Invited Commentary

Invited Commentary: Shift Work and Cancer

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In this issue of the Journal, Parent et al. (Am J Epidemiol. 2012;176(9):751–759) report significant associations between night-shift work and risk of cancer at several sites among men. These findings not only address the need for shift-work studies that evaluate cancers other than breast and prostate cancer but also support the increasing concern that the negative effects of shift work may be broadly applicable to risk of many cancers via the direct oncostatic properties of melatonin. Studies of shift work have been limited by a lack of detailed data for determining which aspects of this multifaceted exposure may be associated with increased cancer risk. Additionally, the influence of individual-level characteristics, such as preference for daytime activity versus nighttime activity or chronotype, has not been considered. In moving forward, launching new cohort studies of shift work and cancer risk is the most tenable approach, though it will be limited by the years of follow-up required in order to accrue adequate numbers of cancer cases. Studies incorporating biomarkers of effect are useful for providing immediate information that can aid not only in identifying the underlying mechanisms of the shift-work–cancer association but also in interpreting existing epidemiologic data and informing the design of future epidemiologic studies of cancer risk.

circadian rhythm; melatonin; neoplasms; night work; occupations; shift work


It has long been recognized that working the night shift can be associated with a number of adverse health effects, including insomnia, excessive sleepiness, fatigue, headache, anxiety, depression, and gastrointestinal disturbances (1). These adverse effects are thought to result from disruption of the 24-hour internal circadian clock, which is synchronized to the daily light-dark cycle. The hormone melatonin, produced by the pineal gland, is key in the regulation of the circadian clock. Circulating melatonin levels are highest at night and lowest during the day, and they peak approximately at the midpoint of the daily light-dark cycle.

There is now considerable evidence from experimental studies that disrupted circadian rhythm, as a result of exposure to light at night, can reduce or effectively eliminate the nocturnal rise in melatonin level (2). This disruption of melatonin secretion has been shown to increase both tumor growth and the occurrence of mammary carcinomas in rodents (3, 4). Altered melatonin secretion may affect hormone profiles, which could increase the risk of hormone-related diseases, including breast and prostate cancer. Alternatively, melatonin may have a more direct effect on the development of cancer; growth-inhibitory and oncostatic properties of melatonin have been well described (5). Epidemiologic studies are now beginning to show that there is an increased risk of some forms of cancer (primarily breast and prostate cancer, but possibly colon and other types) in people whose circadian cycle is disrupted, most notably among persons who work the night shift. These workers are subject to the influence of both light-at-night exposure and sleep disruption. Even though the bulk of evidence points to melatonin disruption as a key factor in the potential carcinogenicity of shift work, other factors may be involved.

An international group of experts convened by the International Agency for Research on Cancer (IARC) recently
conducted a comprehensive review and assessment of shift work and classified night-shift work as "probably carcinogenic" in humans (6). They also highlighted a few limitations of existing studies of night-shift work: the complete lack of consistency in definitions across studies; the crude exposure assessment; and the lack of studies of different cancer sites (other than the breast and the prostate). Additional studies are being called for, and appropriately so, but epidemiologic studies of exposure to light at night in relation to cancer risk are exceedingly difficult to conduct. To be useful in advancing our understanding of the effects of night-shift work, future efforts should focus on two aspects of night-shift work: the influence of characteristics within an individual (e.g., age, gender, race, adaptability) and the details of the shift work typically experienced (e.g., rotation, direction of rotation, fixed, frequency).

In this issue of the *Journal*, Parent et al. (7) report new findings directly related to the IARC group’s concern that few studies of shift work had examined cancer sites other than the breast and prostate. Their study found significant associations in men between ever working at night and cancer risk at several sites, including the lung, colon, bladder, prostate, rectum, and pancreas. An increased risk of non-Hodgkin’s lymphoma was also observed in association with ever working at night. The results were robust to a number of sensitivity analyses, providing some reassurance that the results are not seriously biased in some manner.

While Parent et al. conducted exposure assessment at an individual level (7), their study did not collect information on specific aspects of shift work, of the types described in a recent report by an IARC Working Group tasked with defining “shift work” (8). Information such as frequency, rotation (rotating shift schedules vs. fixed schedules), and direction of rotation are needed not only to facilitate comparison between studies but also to help identify the key aspects of night work that may be associated with negative effects. These data may also provide insight into the lack of dose-response relations seen by Parent et al. and others when examining duration of shift work and cancer risk. For example, the lack of a dose-response may be attributable to nondifferential misclassification of exposure that would result from grouping together subjects with similar durations but differing frequencies of night work. Parent et al. suggest that in their study population the frequency of night work might not vary considerably (7), but this was somewhat speculative.

To our knowledge, individual factors that may modify the impact of night-shift work have thus far not been considered in epidemiologic studies of cancer. Key among individual factors is diurnal preference or chronotype, which is defined as a person’s preference for activity during the daytime versus nighttime. Chronotype is thought to affect adaptability to shift-work schedules, with evening-type individuals reporting better tolerance for night work (e.g., better work performance and higher job satisfaction) than morning-type individuals (9). Genetic polymorphisms in circadian genes have also been linked to shift-work adaptability (10), and some polymorphisms have been associated with diurnal preference (11–13). Adaptability may in fact be the potential explanation for the null association observed between night work and breast cancer risk that was observed in a large cohort of women in Shanghai, China (14). Girschik et al. (15) suggested that night work may have less of an impact on melatonin secretion among Asians, citing previously conducted studies demonstrating that Asians produce lower levels of melatonin relative to Caucasians and that melatonin suppression due to light exposure is reduced among Asians as compared with Caucasians (16–18). Further research on the relation of adaptability with race, cultural factors, and genetics is needed and may eventually lead to the development of strategies to help reduce any negative effects associated with shift work.

There are precious few published findings to compare with the results presented by Parent et al. In a recent cross-sectional study of 172 night-working nurses and 151 day-working nurses, Davis et al. (19) demonstrated that night-working nurses had constitutively lower melatonin levels than day-working nurses. Even when they reverted back to nighttime sleep on off-nights, the night-working nurses’ melatonin levels were significantly lower than those of day-working nurses. The study also evaluated differences in reproductive hormones between the night- and day-working nurses. Although there were differences in follicle-stimulating and luteinizing hormone levels between night-working nurses and day-working nurses, no significant differences in estrogen levels were observed (19). This suggests that mechanisms other than reproductive hormone pathways may be of greater importance in determining cancer risk associated with decreased melatonin levels. For example, melatonin has been shown to have direct oncogenic effects (2), including the protection of cells from oxidative DNA damage and promotion of the repair of oxidative DNA damage once it has occurred (5, 20, 21).

The direct impact of melatonin on human tumor growth was elegantly demonstrated by Blask et al. (20). Venous blood samples were collected from healthy, premenopausal female volunteers under 3 scenarios. One sample was collected during the day, one at night after 2 hours of complete darkness, and one at night after 2 hours of complete darkness followed by 90 minutes of bright white light exposure. When human breast tumors were perfused with these blood samples, the melatonin-rich nighttime samples demonstrated significantly less evidence of tumor growth and activity, as measured by linoleic acid uptake, 13-hydroxyoctadecadienoic acid formation, cyclic adenosine monophosphate (cAMP) levels, and [3H]thymidine incorporation into DNA, as compared with the melatonin-deficient daytime samples. The post-bright white light nighttime samples were also melatonin-deficient, and perfusion of tumors with this blood resulted in near-daytime levels of increased growth and activity. In additional experiments, pharmaceutical melatonin was added to blood samples collected after bright white light exposure and a melatonin receptor antagonist was added to samples collected after 2 hours of complete darkness. The former samples demonstrated significantly suppressed tumor growth and activity, while the latter demonstrated significantly increased tumor growth and activity. These results indicate that melatonin directly affects...
tumor growth and activity, and as such, the negative effects of shift work may be more broadly applicable to many cancers. This is supported by the increased risks observed at several cancer sites by Parent et al. (7).

If night-shift work is indeed an important determinant of cancer risk, it will constitute a significant global public health concern, and there will be an urgent need for detailed data with which to make informed policy decisions. The results reported by Parent et al. provide further support for an etiologic role of night-shift work in cancer and reminds us to avoid an overly narrow approach in our investigative pursuits. In moving forward, launching new case-control studies may be impractical, since recollection of detailed information on shift work and sleep quality is difficult to do with any certainty. Existing occupational cohorts with employment records may be useful, but it is unlikely that employment records will be sufficiently detailed regarding the specific aspects of shift work that are of most interest. While new cohort studies with detailed baseline and follow-up information on shift work offer the most tenable approach, the obvious limitation is the number of years of follow-up that would be required and the numbers of persons who would have to be followed before adequate numbers of cancers were accrued to conduct meaningful analyses. Even with the limited data currently available, it may be difficult to wait for more definitive evidence to emerge. A Danish court, in response to the IARC’s classification, decided to award compensation to 38 women with breast cancer who had worked night shifts for at least 20 years (22).

As other courts face similar decisions, there is another class of studies that can provide much needed understanding of the association between shift work and cancer in a timelier manner. Studies incorporating biomarkers of the effects of night-shift work are a logical next step in investigating whether the findings in laboratory studies of animals that persuaded the IARC to classify shift work as a “probable” human carcinogen translate to real-life working populations. Not only can these studies aid in identifying the mechanisms that may underlie associations between shift work and cancer and inform the design of future epidemiologic studies of cancer risk, they can also aid us in interpreting existing epidemiologic findings. These studies should incorporate potential biomarkers of increased cancer risk, such as markers of DNA damage and inflammation, and they should examine the impact of race, genetic polymorphisms, and chronotype on these biomarkers. As an example, Zhu et al. (23) recently demonstrated that night-shift workers had significant differences in levels of DNA methylation, an intriguing marker of carcinogenesis, across numerous genes, including 2 circadian genes: the circadian locomotor output cycles kaput gene (CLOCK) and the cryptochrome 2 gene (CRY2).

In conclusion, epidemiologic studies with detailed data on the various aspects of shift work are needed to truly understand the associations between shift work and multiple types of cancer that are being increasingly observed. Cohort studies that collect detailed shift-work data at baseline are the best approach, but it will take years of follow-up before meaningful analyses can be conducted. In the meantime, studies incorporating biomarkers of effect may be a useful alternative.

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REFERENCES


