

Light at Night, Shiftwork, and Breast Cancer Risk

Johnni Hansen

Breast cancer is the most commonly diagnosed female non-cutaneous cancer in the United States and in Europe. The etiology of breast cancer is primarily unknown, with an estimated one quarter of all breast cancers possibly due to heritable factors (1) and only a minor proportion possibly due to already established environmental risk factors, such as early age at menarche, older age at first pregnancy, and delayed menopause (2). Because the incidence of breast cancer in many countries is increasing, for unclear reasons, it is not surprising that society is demanding explanations for the increased incidence of the disease and that researchers are searching for new causes. One avenue of research has been the so-called “man-made endocrine disrupting chemicals,” such as 2-(chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane (DDT), polychlorinated biphenyls, or nonyl phenols (3). So far, however, the results from this research have been sparse in expanding our knowledge about risk factors for breast cancer.

In this issue of the Journal, two independent epidemiologic studies by Davis et al. (4) and Schernhammer et al. (5) have provided evidence about another potential risk factor, light at night. These studies (4,5) support a hypothesis published about 10 years ago by the former group that light at night may be a potential risk factor of breast cancer (6,7).

The scientific rationale behind this intriguing hypothesis is that exposure to visible light, including artificial light, sup-

presses the normal nocturnal production of melatonin by the pineal gland (6). Melatonin is a mammalian hormone involved in circadian rhythms and sleep and potentially in restraining tumor growth (8). The synthesis and release of melatonin occur in a dose–response-like manner that is stimulated by darkness and inhibited by light through photic information from the retina. Peak melatonin levels normally occur during sleep in the middle of the night (8). Several experimental studies have provided evidence of an association between melatonin levels and risk of cancer. For example, evidence from rodent studies found that pinealectomy increased tumor growth (9), that administration of melatonin inhibited the promotion of chemically induced mammary tumors (9,10), and that constant light exposure had a growth-promoting effect on chemically induced tumors (11). Evidence in humans is less direct, although impaired pineal secretion of melatonin is associated with an increased release of estrogen by the ovaries (7,8), and low serum melatonin concentrations have been reported in women with estrogen receptor-positive breast cancer (8). *In vitro*, physiologic concentrations of melatonin inhibited the growth of human breast cancer cells

Correspondence to: Johnni Hansen, Ph.D., Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen, Denmark (e-mail: johnni@cancer.dk).

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(12). Several mechanisms involved in the apparent protective effect of melatonin have been suggested; they include a direct antiproliferative effect (13), increased immune responses (8), scavenging of free radicals (8), and modulation of the expression of the tumor suppressor gene p53 (14).

The case-control study by Davis et al. (4) in this issue is based on in-person interviews with 814 breast cancer patients and 793 control subjects. The participation rate for both case patients and control subjects was relatively high, i.e., 78% and 75%, respectively. Graveyard shift work (defined as beginning work after 7:00 PM and leaving work before 9:00 AM) was associated with a 60% increase in breast cancer risk (odds ratio = 1.6; 95% confidence interval = 1.0 to 2.5) and with a trend of increasing risk with increasing number of years of work or with more hours per week of graveyard shift work. Furthermore, Davis et al. found that independently of the shift-work status, women who frequently do not sleep during the period of the night when melatonin levels are typically at their highest have a 14% increase in breast cancer risk for each night per week. Finally, there was an indication of an increased risk among subjects with the brightest bedrooms, but there was no association with interrupted sleep accompanied by turning on a light. The strength of this study is the detailed collection of information on exposure, including sleep patterns, bedroom environments, and shift work.

The prospective cohort study by Schernhammer et al. (5) in this issue uses data from the Nurses' Health Study, in which 78 562 women in 1988 responded to a question regarding how many years they had worked rotating nightshifts, with at least three nights per month. This cohort was followed from 1988 through 1998, during which 2411 first primary breast cancers were diagnosed. Compared with those who had done no nightshift work at all, nurses who had performed nightshift work for between 1 and 29 years showed an 8% increase in relative risk of breast cancer, and nurses with at least 30 years of nightshift work showed a 36% increase in relative risk. The strength of this study is its prospective design and the large number of relatively homogeneous participants and long follow-up.

Although these two well-conducted studies have different approaches to defining exposure to light at night, neither is op-

timal. For example, both studies are prone to exposure misclassification, although the general effect of such misclassification would bias the risk estimates toward unity and, thus, would underestimate the true increased risk. However, both studies have adjusted their outcomes for known confounders, such as reproductive history, family history of breast cancer, use of oral contraceptives and hormone replacement therapy, social class, and alcohol consumption. Therefore, with different epidemiologic designs (each with its own strengths) and with results pointing in the same direction, the studies are complementary.

Evidence is accumulating for an association between exposure to light at night and breast cancer risk. Table 1 provides an overview of three published studies (4,5,15), including the two studies in this issue, where the hypothesis of work at night and breast cancer risk is evaluated, each study controlled for reproductive history. Positive associations between shiftwork and breast cancer risk were also observed in three smaller cohort studies (16-18) conducted for purposes other than testing the melatonin hypothesis, but these studies did not adjust for reproductive history and other confounders for breast cancer. Finally, indirect support for the melatonin hypothesis comes from studies on blind women (19-23) who are not sensitive to changes in light and, consequently, whose melatonin levels do not change. Studies show an approximately 20%-50% reduced risk of breast cancer among such women (19-22), with a tendency toward an inverse dose-response relationship between the degree of blindness and breast cancer risk (23).

Although the possibility exists that work at night or exposure to light at night acts as a proxy for other yet unknown risk factors for breast cancer, and acknowledging that a publication bias may exist, apparently all of epidemiologic studies published so far (4,5,15-18) on different indirect measures of light at night and breast cancer risk seem to relatively consistently point to an increased risk. From an occupational point of view, these recent results are alarming, regardless of the underlying biologic cause for the apparent increased risk of breast cancer among women who work at night. No occupational exposures with known or potential carcinogenicity are as common as work at night. Moreover, during the last few decades, society has increased the diversity of irregular work hours, including work at night, and

Table 1. Studies on breast cancer risk after occupational exposure to light at night, including adjustment for reproductive history*

Type of study	Definition of exposure	Methods for obtaining exposure information	Night work category	No. of exposed case subjects	Adjusted relative risk (95% confidence interval)	P value for test for trend	Investigator(s) (reference No.)	
Nationwide case-control study	Years with employment for at least half a year in occupations with predominant non-daytime work	Employment records from pension fund files	Ever >1/2 y	434	1.5 (1.2 to 1.7)	.02	Hansen (15)	
			>6 y	63	1.7 (1.3 to 1.7)			
Case-control study	Hours with graveyard work (beginning work after 7:00 PM and leaving work before 9:00 AM)	In-person interview	Ever	37	1.6 (1.0 to 2.5)	.04	Davis et al. (4)	
			Hours/week (continuous)	767	1.06 (1.01 to 1.13)			.03
			Years† (continuous)	743	1.13 (1.01 to 1.27)			
Prospective cohort study	Rotating nightshifts with at least 3 nights/month	Mail-in questionnaire	1-14 y	1324	1.08 (0.99 to 1.18)	.02	Schernhammer et al. (5)	
			15-29 y	134	1.08 (0.90 to 1.30)			
			≥30 y	58	1.36 (1.04 to 1.78)			

*Reproductive history includes age (4,5,15), parity (4,5,15), age at birth of first and/or last child (5,15), oral contraceptive use (4,5), hormone replacement therapy (4,5), age at menarche (5), age at menopause (5), family history of breast cancer (4,5), weight change between age 18 years and menopause (5), and body mass index at age 18 years (5).

†With at least one shift per week.

amount of irregular work hours, including work at night. To obtain experience in more ergonomic shift scheduling in general, it is, therefore, important, parallel to initiating new epidemiologic studies, to investigate whether changing shift scheduling may influence melatonin levels. This investigation may be efficiently accomplished by measuring morning urinary 6-hydroxymelatonin sulfate levels as a biomarker of nocturnal melatonin secretion (24). A recent study on Danish hospital workers (25) shows that changing the timing of work at night can positively change biomarkers for cardiovascular disease.

In conclusion, there is an urgent need for further exploration of the relationship between exposure to light at night, shiftwork, including timing during the night, and cancers that may be influenced by melatonin.

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