Seeing the Light: How to Minimize the Health Impacts of Shiftwork

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Towards a cancer-free workplace
The OCRC & Conflicts of Interest

• Created in 2009 through partnership between:

- Ontario Cancer Care Ontario
- Canadian Cancer Society
- Action Cancer Ontario
- Société canadienne du cancer
- Ontario Ministry of Labour
- Ministère du Travail
- United Steelworkers
- Unity and Strength for Workers
- WSIB & CSPAAT

• Research program focused on
  – Studies of the causes of workplace cancer
  – Surveillance of cancer and carcinogens
  – Prevention research
Shiftwork in Canada

- Regular Night or Rotating Shift: 2%
- Regular Evening, Split Shift, On Call or Irregular Schedule: 13%
- Regular Day: 19%
- Other/Don't know: 66%

Bernardino Ramazzini (1633-1714)

Author of the first comprehensive occupational medicine text in 1700.

In 1717 published *The Health of Princes*

“The inversion of sleep with wakefullness, much in vogue in the courts of princes, is little conducive to maintaining health”
“Breast cancer is a disease of modern life. As societies industrialize, risk increases, yet it is unclear which of the myriad changes coming with industrialization drives this increase. One important hallmark of modern life is the pervasive use of electric power. Electric power produces light at night (LAN) and electric and magnetic fields (EMF), either or both of which may alter pineal function and its primary hormone melatonin, thereby, perhaps increasing the risk of breast cancer.”

Richard Stephens & Scott Davis, Environmental Health Perspectives 1996;104(suppl 1):125-140.
In October, 2007, 24 scientists from ten countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of shift-work, painting, and fire-fighting. These assessments will be published as volume 98 of the IARC Monographs.1

About 15–20% of the working population in Europe and the USA is engaged in shift-work that involves nightwork, which is most prevalent (above 30%) in the health-care, industrial manufacturing, mining, transport, communication, leisure, on tumour development. More than 20 studies investigated the effect of constant light, dim light at night, simulated chronic jet lag, or circadian timing of carcinogens, and most showed a major increase in tumor incidence. No clear effect was seen for light pulses at night or constant darkness. A similar number of studies investigated the effect of reduced nocturnal melatonin concentrations or removal of the pineal gland (where melatonin is produced) in tumour development and most showed increases in the incidence or growth of disruption is probably carcinogenic to humans” (Group 2A).15

Painters are potentially exposed to many chemicals used as pigments, extenders, binders, solvents, and additives. Painters can also be exposed to other workplace hazards, such as asbestos or crystalline silica.

Cohort and linkage studies of painters have shown consistent and significant increases in lung cancer compared with the general population. No information on tobacco smoking was available in the cohort studies; however, the increases
Who Decides what Causes Cancer?

• Public opinion?
  – driven by the media, which is often based on the results of a single study...

• Advocacy groups?
  – Often well-intentioned, but highly variable and sometime filtering out conflicting evidence

• Canadian or other regulatory agencies?
  – Generally follow international organizations
IARC Monograph Evaluations
IARC Evaluation of Carcinogens

- **Group 1**: Carcinogenic in humans (117)
- **Group 2A**: Probably carcinogenic in humans (74)
- **Group 2B**: Possibly carcinogenic in humans (287)
- **Group 3**: Not classifiable, generally inadequate evidence in humans and limited or inadequate in animals (503)
- **Group 4**: Evidence of a lack of carcinogenicity in both humans & animals (1, caprolactam in 1999)
Disruption of circadian rhythms and melatonin*

- Light at night disrupts circadian rhythms and decreases the production of melatonin, which impacts other hormones
- Melatonin has direct “oncostatic” effects
- 2-10% of genes in mammals are clock controlled
  - Many processes in the body may be disrupted

* IARC Monographs Volume 98, published in 2010 and available on their website
Oncostatic effects of Melatonin

Free radical scavenging and anti-oxidation
• up-regulates anti-oxidant enzymes: glutathione peroxidase, superoxide dismutase…

Anti-proliferative effects
• inhibits the mitotic action of hormones and growth factors: estradiol, EGF, prolactin…
• induces the up-regulation of cell-surface proteins E-Cadherin and b-integrin
• slows down the cell-cycle at G0- S phase transition

Activation of the immune defence
• enhances INFg and IL-1 production
### Animal studies of cancer considered by IARC in 2007

<table>
<thead>
<tr>
<th></th>
<th>No other exposure</th>
<th>Chemical Initiation / promotion</th>
<th>Tumour cell transplantation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alterations in light exposures*</td>
<td>2 / 3</td>
<td>5 / 6</td>
<td>10 / 10</td>
<td>17 / 19</td>
</tr>
<tr>
<td>Experimental jet-lag (chronic)</td>
<td>-</td>
<td>-</td>
<td>2 / 2</td>
<td>2 / 2</td>
</tr>
<tr>
<td>SCN lesions</td>
<td>-</td>
<td>-</td>
<td>1 / 1</td>
<td>1 / 1</td>
</tr>
<tr>
<td>Pinealectomy</td>
<td>-</td>
<td>2 / 8</td>
<td>11 / 13</td>
<td>13 / 21</td>
</tr>
<tr>
<td>Physiological concentrations of melatonin</td>
<td>-</td>
<td>-</td>
<td>5 / 5</td>
<td>5 / 5</td>
</tr>
<tr>
<td>Clock gene mutations</td>
<td>1 / 1</td>
<td>1 / 2</td>
<td>-</td>
<td>2 / 3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3 / 4</strong></td>
<td><strong>8 / 16</strong></td>
<td><strong>29 / 31</strong></td>
<td><strong>40 / 51</strong></td>
</tr>
</tbody>
</table>

* Continuous bright light at night, dim light at night, intermittent or pulsed light at night
Animal Studies Considered by IARC

- 51 High Quality Studies of Breast Cancer in Rodents
  - Used a variety of protocols
  - Used altered light patterns or direct disruption of circadian rhythms or melatonin
- 40 Studies were positive (showed increased risk of breast cancer)
  - 19/21 that used altered light patterns
Human studies of cancer considered by IARC in 2007

• Focused almost only on breast cancer
  – 8 studies of breast cancer
  – A very limited number of studies for cancers at other sites

• 9 cohort studies of flight crew initiated because of concern over cosmic radiation
### Shiftwork and Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/population</th>
<th>Shiftwork</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schernhammer et al, 2001 (USA)</td>
<td>Prospective nurses cohort</td>
<td>Rotating, evening or night shift</td>
<td>RR=1.4 for 30+ yrs</td>
</tr>
<tr>
<td>Schernhammer et al, 2006 (USA)</td>
<td>Prospective nurses cohort</td>
<td>Rotating, evening or night shift</td>
<td>RR=1.8 for 20+ yrs</td>
</tr>
<tr>
<td>Lei et al, 2005 (Norway)</td>
<td>Registry-based study</td>
<td>Hospital nurses</td>
<td>OR=2.2 for 30+ yrs</td>
</tr>
<tr>
<td>Tynes et al, 1996 (Norway)</td>
<td>Radio &amp; telegraph operators</td>
<td>Night shift work on ships</td>
<td>OR=5.9 for 3.2+ yrs night shift, 50+ age</td>
</tr>
<tr>
<td>Hansen, 2001 (Denmark)</td>
<td>Registry-based study</td>
<td>4 industries w/ 60+% night shift</td>
<td>OR=1.7 for 6+ yrs</td>
</tr>
<tr>
<td>Schwartzbaum et al, 2007 (Sweden)</td>
<td>Registry-based study</td>
<td>Industries w/ 40+% night shift</td>
<td>SMR=1.0 for 10+ yrs</td>
</tr>
<tr>
<td>Davis et al, 2001 (USA)</td>
<td>Population-based case-control</td>
<td>Begin after 19:00 &amp; end before 09:00</td>
<td>OR=1.6 for ever</td>
</tr>
<tr>
<td>O’Leary et al, 2006 (USA)</td>
<td>Population-based case-control</td>
<td>Begin after 19:00</td>
<td>OR=0.6 for ever</td>
</tr>
</tbody>
</table>
# Breast Cancer among Flight Attendants

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pukkala et al, 1995</td>
<td>Finnair flight crew cohort</td>
<td>SIR=1.9, 95% CI=1.2-2.2</td>
</tr>
<tr>
<td>(Finland)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynge, 1996</td>
<td>Danish Census follow-up</td>
<td>SIR=1.6, 95% CI=0.9-2.7</td>
</tr>
<tr>
<td>(Denmark)</td>
<td></td>
<td></td>
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<tr>
<td>Wartenberg et al, 1998</td>
<td>Retired flight attendants cohort</td>
<td>SIR=2.0, 95% CI=1.0-4.3</td>
</tr>
<tr>
<td>(USA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haldorson et al, 2001</td>
<td>Norwegian cabin crew cohort</td>
<td>SIR=1.1, 95% CI=0.8-1.5</td>
</tr>
<tr>
<td>(USA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rafnsson et al, 2001</td>
<td>Icelandic Cabin Crew cohort</td>
<td>SIR=1.5, 95% CI=1.0-2.1</td>
</tr>
<tr>
<td>(Iceland)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reynolds et al, 2002</td>
<td>California flight attendants cohort</td>
<td>SIR=1.4, 95% CI=1.1-1.8</td>
</tr>
<tr>
<td>(USA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linnersjo, 2003</td>
<td>Swedish SAS cohort</td>
<td>SIR=1.3, 95% CI=0.9-1.7</td>
</tr>
<tr>
<td>(Sweden)</td>
<td></td>
<td></td>
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</tbody>
</table>

Towards a cancer-free workplace
<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient Evidence</td>
<td>Causal relationship established: chance, bias, &amp; confounding ruled out with reasonable confidence</td>
</tr>
<tr>
<td>Limited Evidence</td>
<td>Causal interpretation credible, but chance, bias, or confounding not ruled out</td>
</tr>
<tr>
<td>Inadequate Evidence</td>
<td>Studies permit no conclusion about causal association</td>
</tr>
<tr>
<td>Evidence suggesting lack of carcinogenicity</td>
<td></td>
</tr>
</tbody>
</table>
### Preliminary Default Evaluation

<table>
<thead>
<tr>
<th>Cancer in Experimental Animals</th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>Group 1</td>
<td>Group 1</td>
<td>Group 1</td>
</tr>
<tr>
<td>Limited</td>
<td>Group 2A</td>
<td>Group 2B</td>
<td>Group 2B</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 2B</td>
<td>Group 3</td>
<td>Group 3</td>
</tr>
</tbody>
</table>

- **Group 1**: Carcinogenic to Humans
- **Group 2A**: Probably Carcinogenic to Humans
- **Group 2B**: Possibly Carcinogenic to Humans
- **Group 3**: Not classifiable as to its Carcinogenicity to Humans
- **Group 4**: Probably Not Carcinogenic to Humans

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Strong mechanistic evidence can move an evaluation up or down a category.

Towards a cancer-free workplace
IARC Working Group Conclusions

Cancer in humans
• There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

Cancer in experimental animals
• There is *sufficient evidence* in experimental animals for the carcinogenicity of light during the daily dark period (biological night).

Overall evaluation
• Shiftwork that involves circadian disruption is *probably carcinogenic to humans* (Group 2A).

Shiftwork and breast cancer case-control studies published since the IARC evaluation

• 4 case-control studies
  – Increased risks associated with long-term (20-30+ years) shiftwork (Grundy et al. 2013, Rabstein et al. 2013, Menegaux et al. 2013, Papantoniou et al. 2015)

• 3 nested case-control studies
  – Elevated risks for long-term day-night rotating shifts, number of years of night shiftwork, and number of lifetime night shifts (Hansen & Lassen 2012; Hansen & Stevens 2011; Lie et al. 2011)
Meta-analyses of studies of shiftwork and breast cancer

• Assessed potential dose-response and evaluated quality of selected studies published to date (Ijaz et al. 2013, Kamdar et al. 2013, Jia et al. 2013, He et al. 2015)

• Modest, non-statistically significant increases in risk for long-term and ever night shiftwork
  - For example He et al, 2015: mRR=1.19 (95% CI=1.08-1.32) for ever shiftwork, 16% (95% CI=1.06-1.27) increase per 10 years

• Heterogeneity observed between studies
Shiftwork and prostate cancer

• 4 positive, 1 negative (Schwartzbaum et al. 2007)
• Modest evidence from two Canadian case-control studies (Parent et al. 2012, Conlon et al. 2007), one Spanish case-control study (Papantoniou et al. 2015), and one Japanese cohort study (Kubo et al. 2006) that ever night shiftwork and rotating shiftwork may be associated with increased risk
• Positive link between shiftwork and PSA levels in a cross-sectional study of US men needs to be further assessed (Flynn-Evans et al. 2013)
Some Other Known or Potential Health Effects of Shiftwork

**Acute**
- Injury
- Sleepiness and sleep disorders
- Absence due to sickness

**Chronic**
- Diabetes & metabolic syndrome?
- Gastro-intestinal disorders?
- Cardiovascular disease
- Reproductive problems?

**Psycho-social**
- Disrupted work-life balance
- Depression
- Psychological stress
- Negative well-being
Shiftwork and Cancer: Some theories (Fritschi, 2011)

Fig. 1. Theoretical framework of possible mechanisms by which shiftwork might cause breast cancer.

How can the health effects (perhaps not cancer!) of shiftwork be reduced?

Schedule Changes

• Backward (counter-clockwise) → forward (clockwise) and changing the speed of rotation
  – ↑ sleep length and sleep quality
  – ↑ triglycerides, glucose, blood pressure

• 8 hours → 12 hours
  – ↑ sleep length and sleep quality
  – ↑ physical fitness

• Work schedule flexibility
  – ↑ health, work-life balance, performance, motivation
  – ↓ stress, absenteeism, turnover

Towards a cancer-free workplace
Controlled Exposure to Light/Dark

• Timed bright light
  – Positive effects on body temperature, cortisol, melatonin
  – Various effects on sleep

• Glasses or goggles that block or filter light
  – Little effects on health

• Timed bright light AND glasses or goggles
  – Evidence of circadian adaptation
  – More effective than bright light or glasses/goggles alone
Behavioural Changes

• Physical training and lifestyle changes
  – ↑ strength, lung capacity, sleep length, weight/BMI, blood pressure

• Scheduled rest period
  – ↑ quality of life
  – Adopting strategies in the workplace is important

Pharmaceuticals

• Pharmaceutical melatonin
  – Improved sleep length in some studies
  – May facilitate adaptation to long-term night work

• Stimulants (e.g. caffeine, amphetamines) and hypnotics (e.g. zopiclone, nitrazepam) likely pose health risks to workers and public safety
Factors that can Affect Tolerance to Shiftwork

- **Family and living conditions**
  - Marital status
  - Number and age of children
  - Partner’s (shift)work
  - Housing conditions
  - Family attitudes
  - Incomes

- **Working conditions**
  - Compensative measures
  - Monetary compensation
  - Work organization
  - Job satisfaction
  - Work load
  - Counselling

- **Individual characteristics**
  - Age
  - Gender
  - Circadian structure
  - Personality and behaviours
  - Sleep strategies
  - State of health

- **Social conditions**
  - Shiftwork tradition
  - Community organization
  - Social involvement
  - Social support
  - Commuting
  - Public services

- **Working hours**
  - Shift schedules
  - Timetables
  - Overtime
  - Amount of night work
  - Flexible times arrangement

Conclusions

• Evidence for shiftwork & cancer slowly growing

• Many other potential health effects of concern

• Some interventions show promise
  – Direction and speed of rotation, flexible scheduling, possible others

• Much more research needed on interventions

• New research focusing on combinations (e.g. melatonin + bright light + scheduling)

Some Resources

IARC Monograph on Shiftwork

From the Occupational Cancer Research Centre:
http://www.occupationalcancer.ca/2012/shiftwork-interventions-symposium/

From the Occupational Health Clinics for Ontario Workers:
Shiftwork: Health effects & solutions:
http://nupge.ca/sites/nupge.ca/files/Shiftwork.pdf

From the Canadian Centre for Occupational Health and Safety:
Shiftwork – OHS Answers:
http://www.ccohs.ca/topics/hazards/ergonomic/shiftwork/#ctg_t_wb-auto-3
Some References: Recent Meta-analyses of Shiftwork and Breast Cancer


Some References: Selected intervention studies


**Controlled light exposure:**

**Changes in shift scheduling:**
Some References: Selected intervention studies

**Behavioural:**


Towards a cancer free workplace

http://occupationalcancer.ca

Thanks to Manisha Pahwa and Sarah Neil-Sztramko