrected the disturbed sleep–wake cycle in one blind man [30], and in 4 men with an intact CNS who had been blind for 30 years or more following war injury to the eyes, higher levels and reversed-phase periodicity of diurnal melatonin secretion were observed [31].

In summary, environmental light clearly dominates control of the diurnal rhythm of melatonin secretion in humans, and other regular activities such as the sleep–wake cycle and eating patterns cannot fully replace it; melatonin secretion cycles in the blind may be abnormally prolonged, high and/or out of phase with the photoperiod; and finally this disturbance may have endocrine effects in the blind such as to reduce the risk of breast cancer.

Hahn's recent analysis of hospital discharge records [32] showed that among women with a discharge diagnosis of breast cancer, the odds ratio for a mention in the record of profound bilateral blindness was 0.57 (95% CI 0.35–0.92), compared with women with a discharge diagnosis of coronary heart disease or stroke (records with a mention of diabetes were excluded). Excluding women over 65 years of age, among whom there was no association (OR = 0.99), only two discharge records mentioned both breast cancer and blindness, compared with about the 5.5 expected. The available data did not allow for control of breast cancer risk factors such as nulliparity, or of any effect of age at onset of blindness, but the result of this study (40% reduction in risk under age 65) is consistent with the hypothesis, and suggests a major protective effect of blindness, comparable with that induced by ovarian irradiation (35%) [33]. Kothari [15] even suggested that melatonin might prove useful in the chemoprevention of breast cancer in young women at high risk. Women who have been blind since before the menarche constitute a group in which this suggestion could be tested in a natural experiment.

We suggest that a retrospective cohort study of blind women, carried out by linking a comprehensive register of blind persons

to a long-standing cancer registry of adequate quality, would enable the hypothesis that long-term blindness protects against breast cancer to be tested fairly rapidly. Such a design would allow evaluation of the age at onset and degree of blindness on the extent of any risk reduction. A nested case-control study would also enable evaluation of conventional risk factors for breast cancer, such as family history, age at menarche, age at first term birth, parity and relative weight. This study might provide direct evidence of a rôle for melatonin in the prevention of human cancer. Melatonin might thus prove to be of value in chemo-prevention of breast cancer in women at high risk, or even as a component of oral contraceptives.

1. Reiter RJ. The mammalian pineal gland: structure and function. *Am J Anat* 1981, **162**, 287–313.
2. Fetell MR, Stein BM. Neuroendocrine aspects of pineal tumors. In: Zimmerman EA, Abrams GM, eds. *Neurologic Clinics*. Philadelphia, PA, WB Saunders Company, 1986, 877–905.
3. Tamarkin L, Baird CJ, Almeida OFX. Melatonin: a coordinating signal for mammalian reproduction? *Science* 1985, **227**, 714–720.
4. Reiter RJ. The pineal and its hormones in the control of reproduction in mammals. *Endocrine Rev* 1980, **1**, 109–130.
5. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. *Science* 1980, **210**, 1267–1269.
6. Reiter RJ. Action spectra, dose-response relationships, and temporal aspects of light's effects on the pineal gland. *Ann NY Acad Sci* 1985, **453**, 215–230.
7. Kauppila A, Kivelä A, Pakarinen A, Vakkuri O. Inverse seasonal relationship between melatonin and ovarian activity in humans in a region with a strong seasonal contrast in luminosity. *J Clin Endocrinol Metab* 1987, **65**, 823–828.
8. Kirkham N, Machin D, Cotton DWK, Pike JM. Seasonality and breast cancer. *Eur J Surg Oncol* 1985, **11**, 143–146.
9. Silman RE, Leone RM, Hooper RJL, Preece MA. Melatonin, the pineal gland and human puberty. *Nature* 1979, **282**, 301–303.
10. Waldhauser F, Weiszenbacher G, Frisch H, Zeitlhuber U, Waldhauser M, Wurtman RJ. Fall in nocturnal serum melatonin during prepuberty and pubescence. *Lancet* 1984, **i**, 362–365.
11. Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet* 1978, **ii**, 814–816.
12. Mullen PE, Smith I. The endocrinology of the human pineal. *Br J Hosp Med* 1981, **25**, 248–256.
13. Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol* 1987, **125**, 556–561.
14. Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B. Melatonin inhibition and pinealectomy enhancement of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in the rat. *Cancer Res* 1981, **41**, 4432–4436.
15. Kothari LS. Influence of chronic melatonin on 9,10-dimethyl-1,2-benzanthracene-induced mammary tumors in female Holtzman rats exposed to continuous light. *Oncology* 1987, **44**, 64–66.
16. Blask DE. The emerging role of the pineal gland and melatonin in oncogenesis. In: Wilson BW, Stevens RG, Anderson LE, eds. *Extremely Low Frequency Electromagnetic Fields: The Question of Cancer*. Columbus, OH, Battelle Press, 1990, 319–335.
17. Karmali RA, Horrobin DF, Ghayur T. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet* 1978, **ii**, 1002.
18. Shah PN, Mhatre MC, Kothari LS. Effect of melatonin on mammary carcinogenesis in intact and pinealectomized rats in varying photoperiods. *Cancer Res* 1984, **44**, 3403–3407.
19. Maestroni GJM, Conti A, Pierpaoli W. Pineal melatonin, its fundamental immunoregulatory role in aging and cancer. *Ann NY Acad Sci* 1988, **521**, 140–148.
20. Angeli A, Gatti G, Sartori D, Del Ponte D, Carignola R. Effects of exogenous melatonin on human natural killer (NK) cell activity. An approach to the immunomodulatory role of the pineal gland. In: Gupta D, Attanasio A, Reiter RJ, eds. *The Pineal Gland and Cancer*. London, Brain Research Promotion, 1988, 145–56.
21. Arbesman H, Byers T. Possible association between breast cancer and malignant melanoma. *Arch Dermatol* 1988, **124**, 1007.
22. Danforth DN Jr, Tamarkin L, Lippman ME. Melatonin increases oestrogen receptor binding activity of human breast cancer cells. *Nature* 1983, **305**, 323–325.
23. Tamarkin L, Almeida OFX, Danforth DN. Melatonin and malignant disease. In: *Photoperiodism, Melatonin and the Pineal*. London, Pitman, Ciba Foundation Symposium, 1985, **117**, 284–299.
24. Hill SM, Blask DE. Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. *Cancer Res* 1988, **48**, 6121–6126.
25. Tamarkin L, Danforth D, Lichter A, *et al*. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. *Science* 1982, **216**, 1003–1005.
26. Chang N, Spaulding TS, Tseng MT. Inhibitory effects of superior cervical ganglionectomy on dimethylbenz(a)anthracene-induced mammary tumors in the rat. *J Pineal Res* 1985, **2**, 331–340.
27. Blask DE, Hill SM, Pelletier DB. Oncostatic signaling by the pineal gland and melatonin in the control of breast cancer. In: Gupta D, Attanasio A, Reiter RJ, eds. *The Pineal Gland and Cancer*. London, Brain Research Promotion, 1988, 195–206.
28. Miles LEM, Raynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 hours. *Science* 1977, **198**, 421–423.
29. Lewy AJ, Newsome DA. Different types of melatonin circadian secretory rhythms in some blind subjects. *J Clin Endocrinol Metab* 1983, **56**, 1103–1107.
30. Arendt J, Aldhous M, Wright J. Synchronisation of a disturbed sleep–wake cycle in a blind man by melatonin treatment. *Lancet* 1988, **i**, 772–773.
31. Smith JA, O'Hara J, Schiff AA. Altered diurnal serum melatonin rhythm in blind men. *Lancet* 1981, **ii**, 933.
32. Hahn RA. Profound bilateral blindness and the incidence of breast cancer. *Epidemiology* 1991, **2**, 208–210.
33. Boice JD Jr, Blettner M, Kleinerman RA, *et al*. Radiation dose and breast cancer risk in patients treated for cancer of the cervix. *Int J Cancer* 1989, **44**, 7–16.

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