Shift Work

by Richard Stevens PhD

Citation for most recent IARC review

IARC Monograph 98, in preparation

Current evaluation

Conclusion from the previous Monograph:
On the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves nightwork", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)", the Working Group concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Group 2A) (Straif et al., Lancet Oncol, 8:1065-66, 2007)

Exposure and biomonitoring

Exposure to 'Shift Work' is common in the industrialized world (Costa, 2003), and increasing in prevalence worldwide. About 27% of the European Union work force works an evening shift 5 or more evenings per month, and about 10% work the night shift 5 or more nights per month (EWCS, 2005). The sectors with the highest percentage of workers on a non-day shift are Hotels and Restaurants, Agriculture, Health, and Transport and Communication. Of all workers, about 6% are on a permanent non-day shift whereas about 8% are on a rotating shift schedule. In the United States about 15% of workers are on non-day shifts, with 3.2 % on night shift and 2.5% on rotating shifts (BLS, 2004). Although there is less variability in number of hours worked per week among non-day shift workers compared to day workers, there is also considerably less autonomy on the job.

Occupational exposure

The 'exposure' is by definition occupational. However it is based on a theory that light at night (LAN) would disrupt circadian rhythms and that this disruption might increase cancer risk.

Environmental exposures

Other exposures to LAN are many and include short sleep duration, late-night reading or television, nocturnal awakening and consequent exposure to light for example in the bathroom, strong street lights at night shining thru the window shade of the bedroom.

Biomarkers of exposure

Mirick and Davis (2008) provide an extensive review of melatonin as a biomarker. Assay of melatonin in urine and blood can reveal disruptions of circadian rhythms, and melatonin itself has impact on the circadian rhythm; it can be both a biomarker of exposure and of effect. Burch et al. (2005) found that night workers had altered melatonin excretion, disrupted sleep, and greater symptom (e.g., 'feeling tired', 'not alert', etc.) prevalence compared to day workers and that when workers were ranked on their sleep to work urinary 6-sulphatoxymelatonin ratio, this ratio was a better predictor of adaptation than the shift worked. In a normal healthy day worker, the sleep:work ratio is between 5 and 20, whereas for non-day workers the ratio is often close to 1. A ratio close to or less than one was highly predictive of disrupted sleep and symptom prevalence in Burch's study. This innovative metric provides a new tool for investigating shift and personal factors that most strongly disrupt circadian rhythms and thereby, perhaps, risk of two of the most common cancers in people, breast and prostate.

Cancer in humans

(*limited***,** Vol 98, in preparation)

Very few new epidemiological studies have been published since the Monograph meeting that focus on non-day shift work and cancer. One study (Lahti et al., 2008) reported an increased risk of non-Hodgkin's Lymphoma in non-day workers in Finland. Another (Marino et al., 2008) found an elevated risk of endometriosis in shift workers, although this may not be directly relevant to cancer.

Epidemiological studies of other LAN exposures

Since the 2007 Monograph meeting several epidemiological studies have been published of other predictions of the LAN theory for cancer causation. These are not studies of shift work, but are based on the same idea that exposure to light-at-night (LAN) might increase risk of certain cancers (e.g., breast and prostate), and thereby these studies contribute to the rationale that non-day shift work might increase risk of cancer as well.

Two studies by Kloog et al. (2008, 2009) examined the co-distribution of nighttime light level of communities and risk of cancer. In Israel there was a significant association of community nighttime light level and breast cancer in women; and a global analysis found a significant association of nighttime light in 164 countries and risk of prostate cancer in men. In both studies, there was adjustment for per capita income and some other measures of affluence.

There have been three new prospective studies of sleep and cancer risk based on the idea that self-reported sleep duration would be a rough estimate of hours of exposure to dark at night. Wu et al. (2008) utilized the Singapore Chinese Health Study cohort and reported an inverse association of risk and sleep duration among post-menopausal women. Similarly, Kakizaki (2008a, 2008b) used the Ohsaki Cohort Study, a large prospective study in northeastern Japan, to show an inverse association of reported sleep duration and risk of breast cancer in women and prostate cancer in men.

There have been reported two more prospective studies of baseline urinary melatonin metabolite and breast cancer risk both of which reported significant inverse relationships (Schernhammer et al., 2008; 2009).

Bias and/or confounding

Known risk factors for breast cancer include reproductive factors and exogenous hormones, physical activity and BMI, as well as alcohol consumption. Some of the positive cohort studies adjusted for known risk factors for breast cancer and did not provide evidence for confounding. In the case-control studies, there is additional concern for selection bias since success to enroll potential controls who work shifts may differ from other controls. There is limited evidence for an increased risk of breast cancer with low serum 25-hydroxyvitamin D levels (IARC 2008) and a few studies have also suggested an inverse association between sun exposure and risk of breast cancer (IARC, in press). If these associations are corroborated by further studies, the potential lack of sun exposure in night-shift workers needs to be considered as a potential confounder for the association between shift-work and breast cancer or may act as on the causal pathway from shift-work to cancer.

Cancer in experimental animals

(*sufficient***,** Vol 98, in preparation)

The experimental work on cancer in experimental animals, (e.g. Blask et al., 2005), was judged to be sufficient by the Working group for a LAN role in cancer etiology.

Mechanisms of carcinogenicity

The cancer bioassays also explore a mechanism by which LAN-induced suppression of melatonin leads to release from growth inhibition of a small existing breast tumor. It has not yet been established if this mechanism also operates in exposed humans, and there may be other potential mechanisms that contribute to the carcinogenicity of shift-work. As it has become clear that the core circadian genes have many other functions including direct regulation of a large portion of the genome, a number of possible mechanisms for cancer causation are emerging (Stevens et al., 2007; Haus and Smolensky, 2006). These include circadian regulation of cell cycle checkpoint genes such as Cyclin D1 (Fu and Lee, 2003), histone-acetyl transferase (HAT) such as cmyc, and the WEE1 pathway (Matsuo et al., 2003). The Clock protein itself also has HAT activity (Sahar and Sassone-Corsi, 2007).

Also of potential importance is an effect of LAN on normal mammary tissue development. Based on Dimitrios Trichopoulos's (1990) hypothesis that early life experience, even beginning in utero, affects lifetime risk of breast cancer, LAN during these critical developmental periods could also affect lifetime risk perhaps by affecting melatonin and other hormones and/or altering circadian gene function (Stevens, 2005; Metz et al., 2006). This possibility could have serious implications for light exposure to pregnant women (e.g., shift work) and for the lighted environment of children.

Advancing understanding of the biology of circadian rhythms and of how light affects the rhythm (Brainard et al., 2008), the scientific and architectural lighting communities could help to design shift schedules, and the lighting of non-day shift environments that better accommodate circadian health. Although the suprachiasmatic nuclei (SCN) is the master circadian pacemaker in mammals, there are peripheral oscillators in tissues that can be decoupled from the SCN by, for example, feeding schedule (Stokkan et al., 2001).

Circadian disruption is characterized by at least two interrelated issues, melatonin suppression

(which may or may not induce phase shifting), and phase shifting and the attendant desynchrony of the master pacemaker with the sleep cycle and with the peripheral oscillators in tissues such as digestive system, breast, and prostate. The first, melatonin suppression, may be linked to alterations in hormone levels that directly increase risk of cancer and to the direct oncostatic effects of melatonin itself, and the second may be linked to clock gene influence on expression of genes in tissues for cellular processes (cell cycle regulation, DNA repair, apoptosis, etc.) that influence the chance that a normal cell will become transformed into a cancer cell. The two aspects might work together in which clock gene alteration results in a normal cell transforming into a cancer cell, and then melatonin suppression resulting in release of cancer cells from growth inhibition through estrogen signaling (Cos et al., 2006), or increased linoleic acid availability to cancer cells in a small tumor that would otherwise have remained indolent (Blask et al., 2005). Another related possibility is that the sleep disruption and deprivation in non-day workers contributes to cancer risk. This might occur from a couple of mechanisms including effects on immune function (van Leeuwen et al., 2009) or metabolism (Knutson and Van Cauter, 2008; Spiegel et al., 2009).

Biomarkers of effect

It is difficult to disentangle biomarkers of 'exposure' from biomarkers of 'effect', as one biological change can indicate both. A potentially important biomarker of effect may be gene promoter methylation (Weaver et al., 2004) which can occur from environmental exposures and may be reversible (Weaver et al., 2006). Although circadian gene expression and promoter methylation has been examined in cancers (Chen et al., 2005), it has not yet been investigated in normal tissues after environmental exposures.

Research needs and recommendations

An important limitation of the available epidemiological studies is that there have not been clear and uniform definitions of 'shift work' used. A manuscript is in preparation based on an IARC Workshop on defining 'shiftwork' which was held April 2 and 3, 2009 (Stevens et al., in preparation). There are several characteristics of a shift and shift schedule that the working group believes to be important to capture in epidemiological studies of cancer. These include 1) based on start and stop time, characterization of shift as 'day', evening', or 'night', 2) whether rotating, and if so, whether fast or slow, forward or backward, and 3) numbers of years on the shift. The approach to shift-work assessment will depend on the study design. Industry-based cohort studies may offer the opportunity to extract from company records clearly defined shift-schedules prevailing in a study plant. In most other study settings, such as population-based cohort studies or case-control studies in general, this information needs to be collected from the study subjects. Here, further criteria for exposure assessment, e.g. the strength and limitations of self-administered questionnaires vs. telephone interviews vs. face-to-face interviews need to be taken into consideration and validation of a questionnaire in a pilot study would be desirable. Preferably, data on shift-work should be collected separately for each job in an individual's lifetime occupational history. This would also allow assigning shift-work to certain periods of the individual's life history and may thus offer the opportunity to explore, for example, age-specific susceptibility to shift-work-related cancers.

Recommended are studies of the effect of non-day shift work on circadian biomarkers (e.g., melatonin and cortisol profiles), on circadian gene expression (e.g., promoter methylation),

and on expression of clock-controlled genes relevant to cancer risk such as of cell cycle regulation, apoptosis, and DNA repair.

Shift work and susceptibility to chemical toxicants

There are known genetic polymorphisms in detoxifying enzymes that changes an individual's sensitivity to exposure to a toxic chemical (Christiani et al., 2008). Similarly, there may be significant differences in susceptibility to adverse effects from chemical exposures in non-day workers compared to day workers. This is based on the known circadian variations in DNA excision repair (Kang et al., 2009), cell proliferation and activity of detoxifying enzymatic capacity (Schibler, 2007; Lévi et al., 2008). These variations by time of day have begun to be exploited in delivery of cancer chemotherapy to optimize killing of cancer cells while minimizing damage to normal cells (Lévi et al., 2008), but the important possibility that time of day of occupational exposures could affect risk has not been investigated to date.

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