Scientific Symposium

The Health Effects of Shift Work

Toronto, April 12, 2010

Shift Work and Adverse Health Effects: Possible Biological Mechanisms

Scott Davis
University of Washington

Institute for Work & Health | Research Excellence Advancing Employee Health

Occupational Cancer Research Centre

Background

- There is increasing interest that the disruption of the normal circadian (24-hr) cycle may have a role in the etiology of some types of cancer
- The release of nearly all hormones exhibits a circadian timing pattern; thus, the disruption of the normal circadian rhythm due to environmental and/or lifestyle factors may alter the regulation of hormones that are directly relevant to cancer etiology.
- Of particular interest is the influence of both exposure to light-at-night (LAN) and sleep disruption on the regulation of melatonin produced by the pineal gland and estrogen release from the ovary.
- Several recent epidemiologic studies suggest that women who work shifts at night, and consequently may experience sleep deprivation, circadian disruption, and exposure to LAN, are at an increased risk of breast cancer.

Importance of the Problem

Prevalence of Night Shift Work

- A substantial number of employed women work in jobs involving some degree of night shift work.
- In the US, approximately 12% of female full-time wage and salary workers were employed in a job with some degree of shift work in 2004.
- Among non-married women, the percentage is higher: 16%
- In Canada, approximately 26% of employed women worked some type of shift work in 2000–2001.
- In Europe, 15–20% of the working population is engaged in night shift work.
- In the health-care, industrial manufacturing, mining, transport, communication, leisure, and hospitality sectors, the prevalence of night shift work can exceed 30%.

Normal Pineal Function And Melatonin

- Melatonin is the primary circadian pacemaker that synchronizes the internal hormonal environment to the light–dark cycle of the external environment.
- Melatonin is produced and secreted by the pineal gland, which is stimulated by darkness and suppressed by light as perceived by the retina.
- Melatonin is synchronized to the daily light/dark cycle
- Underlying biological mechanisms which could provide an explanation for the observed associations between night shift work and breast cancer risk may be related directly to the effects of light exposure and/or sleep disruption, or more fundamentally to altered pineal function and the resulting effects on hormonal regulation.

Hormonal Regulation

- Melatonin appears to be involved in the regulation of gonadal function
- There is evidence that indicates that decreased concentrations of circulating melatonin can result in increased release of the gonadotropins LH and FSH from the pituitary and estrogen release by the ovaries.
- Thus, melatonin may exert an important modulatory effect on ovarian function and estrogen production and consequently have an inhibitory effect on hormone-dependent tumors, including breast cancer.

Direct Action of Melatonin

- Experimental studies have generally shown that melatonin can have a beneficial effect in a number of experimental settings
- Pinealectomy in rats
  - Increased DNA damage after treatment with a carcinogen
  - increased incidence of chemically-induced mammary tumor

Beneficial Effects of Melatonin

- Inhibit the development and/or growth of tumors in a variety of experimental animal models
- Anti-proliferative effects on human cancer cells
- Suppress the accumulation of DNA adducts
- Act as a free radical scavenger, and can detoxify carcinogens via activation of antioxidative pathways
- Can reduce the activity of telomerase in MCF-7 cells
- Can reduce the invasive and metastatic properties of MCF-7 cells
- Promote the repair of DNA once damage has occurred
- Up-regulate anti-oxidant enzyme systems

Melatonin and Cancer

Direct Experimental Findings

- Expose rats with human breast cancer xenographs to light during each 12-h dark phase: a dose-dependent suppression of melatonin
- Tumors from these rats perfused *in situ* with nocturnal, melatonin-rich blood from healthy premenopausal women: markedly suppressed proliferative activity compared with rats perfused with daytime-collected melatonin-deficient blood
- Tumors perfused with melatonin deficient blood collected following exposure to light at night exhibited the daytime pattern of high proliferation
- Others have shown that melatonin significantly reduced the number of prostate cancer cells and stopped cell cycle progression in both androgen-dependent and androgen- independent epithelial prostate cancer cells

Light-at-Night and Cancer

- Constant light
  - Increased incidence of mammary tumors in mice
  - Increased number of DMBA-induced mammary tumors in rats
  - Increased tumor growth and decreased circulating melatonin in rats with human MCF-7 breast cancer xenografts
  - Dose response in tumor growth rates and reduction in nocturnal circulating melatonin with increasing light intensity

Melatonin Receptors

- **Melatonin receptors may play a major role in mediating several of melatonin's actions at the cellular level.**
  - facilitate sleep
  - pituitary hormone release
  - testosterone production
  - cortisol secretion
  - fatty acid transport
  - immune activity
  - cancer cell proliferation and tumor growth

Other Mechanisms

- Nocturnal rise in melatonin is associated with:
  - Production of a number of specific cytokines
  - Nocturnal rise in circulating T lymphocytes
- A reduction in endogenous melatonin:
  - Reduction of natural killer cells and/or cytotoxic lymphocytes
  - Decrease in the production of a number of cancer-inhibiting cytokines

Vitamin D

- Vitamin and hormone that regulates calcium and bone homeostasis.
- Large amounts of vitamin D3 are produced in the skin with adequate sunlight exposure
- Shift work may reduce exposure to sunlight
- Reduced sunlight exposure can result in lower levels of vitamin D production, which in turn may result in a less protective environment against the development of cancer
- Primary metabolite of Vitamin D inhibits the growth of breast cancer cells and can suppress mammary tumor development
- Limited epidemiologic evidence suggests that vitamin D and sunlight exposure reduce the risk of developing breast cancer

Clock Genes

- Circadian genes have been identified that control and maintain the regulation of circadian rhythms
  - *Period (Per)* gene family
  - *h*CLOCK
- *Per3* associated with breast cancer
- *Per2* affects tumor suppression and DNA repair
- There may be a genetic component affecting a person's ability to adapt to circadian disruption

Summary

- Increasing research regarding the possibility that disruption of the normal circadian (24-hour) cycle may increase the risk of cancer
- To date, the focus has been primarily on the effects of working at night
- Increasing evidence that regular and prolonged work at night may result in adverse health effects, including breast and other forms of cancer
- The general mechanism that has been proposed to account for these effects is the disruption of the normal 24-hour circadian cycle
- Lower melatonin levels may influence the development of cancer in a number of ways. At present, little is known about specific mechanisms
- Two principal mechanisms
  - influence the regulation of gonadal function, and thereby the production and release of melatonin and reproductive hormones
  - Melatonin may have direct effects.

Future Directions

- Must attempt to determine exactly what aspects of night shift work are causing the increase in risk.
- Studies should be undertaken to evaluate the association between LAN exposure and the risk of not only breast but also other cancers, including cancer risks in men.
- A need for research that addresses individual susceptibility
- With a better understanding of the biological basis for the detrimental effects of night shift work, it should be possible to design preventive interventions to reduce the relevant exposure or exposures.


Thank You For Your Attention