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Cancer Epidemiology, Biomarkers & Prevention

Hypothesis/Commentary

Does Electric Light Stimulate Cancer Development in Children?

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Abstract

Incidence of cancer in children has increased in recent decades, and known risk factors can account for only a small minority of cases. Gestation and early childhood are particularly vulnerable periods in human development and an important aspect of development is in circadian rhythmicity. Emerging evidence implicates the molecular circadian mechanism in a vast array of other physiologic functions including metabolism, DNA damage response and cell-cycle regulation. Electric light exposure at night can disrupt circadian rhythms and, thereby, many other physiologic processes that are under circadian control. On this basis, it is proposed that ill-timed electric light exposure to pregnant women, to neonates, infants, and small children may increase cancer risk in those children. There are practical implications and interventions that accrue from this idea should it later be confirmed to be true. *Cancer Epidemiol Biomarkers Prev; 21(5); 701–4. ©2012 AACR.*

The Problem

The incidence of cancer in children has increased since the mid-1970s in the United States (1) and in Europe (2) where increases have occurred for each of the major diagnostic categories of leukemias (0.6% per year), lymphomas (0.9% per year), and central nervous system (CNS; intracranial) tumors (1.7% per year). There is also a rough correlation among societies between leukemia incidence in children and degree of industrialization; although known risk factors can account for only a minority of cases (3).

Gestation and early life are particularly vulnerable periods in human development, and establishment of circadian rhythmicity is a crucial part of a healthy development. Human circadian rhythmicity begins forming in early gestation but is not robust at birth and takes several more months to become consolidated (4). In the modern world, electric light, which can disrupt circadian rhythms, intrudes on nearly all aspects of life, from our very beginnings *in utero*, to our end. Maybe that is a problem (5).

Hypothesis

Exposure to ill-timed electric light that disrupts circadian rhythmicity of a pregnant woman may alter circadian gene expression and may also alter circadian hormones relevant to cancer. For her fetus, who is exposed to the disruption as well, this might later lead to increased risk of cancer. After birth, ill-timed electric light exposure to a child may disrupt circadian rhythmicity and contribute to increased risk of cancer in early life.

Trichopoulos (6) reasoned that factors that might increase circulating estrogen in a pregnant woman might increase the lifetime risk of breast cancer in her daughter. A growing number of epidemiologic studies of predictions of this idea (e.g., high birth weight, pre-eclampsia, twin birth) lend support to it. Another prediction tested in rats by Hilakivi-Clarke and colleagues (7) was that maternal ethanol ingestion during pregnancy (far below that required to cause fetal alcohol syndrome) would increase mammary tissue development and susceptibility to chemically induced mammary tumorigenesis in her female pups later in life; both were confirmed in their experimental model.

By analogy, maternal exposure to electric light during the night might also cause changes in fetal development such that potential for malignant transformation is stimulated in hematopoietic and CNS tissues as well as in mammary tissue.

Circadian Rhythms and Disruption by Electric Light

There are many biologic rhythms in humans with periods ranging from milliseconds as in nerve cells, to many weeks as in the menstrual cycle (8). Circadian rhythmicity (comprising many coordinated rhythms) includes endogenous, approximately 24-hour oscillations in melatonin production, activity, sleep, metabolism, body temperature, gene expression, and many other aspects of physiology; they continue to oscillate in the temporal isolation of constant darkness (9). Circadian rhythms are maintained in nature at exactly 24 hours by the sun. However, in the modern world, light and dark are increasingly determined by electric light inside buildings,

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and not by the solar cycle of day and night. Light is the major determinant of circadian entrainment (10), although meal timing can also play an important role in many organs (11). It has become clear that circadian rhythmicity can be severely disrupted by ill-timed exposure to electric light (12).

Monochromatic light during the night under experimental conditions was shown by Brainard and colleagues (13) to suppress circulating melatonin concentrations in humans in a dose-dependent manner with a peak effectiveness at about 460 nm (blue) and very little impact at 600 nm (red); even very low light intensity at short wavelengths exhibited a measurable lowering of blood melatonin level. For polychromatic light as used in buildings, it has recently been shown that even a relatively low level (60–130 lux) from a standard fluorescent bulb in the evening can delay the melatonin onset and blunt its amplitude in human subjects (14). Altered timing of light exposure can also change expression of circadian genes (15).

Circadian Gene Expression and Action

The 24-hour time course of expression of the clock genes (of which there are less than 10 so far identified; ref. 16) has been described in humans and will be important in helping unravel the connections of these genes to the control of so many aspects of our physiology (17). As much as 10% of human genes are under circadian control (16); of particular interest is the fact that many of these are genes of cell-cycle regulation and apoptosis. Importantly, it has become evident that the circadian clock mechanism is closely intertwined with cell-cycle regulation at the molecular level (18), and so circadian disruption can be expected to result in cell-cycle disruption as well. As with cancer in adults, cancer in children is a highly heterogeneous group of diagnoses (2); however, as the rubric "cancer" denotes, these diagnoses share certain features in common, high on the list of which is loss of cell-cycle control (19).

Early environmental exposures can effect epigenetic changes that may last a lifetime (20). In particular, epigenetic modification of gene expression may be an important link between the circadian system and metabolism, with the gene CLOCK playing a central role (21). The first epidemiologic evidence showing an environmental influence on epigenetic modification of CLOCK reported that shift working women display significant hypomethylation of the CLOCK promoter compared with day-working women; a finding consistent with previous reports of CLOCK promoter hypomethylation in women with breast cancer (22). An interesting question is whether shift work by a pregnant woman might have epigenetic consequences for her child that could affect fetal growth and development.

High birth weight has been consistently shown to be associated with risk of leukemia in children, and Ross appropriately asks "...should we work to understand mechanistically how birth weight and fetal growth are related to leukemia risk?" (23) Evidently maternal prepregnancy weight and pregnancy weight gain are associated with the birth weight of baby (24). Perhaps, birth weight reflects, in part, maternal circadian disruption which leads to her elevated weight. This might occur from a perturbation of metabolism from the circadian disruption (21) which could also manifest as short and disrupted sleep (25).

Melatonin

Circulating melatonin level is a robust marker of circadian rhythmicity in mammals, including humans. Melatonin plays a crucial role in maintenance and manifestation of circadian rhythmicity and has potent physiologic impacts of its own. It has been shown to have powerful antitumor activity in rodent experiments on the effect of light-at-night on growth of a human breast cancer xenograft (26). However, there is a paucity of data on a possible role of melatonin in etiology of childhood cancers.

Mechanisms of Carcinogenesis

For cancer in general, the time from the beginning of the carcinogenic process to the diagnosis of cancer is believed to be long. This does not mean that an exposure that causes a first mutation in a multistage pathway is the beginning of this process; even before that, factors which alter the normal growth and development of a tissue can have a large impact on later risk of cancer by changing the probability of mutations, either spontaneous or exposure-induced (27). There are a number of features of light-induced circadian disruption that could affect risk of cancer based not only on gene mutation but also alterations in the physiology of normal tissue (28).

Many of the leukemias diagnosed in children are thought to have originated *in utero* (29), as may be the case for many forms of cancer (30). Although as much as 1% of newborns show evidence of preleukemic t(12;21)-positive cells, a vastly lower percentage are ever diagnosed with B-cell acute lymphocytic leukemia (ALL), suggesting that other or exogenous factors are required to cause the clearance of these premalignant cells (31). Circadian disruption may impede this clearance process by compromising apoptotic pathways (32).

Perhaps of particular relevance to childhood leukemia, Méndez-Ferrer and colleagues (33) have shown that circulating hematopoietic stem cell (colony-forming units; CFU) concentrations in mice exhibit circadian fluctuations with a peak at 5 hours after beginning of the light period and a Nadir at 5 hours after lights out; the peak to nadir ratio was more than 5-fold. This pattern was obliterated by constant light, and total 24-hour concentrations were markedly higher. There is also evidence from study of infants that fetal hormone levels are strongly associated with markers of stem cell potential (30). This provides a possible link from circadian

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disruption, to stem cell concentration, to hormone levels in fetal development.

Specific Epidemiologic Predictions

There are several facets to the possibility that disruption of circadian rhythms by electric light increases risk of cancer in children. These include *in utero* exposures to the mother, immediate postnatal exposure in the hospital, and lighting at home during early childhood.

Specific predictions of the hypothesis are as follows:

- Maternal circadian disruption by light at night (e.g., from shift work) during pregnancy increases subsequent risk of cancer in her child.
- Shorter gestation time increases risk because earlier birth, while infant circadian rhythmicity is still maturing, results in earlier exposure to the circadian disruptive effects of electric lighting, for example, in an NICU. There is some evidence in support of this for leukemia (34) and for CNS tumors (35); these studies focused on birth weight and risk but also report an inverse association of gestational age and risk.
- Parental behaviors such as use of bright light at night for attending to a newborn infant increases risk of cancer for that child. Use of night lights in a child's bedroom increases risk.

Practical Implications

Of all the terrible forms that cancer can take, cancer in a child is the most distressing. If the idea that electric lighting plays a role turns out to have merit (be true), then there are a number of practical implications and feasible interventions that could be implemented. For pregnant women, avoid shift work if possible and stick to a constant diurnal pattern of light exposure with sunlight during the day and as dark as possible during the night. For care of premature newborns, maintain as nearly as possible a diurnal pattern of lighting in the hospital; use light only where needed and only as bright as required for care. For parents of a child, from birth onward, avoid night lights, and when feeding or caring for a child at night, use dim red light sources.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Authors' Contributions

Conception and design: R.G. Stevens
Writing, review, and/or revision of the manuscript: R.G. Stevens

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