Tors for breast cancer that are associated with sleep disruption. For example, our laboratory has recently reported, also in the Journal, that loss of normal diurnal variation in cortisol predicts early mortality in metastatic breast cancer (3). Cortisol normally shows marked diurnal variation, peaking in early morning and declining throughout the day. In our study, patients with flattened salivary cortisol rhythms or aberrant peaks and troughs suffered earlier mortality. The prognostic effect of cortisol rhythm on survival emerged approximately 1 year after cortisol assessment and extended at least 7 years after the assessment (3). A similar association between 24-hour rest–activity rhythms and survival has been noted in patients with colorectal cancer (4). Furthermore, patients at high risk for primary breast cancer show abnormal circadian patterns among an array of hormones including cortisol (5).

Similar endocrine disturbances have been linked with advancing age and with sleep loss in young subjects (6). In our study, patient self-reports of sleep disruption were associated with flattening of the diurnal cortisol rhythm (3). There is evidence that the early morning transition from dim to bright light not only suppresses melatonin secretion; it also induces a marked elevation of cortisol levels (7). Thus, sleep disruption coupled with exposure to light at night may not only suppress the melatonin peak but may also interfere with the normal cortisol nadir. Although mere sleep disruption was not associated with elevated breast cancer risk in the Davis et al. study (2), it is likely that shift workers have altered diurnal cortisol patterns engendered through alterations of sleep and nutritional patterns, abnormal photic stimuli, and altered rest–activity cycles. In addition, the stress incurred from frequent transitions between daytime and nighttime shift work should not be overlooked. Indeed, chronic sleep debt has been linked with the disruption of carbohydrate metabolism and thyroid hormone function, elevation of sympathetic nervous system activity, as well as with hypothalamic–pituitary–adrenal axis dysfunction. Because these effects are similar to those seen in normal aging, it is reasonable to propose that sleep debt may increase the incidence or severity of age-related diseases, including cancer, by processes similar to those seen with advancing age. Thus the association of sleep disruption with cancer risk may be mediated by a number of pathways, including, but not limited to, the disruption of melatonin secretion. There are now sufficient data to support the notion that the loss of normal diurnal variation in cortisol is another possible mechanism that could account for the observed association between shift work and breast cancer incidence.

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Our interest in the article “Night Shift Work, Light at Night, and Risk of Breast Cancer” (1) began with the media coverage of the research in a number of newspapers across the country. Shift
The night shift [no wonder Davis et al. (1) refer to it as the "graveyard shift"]).

The study by Davis et al. (1) is based on 1) the link between exposure to estrogen and the risk of breast cancer and 2) the fact that exposure to light at night increases exposure to estrogen through mechanisms associated with the circadian rhythm. This is not an illogical train of thought. Four studies were cited [references within (1)], reporting an increased risk of breast cancer in women who work during the night. Of the four studies, three were conducted in Scandinavia, a geographic location known for its long nights in winter, and two focused on airline crews, who have greater exposure to cosmic radiation. Furthermore, in the “Discussion” section, Davis et al. (1) make reference to research that found women with bilateral blindness had a statistically significantly lower risk of breast cancer, thus supporting the notion that there is an association between light at night and breast cancer risk.

However, in Davis et al. (1), the data collection is based on recall of occupational history, sleeping habits, bedroom environment over a decade, and other known risk factors. To minimize the known limitations of recalled data, the manuscript would have benefited from a discussion of the reliability of the recalled data, the development of the questionnaire, any pilot work, and the training of the interviewers.

Table 3 in Davis et al. (1) reported the findings on occupational history—the one variable that is likely to have some reliability because, understandably, women who have worked the “graveyard shift” would remember the years of that employment. The major thrust of the authors’ work is predicated on a small difference between the number of women among the case patients (n = 54 of 767 [7%]) and those among the control group (n = 37 of 743 [5%]) who had ever worked a night shift. Although the difference may be statistically significant in this analysis, the question is whether a 2% difference is clinically significant. A difference in the rates of breast cancer for night shift workers and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–8.

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A very thoughtful and thorough editorial (1) and two most interesting and valuable publications (2,3) focus attention on the role of light and melatonin production and the risk of breast cancer.

In 1990, our group put forward a comprehensive hypothesis that one of the most important etiologic factors in the increasing rate of cancers is the change in light exposure that has taken place during the last 100 years (4). The introduction of electric light generally increased the average daily light exposure by 4–6 hours. The increase in light exposure decreases the amount of time that is available for melatonin production, which reduces the nonspecific oncogenic effect of the pineal gland. This adverse effect of light exposure, according to our hypothesis, may increase the risk of other cancers. Beral et al. (5) reported that the exposure to fluorescent light in the workplace was associated with a twofold increase in the risk of melanoma compared with a matched control group. The risk increased with increasing duration of exposure to fluorescent light, with a relative excess of lesions on the trunk (5). By contrast, blind women who are not ocularly receptive to light are not influenced by the extended light exposure and have a reduced risk of breast cancer (6). Women with a milder degree of visual impairment did not have a similar reduced risk (6).

Our group surveyed workers who, every day, worked for 6–7 hours in darkness, producing films at the Canadian Kodak factory. We found that the film production workers had a reduced risk of breast cancer and of malignant melanoma compared with workers in administration or other manufacturing areas (Kerenyi N: unpublished findings).
The conclusion of the editorial by Dr. J. Hansen (1) emphasizes that there is an urgent need for further exploration regarding the effects of light exposure on cancers. I strongly agree with this conclusion. In 1973, el-Domeiri and Das Gupta (7) found that the accelerated growth of transplanted melanoma in pinealectomized hamsters could be reversed by the addition of exogenous melatonin. Considering all these facts, raising the question of whether melatonin replacement could be beneficial for the light-exposed night shift workers is justifiable. A controlled clinical study may answer this question.

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RESPONSES

We thank Dr. Spiegel et al. for their interesting contribution.

The elevated breast cancer risk observed among women who work rotating night shifts (1–3) stimulates novel hypotheses for underlying biologic causes of potential health risks associated with exposure to artificial light at night. One avenue is to view work at night as a proxy for other potential risk factors for breast cancer, such as stress and related cortisol levels. For example, studies have shown that cortisol levels are low during the night shift but that married nurses had higher cortisol levels than single nurses (4). Such observations support the notion that domestic stress, possibly mediated through role conflicts among married nurses, alters cortisol levels in shift workers. Dr. Spiegel’s and recent other work have implicated that altered cortisol levels predict survival time among breast cancer patients. Yet, their appealing theory that a healthy woman’s breast cancer risk may also be elevated through altered cortisol levels (caused by sleep deprivation and anticipated higher stress levels among shift workers) still requires confirmation.

Alternatively, there is evidence regarding the responsiveness of the pineal gland to changes in emotional state, thereby inducing alterations in melatonin levels. Rodent studies suggest that the suppression of melatonin by light could be modified by changes in emotional state, produced by adrenergic conditioning. On the contrary, in humans, activation induced by physical stress in the middle of the dark phase did not alter melatonin levels (5).

The strongest biologic evidence to date supports cancer risk emerging directly from the exposure to light at night through the melatonin pathway. Artificial light was repeatedly shown to profoundly suppress humans’ melatonin levels and, in particular, those of women (6). On average, melatonin concentrations decrease by approximately 35% after 2 weeks of intermittently nightly light exposures. Moreover, the widely established antiproliferative effect of melatonin through its antioxidative activity and potential other immunomodulating mechanisms is not only limited to modulations on estrogen receptors, thereby affecting breast cancer risk, but has already been extended to other cancers.

Based on these novel findings, we propose that the exposure to light at night and subsequent melatonin suppression may also affect other cancers in humans. We believe that our hypothesis is given further importance by recent evidence for a unique photopigment in the human eye that mediates circadian photoreception. The new photoreceptor influences the biologic effects of light, specifically, the control of the hormone melatonin (7), a phenomenon that has been poorly understood until very recently. It was further determined that wavelengths of light in the blue region of the visible spectrum (e.g., fluorescent light, commonly used in environments with artificial light) have the highest potency in causing changes in melatonin levels.

Light at night is one of the most common occupational exposures in our industrialized societies. Therefore, further research to improve our current understanding of the effects of light at night on human health is prudent.

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Drs. Spiegel and Sephton rightly point out that the association we reported (1) between being employed in graveyard shift work and an increased risk of breast cancer might be accounted for by mechanisms other than or in addition to suppression of the normal nocturnal rise in melatonin, and they suggest that loss of diurnal variation in cortisol levels might be one such alternative. Women who engage in night shift work are subject to the influence of both sleep disruption and exposure to light-at-night (LAN). Sleep deprivation can have a profound effect on endocrine function and hormones such as melatonin and cortisol (2), and it is well established that exposure to LAN can affect pineal function and the production of melatonin (3). Spiegel and Sephton cite recent evidence (4) of a similar effect on cortisol. In addition to the prognostic significance of altered cortisol patterns that they describe, there is beginning to emerge some limited evidence (5,6) that cortisol may be associated with the risk of developing breast cancer as well.

If breast cancer risk is affected by the suppression of the normal nocturnal rise in melatonin, one would predict that 1) persons who do not perceive light on the retina (e.g., those who are blind) would be at a decreased risk of breast cancer and 2) those who work in occupations that are characterized by circadian disruption (e.g., flight attendants) and those who work the graveyard shift in whatever occupation would be at an increased risk of developing the disease. Our results, as well as those from a number of other studies, are consistent with these predictions, but they could also be consistent with other mechanisms. Indeed, Funk and Amir (7) have raised the intriguing possibility that factors such as stress and fear may modify the effect of light on hormone production. Epidemiologic studies cannot distinguish with much certainty which underlying biologic mechanisms account for or can best explain associations observed on a population basis. However, they can inform the design of laboratory-based investigations that are capable of identifying specific mechanisms.

Dr. Porock and Mr. Gentry also point out that a number of different factors may be important in the development of breast cancer and express concern that our results are derived from self-reported data obtained through an in-person interview. The limitations of this approach are well recognized, and we used several techniques (e.g., structured interview, pilot tests, extensive interviewer training and monitoring, and a random sample of abbreviated re-interviews) to help ensure that the data were collected in an unbiased manner and were as accurate as possible. The potential impacts of imperfect or biased recall were considered in our original paper (1). Porock and Gentry are also concerned that our primary findings are based on a small difference in graveyard shift work between cases and controls and that a simple statistical test of the difference is not significant. Although a relatively small number of study participants worked the graveyard shift, the more relevant comparison is that a considerably higher proportion of those who did work the graveyard shift were cases (60%) than were controls (40%). These and similar statistically significant results summarized in Table 3 of our original paper (1) are more informative and also allow for the independent effects of other factors related to breast cancer risk when evaluating the effect of graveyard shift work. We concur that the potential importance of our findings dictates that future research be thoughtfully designed and carefully executed, and we hope that our results help direct the design of the next generation of epidemiologic and laboratory studies.

We appreciate the thoughtful comments of Dr. Kerenyi and encourage him to more fully describe and publish his findings regarding workers who spend much of their time in darkness. We have also had a long-standing interest in the etiologic role of exposure to LAN in the development of cancer (8) and agree that accumulating evidence warrants further study of the potential effects of such exposure. We currently have a proposal under review to initiate a study to measure melatonin and reproductive hormone levels in women who work at night and in women who work during the day. The results of such a study may be useful in designing a trial of the potential beneficial effect of melatonin replacement by providing information on hormone patterns associated with different work and sleep schedules. We agree that such approaches may lead to a better understanding of the health impacts of exposure to LAN and the resulting disruption of normal circadian biology.

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I thank Dr. Kerenyi for his comments regarding the recent editorial on light at night and breast cancer risk (1), and appreciate the opportunity to further comment on this issue of light as a potential carcinogen.
Recent studies on light and breast cancer risk have primarily focused on people who work at night (2–4). Dr. Kerenyi refers to an interesting unpublished study regarding the opposite situation, i.e., of people who worked in darkness during the day in a film-producing factory in Canada. Compared with other workers with normal light exposure within the same factory, the workers with low light exposure had a reduced risk of breast cancer and melanomas, thus supporting the “melatonin-hypothesis”, which, in this opposite situation with low exposure to light, may argue that excess darkness, including blindness, may decrease the risk of certain cancers, including breast cancer and melanomas (5–8).

To explore the results of Dr. Kerenyi, we estimated the relative risk of breast cancer and malignant melanomas among workers employed in photographic laboratories in Denmark, on the basis of our comprehensive nationwide case–control data linkage on occupational history (1964–1989) and cancer (1970–1989) (9). The odds ratio (OR), adjusted for sex and birth year, for female breast cancer (including at least 1 year of employment and a lag period of at least 10 years) was statistically significantly decreased (OR = 0.4; 95% confidence interval [CI] = 0.2 to 0.9; N = 11) among the photo laboratory workers compared with other employees. The corresponding OR values for melanomas among women and men, respectively, were 1.4 (95% CI = 0.5 to 3.7; N = 6) and 0.4 (95% CI = 0.1 to 1.8; N = 2). Considering 1) the limitations of a small number of included cases and 2) that no further information is available on exposure to light for this occupational group, we found that the results for breast cancer are in line with the findings by Dr. Kerenyi. This may put further impetus on the need for studies with detailed information on light exposure and cancer risk among workers with extreme exposure to light either as darkness during the day or as artificial light during the night.

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