

Light at night as a potential cause of breast cancer

Michael Leung
February 24, 2017



Breast
Cancer
Action
Kingston





DISCLOSURE

Presenter:

Michael Leung

I have no conflicts of interest to disclose.



OUTLINE

- A short history of cancer
 - Treatment through the ages
 - Shift to prevention
 - Importance of research
- Causes of breast cancer
 - What is known?
 - Emerging risk factors
- Shift work in Canada
- Circadian rhythm
- Evidence
 - Shift work and cancer
 - Shift work and melatonin
- Future directions

A SHORT HISTORY OF CANCER

Treatment through the ages



2500 BC

First description of cancer found in an Egyptian text:

“a bulging tumor in [the] breast... like touching a ball of wrappings.”

Discussing treatment:

“[There] is none.”

A SHORT HISTORY OF CANCER

Treatment through the ages



500 BC

The Persian queen, **Atossa**, is troubled by a bleeding lump in her breast

Greek slave performs a primitive mastectomy

A SHORT HISTORY OF CANCER

Treatment through the ages



*“black bile without boiling
causes cancer”*

Claudius Galen, 130 AD

“Melas” – Black

“Khole” – Bile

Melancholia

A SHORT HISTORY OF CANCER

Treatment through the ages



16th century

Vesalius searched for black bile,
but couldn't find it

Cause remained elusive.

A SHORT HISTORY OF CANCER

Treatment through the ages

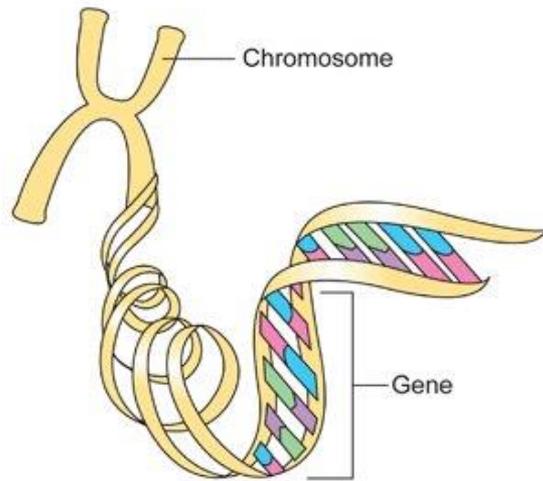


Medieval surgeons understood little about the disease, but they chisel away with knives and scalpels

Some use lead, fire or acid.

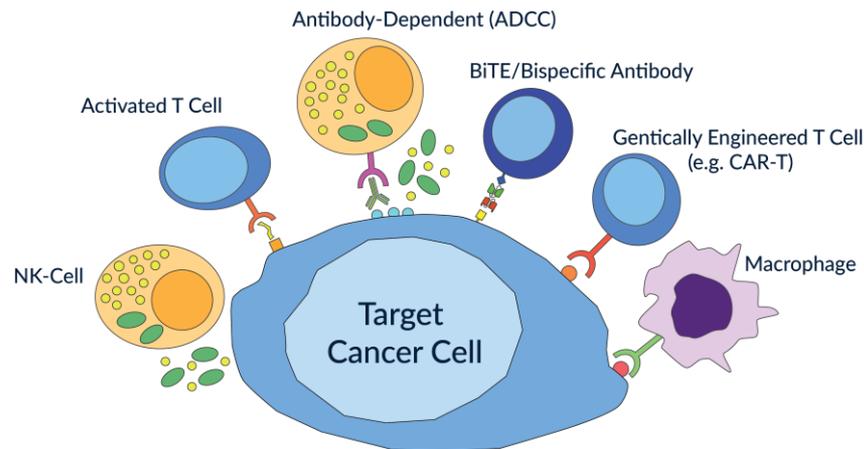
A SHORT HISTORY OF CANCER

Treatment through the ages



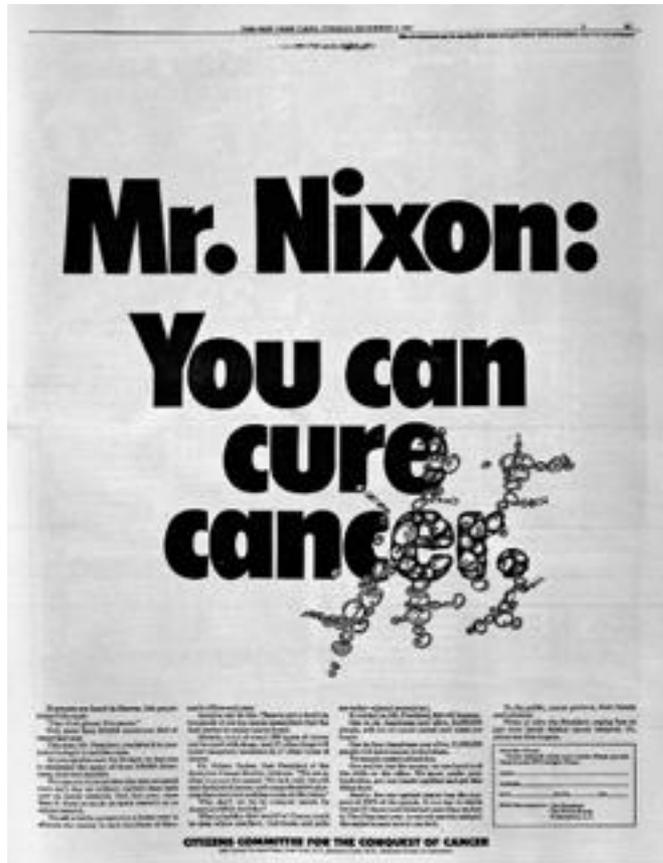
Late 19th/Early 20th century

Surgery
Radiation therapy
Chemotherapy
Immunotherapy
Other



A SHORT HISTORY OF CANCER

Treatment through the ages



New York Times, 1970

Focus has been on cure
Little known about the disease

Understanding and treatment of
cancer keeps morphing radically over
time

A SHORT HISTORY OF CANCER

Treatment through the ages

Case 1:

Chronic myeloid leukemia (CML) or Hodgkin's lymphoma, then we can now increase a life span by decades

Case 2:

Metastatic pancreatic cancer, prognosis hasn't really changed

Case 3:

Breast cancer, estrogen-receptor negative, HER2-negative, unresponsive to chemotherapy, chances of survival has only marginally improved

A SHORT HISTORY OF CANCER

Shift to prevention

Nicholas von Hoffman

False front in war on cancer



WASHINGTON—The operations last fall on Betty Ford and Happy Rockefeller to remove cancerous tumors from their breasts set off a mass-media avalanche that must have been at once frightening and comforting to many women.

Along with the worrisome adjurations to give one's self frequent breast examinations, women were repeatedly told that early detection almost certainly means that things will work out all right.

Unhappily, the prospects for recovery aren't that good. Only 84 per cent of the women diagnosed as having breast cancer live five years or longer. This is a 4 per cent improvement over the recovery rate of 15 years ago and is much better than for cancer of the cervix uteri, a disease for which expectations for survival have actually worsened during the same period.

THESE FIGURES are drawn from an analysis of cancer statistics and how they are presented to the public in January-February issue of the Columbia Review of Journalism. The author is Daniel S. Greenberg, perhaps our finest science journalist, and his conclusion is that the war against cancer has turned into a medical Viet Nam.

Greenberg says that not only have there been none of the breakthroughs we're always being promised, but that there really has been little if any progress in cancer treatment since the mid-1950s. He did find considerable improvement in the death rates between 1949 and 1953, attributable not to cancer cures, however, but to patients "surviving cancer operations that previously killed them."

Greenberg suggests that when the American Cancer Society announces that "cancer is one of the most curable diseases in this country," it's basing its assertion on suspect statistics which are then presented to the public in a context of misleading optimism. No doubt this helps keep the collection plate full, just as it probably encourages Congress to continue kicking in \$600 million for cancer research every year.

Nevertheless, the cupidity, bureaucracy, and entrenched obtuseness of the cancer industry can't entirely explain how this branch of medicine goes on falling with such unquestioning public support. Greenberg isn't the first person to say the cancer effort has dead-ended, but the objections do no good.

Part of the explanation is that people don't like to think about cancer and, when they do, they would just as soon think all those scientific folks in white smocks with reports and pipettes know what they're doing. After all, if chemotherapy, radiation, and surgery are statistically nearly indistinguishable from the fake cancer cures the quacks administer, where are we to place our hopes if the disease strikes us?

Then, the style of the prevailing medical approach is one we Americans cotton to. The "war" on cancer, the "attack" on cancer, or the phrases like mobilizing resources, massing scientific know-how to "beat" cancer, suit our thinking. We've been taught to conceive of diseases, too, as foreign invaders, as enemies.

The tools of cancer therapy are weapon-like, and we believe in that also. Surgery, radiation, chemical warfare all are aggressive, intrusive and powerful, just the stuff to knock out

tough enemies like the Viet Cong or a cancer cell.

It's comforting for us to believe we have the kind of firepower therapy that can intervene to smash our biological opponents. Or, we beat them with technological superiority as with the latest cancer gimmick, immunotherapy, which, Greenberg reports, wiser medical minds place little hope in.

What they do hold out hope for is cancer prevention. The greatest promise lies not in curing the disease, but in making sure people don't get it. Instead of big X-ray guns we should be looking at cigarets, drinking water, food additives, air, and nutrition in general. According to Greenberg, the amount of money being spent on nutritional research is "close to nil."

THE IDEA of preventive medicine is faintly un-American. It means, first, recognizing the enemy is us and that we have to give up the idea that we can abuse ourselves and expect the doctors to put us back together when we have disease. It also means a different sort of practice of medicine, one in which the physician doesn't play the role of hero. Finally, of course, preventive medicine isn't gimmicky, aggressive or lucrative to the hospital, drug and medical equipment industries.

The times still aren't ready for such ideas.—Congress is aching to pass a national health bill which will encourage yet more "heroic" cancer therapy. The Ford administration still thinks that clean water and air is a plot against the free-enterprise system and would rather put the dough in bombers.

So, pray that Dr. Miraculous will find the cancer cure, and phone in your pledges to all medical telethons.

King Features Syndicate

"the idea of preventive medicine is faintly un-American. It means, first recognizing that the enemy is us"

Chicago Tribune 1975

A SHORT HISTORY OF CANCER

Shift to prevention

Primary Prevention

Identification of risk factors and implementation of interventions to reduce or eliminate cancer risk

(SOURCE: WHO Primary prevention of cancer through mitigation of environmental and occupational determinants, http://www.who.int/phe/news/events/international_conference/Background_interventions.pdf, 2011)

Action

- Need research evidence to take action
- As we learn more, research can refine action



CAUSES OF BREAST CANCER

What is known?

- Leading cause of cancer incidence and second leading cause of cancer deaths among Canadian women
- 25,000 new cases among Canadian women in 2015
- 68 new cases each day

CAUSES OF BREAST CANCER

What is known?



Personal



Lifestyle



Environmental



Genetic

CAUSES OF BREAST CANCER

What is known?

- Known genetic mutations account for about 5-10%
- Established risk factors (high breast density, late age at childbirth, alcohol, lack of physical activity etc): 30-40%
- Unknown cause: ~50%
- Shift work/light at night?

CAUSES OF BREAST CANCER

Emerging risk factors

1. Persistent organic pollutants

- Plasticizers: phthalates, biphenol A
- Some fungicides (organotins) and organochlorines (pesticides and PCBs)
- Flame retardants (PBDEs)
- Polycyclic aromatic hydrocarbons

2. Pharmaceuticals

3. Shift work/ Light at night

Ref: Aronson KJ, Woolcott CG. Emerging hypotheses and methodologic approaches. In: Review of Lifestyle and Environmental Risk Factors for Breast Cancer: Report of the Working Group on Primary Prevention of Breast Cancer. Canadian Breast Cancer Initiative, 2001.

SHIFT WORK



“No, your mom isn’t rehearsing for the next ‘Night of the Living Dead’ movie. She always looks like that after working four 12-hour shifts.”

SHIFT WORK

Definition

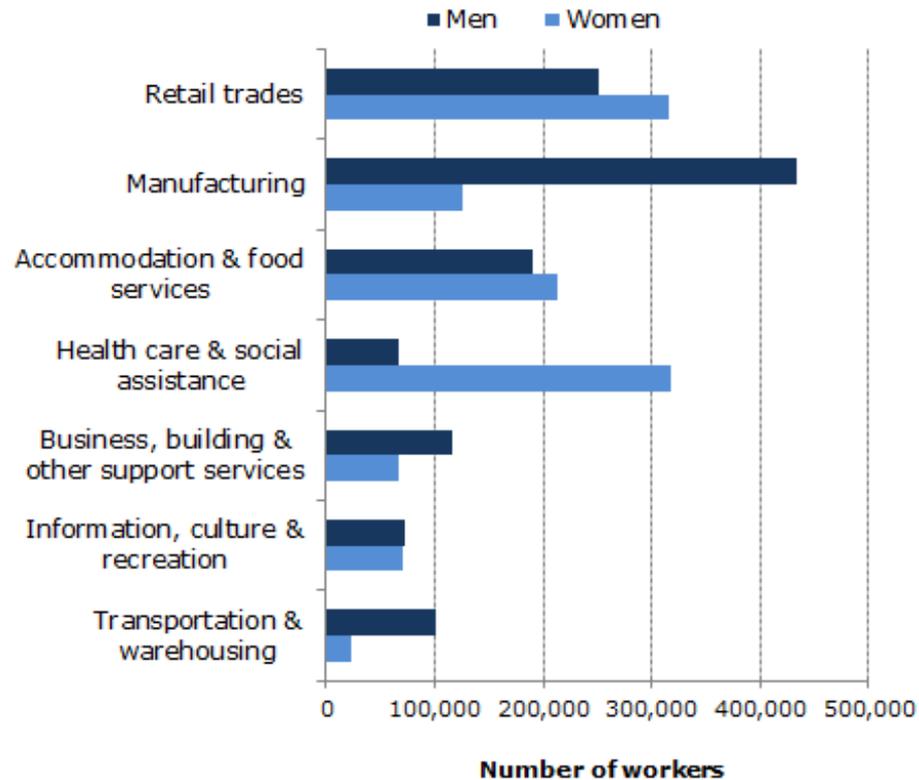
- Shift work: occupational schedule that is consistently outside of, or rotates from, standard daytime work hours; various schedules (permanent, rotating) and timing
- \approx 27% of the working population works a schedule other than a regular day schedule

Currently 4.1 million Canadians

SHIFT WORK

Shift work in Canada

Industries with the highest number of shift workers in Canada



Source: Canadian Survey of Labour and Income Dynamics, 2006.
Demers PA et al. 2001. See <http://www.iwh.on.ca/shift-work-symposium/>

SHIFT WORK

Shift work in Canada



SHIFT WORK

Shift work as a necessity

Technological necessity:

e.g. power generation

Maximize productivity and profit:

e.g. call centers, restaurants, casinos

Vital social service:

e.g. healthcare

40% of healthcare employees are shift workers

84% of hospital employees are women

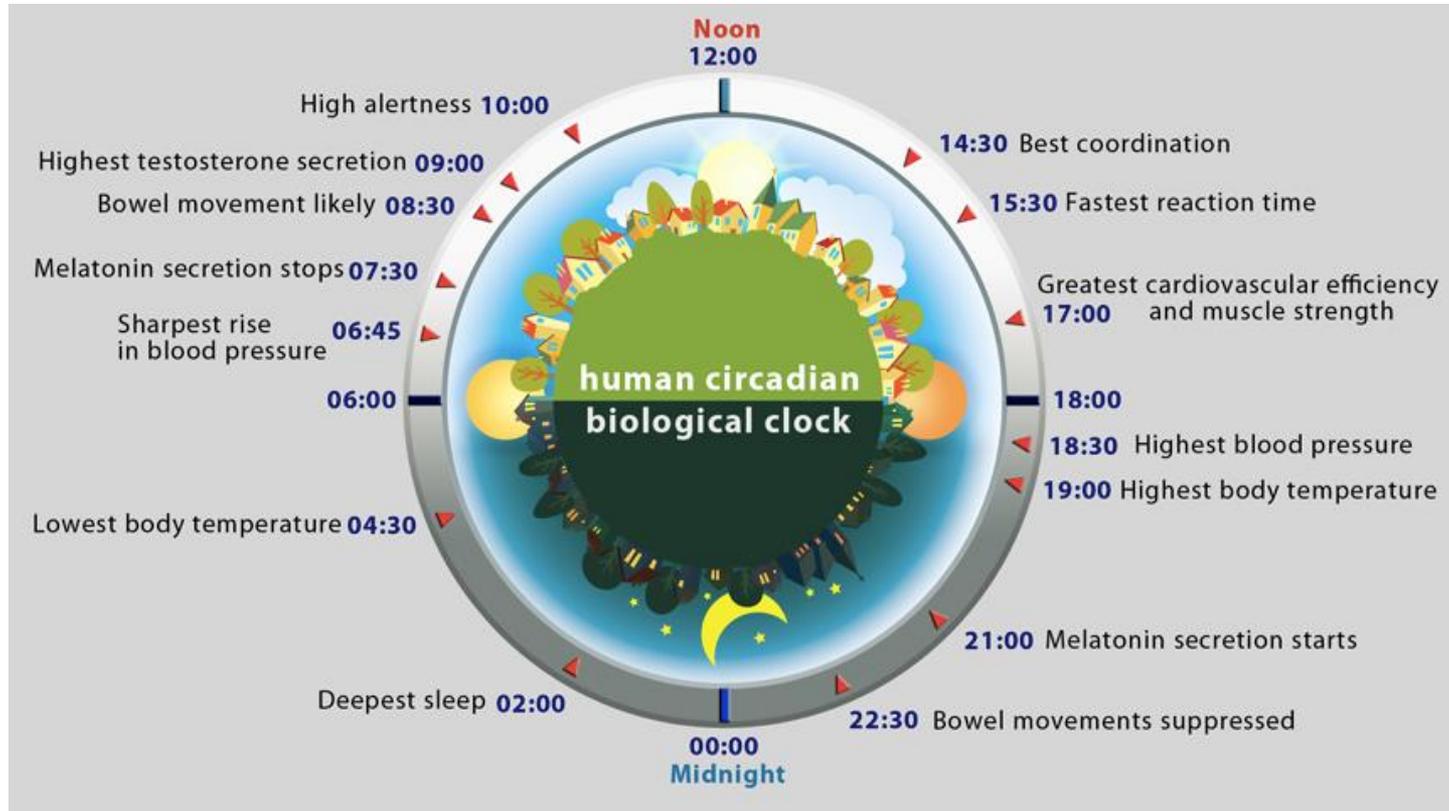
CIRCADIAN RHYTHM



CIRCADIAN RHYTHM

- Daily oscillations in physiological and behavioral processes
- Internal body clock = circadian (daily) rhythm: regulates many biological processes in (approximately) 24-hr cycle:
 - brain wave activity
 - hormone production
 - cell regeneration
 - sleep patterns
- External cues: light/dark cycles, eating/drinking, exercise

CIRCADIAN RHYTHM



CIRCADIAN RHYTHM

Disruption through night work



- Jet lag: body clock out of sync with destination time
- Shift work including nights: simulated jet lag... but worse
- “Social jet lag”: discordance between when your body “wants” to sleep and when you need to be awake

CIRCADIAN RHYTHM

Night work and health outcomes

Psychosocial

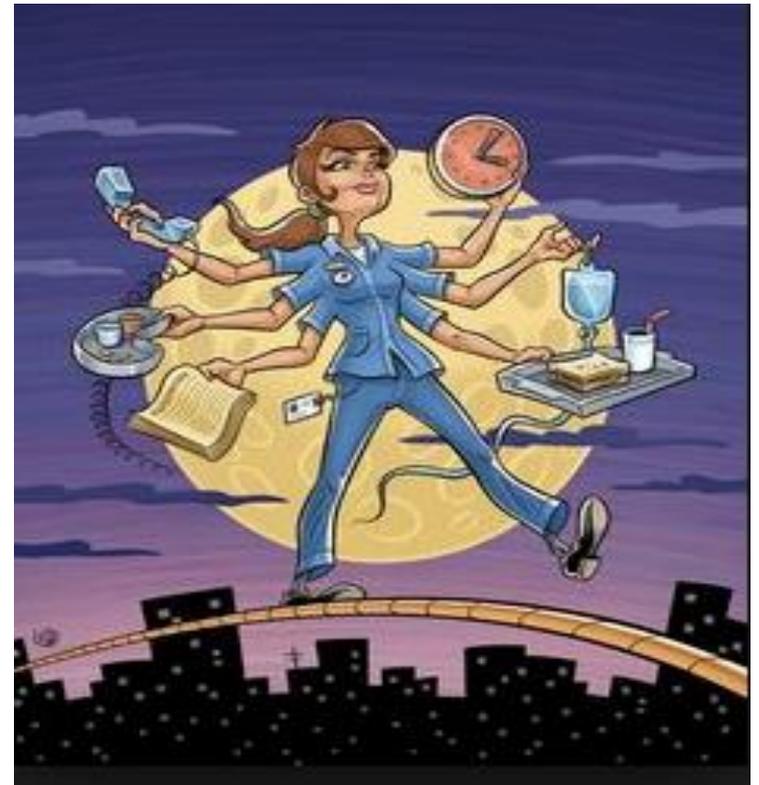
Work/life “balance” issues

Physiologic

Changes in cortisol, melatonin, other hormones; glucose etc

Physical

Sleep, GI, CVD, reproductive problems, diabetes, metabolic syndrome, several cancers etc



EVIDENCE

Shift work and cancer

Pre-2007

- Several early epidemiologic studies identified shift work as a risk factor for cancer sites including breast, prostate, colon and endometrium
- In 2007 the International Agency for Research on Cancer (IARC) classified ‘shift work involving circadian disruption’ as a probable carcinogen (sufficient in animals; limited in humans)
 - Strongest evidence/ most studies: breast cancer, mainly among nurses and flight crew
- Mechanisms linking shift work with human cancer risk has not been definitively established.

EVIDENCE

Shift work and cancer



- ~ 15 to 50% increased risk of breast cancer, and some increases in other cancers such as colon, prostate, ovarian, endometrial etc
- Definitions of shift work have varied
 - Based on response to specific questions
 - Based on job title/job exposure matrix
 - Most studies limited to nurses and flight crew

EVIDENCE

Shift work and cancer

Update since 2007

- Prostate, ovarian, colon, lung cancers
- Breast cancer
 - 3% increased risk for every 5 years of shift work
 - 80% increased risk for every 5 years of shift work with 6+ consecutive nights (Norway)
 - Higher risk:
 - » 20yrs+ work including nights (Sweden)
 - » 30yrs+ work including nights (Canada)

EVIDENCE

Shift work and cancer

ORIGINAL ARTICLE

Increased risk of breast cancer associated with long-term shift work in Canada

Anne Grundy,¹ Harriet Richardson,¹ Igor Burstyn,² Caroline Lohrisch,³ Sandip K SenGupta,⁴ Agnes S Lai,³ Derrick Lee,³ John J Spinelli,^{3,5} Kristan J Aronson¹

Study Design

Case-control study conducted in Vancouver, British Columbia and Kingston, Ontario

- 1200 cases of incident breast cancer (registry)
- 1100 controls (healthy screened women)

Objective

Evaluate relationship between long-term shift work and breast cancer risk in general population

EVIDENCE

Shift work and cancer

| Years Shift Work History | Cases N (%) | Controls N (%) | Odds Ratio (95% CI) |
|--------------------------|-------------------|-------------------|---------------------------|
| Overall* | | | |
| None | 756 (66.20%) | 772 (65.53%) | - |
| 0 - 14 | 286 (25.04%) | 312 (26.49%) | 0.96 (0.79 – 1.16) |
| 15 - 29 | 72 (6.30%) | 81 (6.88%) | 0.92 (0.66 – 1.29) |
| ≥ 30 | 28 (2.45%) | 13 (1.10%) | 2.21 (1.14 – 4.28) |

*Model adjusted for age and centre

EVIDENCE

Shift work and cancer

| Years Shift Work History | Health Occupations OR (95% CI) | Non-Health Occupations OR (95% CI) |
|--------------------------|--------------------------------|------------------------------------|
| None | - | - |
| 0 - 14 | 0.80 (0.48 – 1.33) | 1.04 (0.84 – 1.29) |
| 15 - 29 | 1.06 (0.58 – 1.92) | 1.05 (0.69 – 1.62) |
| ≥ 30 | 3.11 (1.10 – 8.77) | 2.25 (0.92 – 5.52) |

EVIDENCE

Shift work and cancer

Findings

- Overall positive association between >30 years of shift work and breast cancer risk in a population-based case-control study
- Association has same pattern in health occupations

Strengths

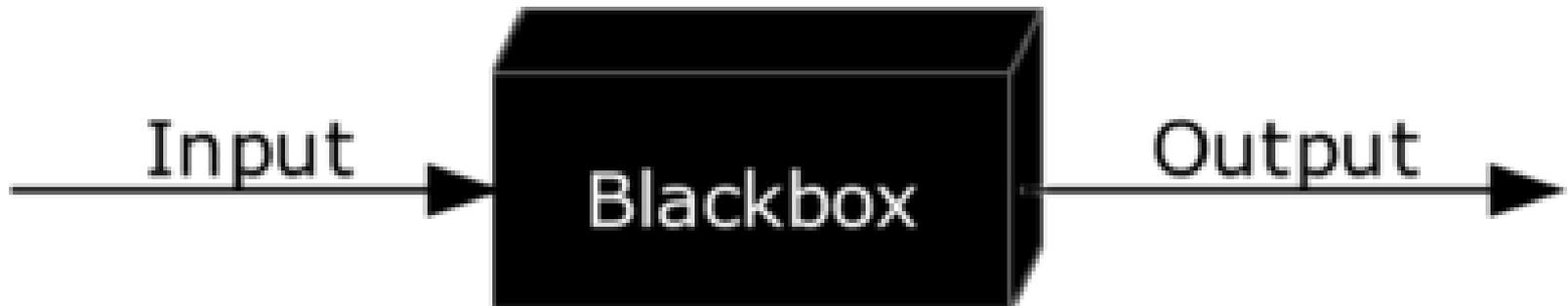
- Large sample size
- Questionnaire – comprehensive exposure assessment

Limitations

- Selection bias – sensitivity analysis
- Response bias – balanced responses

EVIDENCE

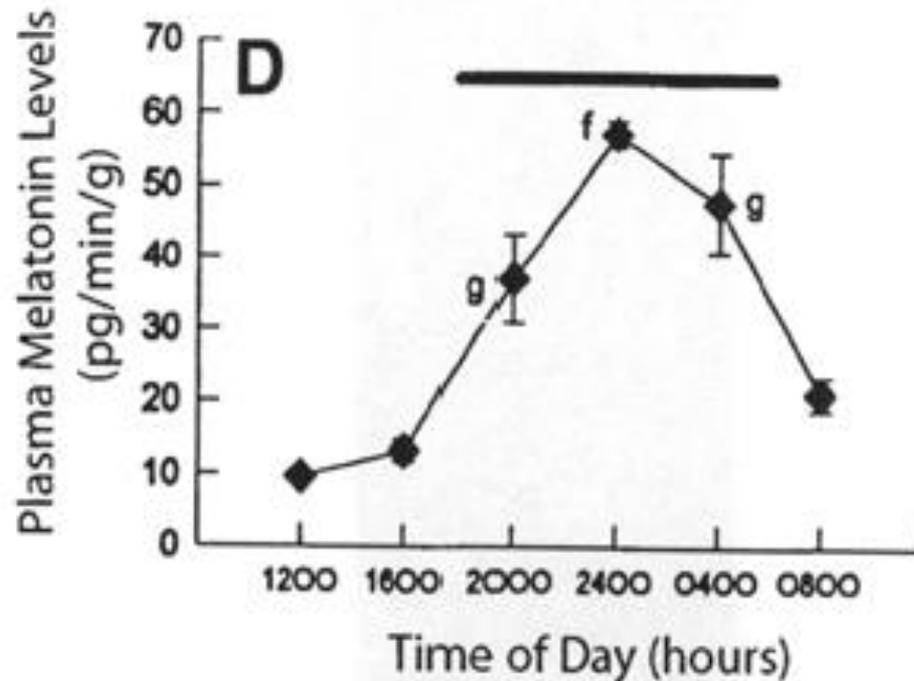
Shift work and cancer



EVIDENCE

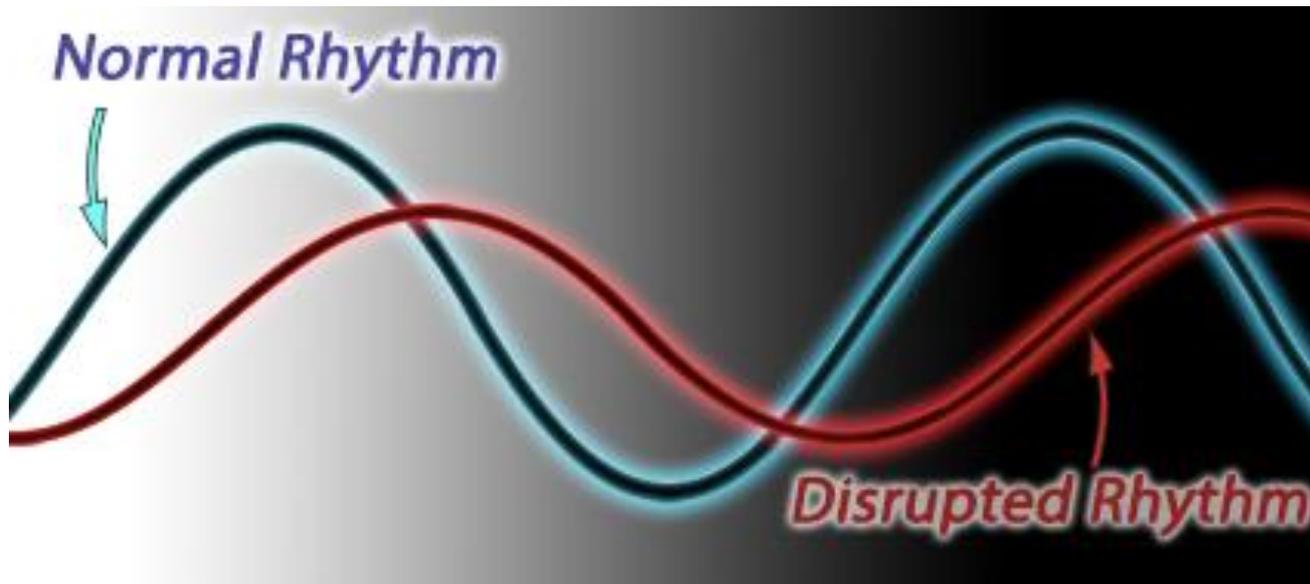
Shift work and melatonin

Melatonin levels vary with circadian rhythms and are high at night and low during the daytime hours



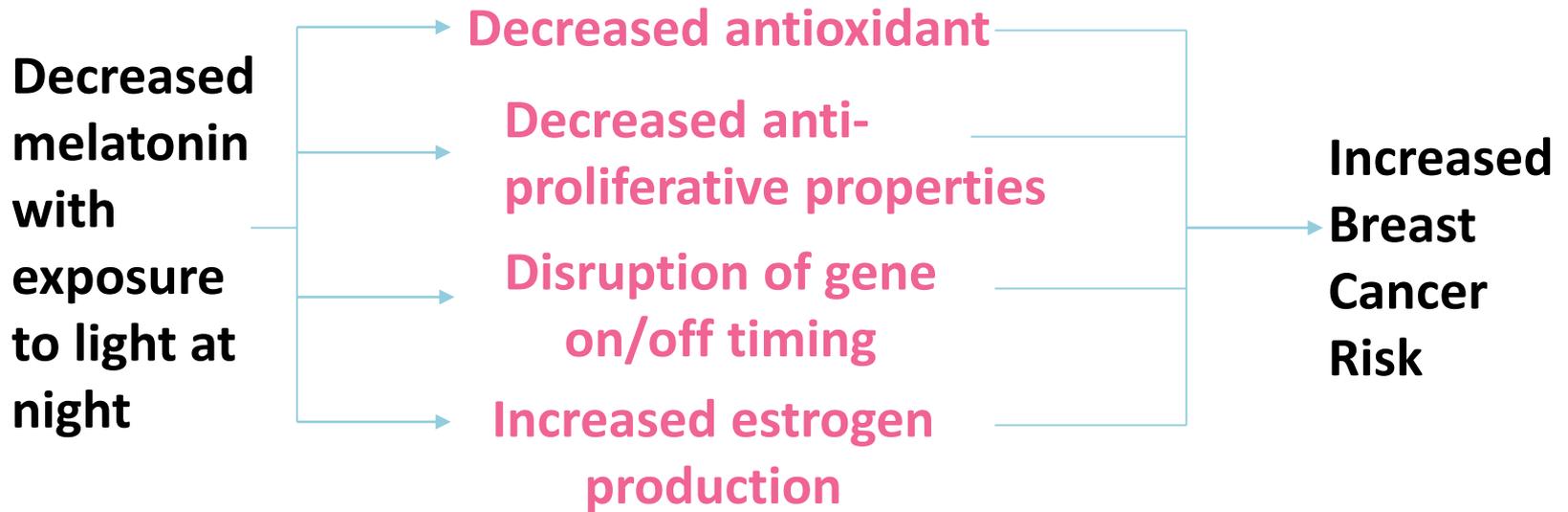
EVIDENCE

Shift work and melatonin



EVIDENCE

Shift work and melatonin



Refs: Anisimov et al. 1997; Blask et al. 2005; Cini et al. 1998; Tamarkin et al. 1981; Cos et al. 2006; Reiter 2004

EVIDENCE

Shift work and melatonin

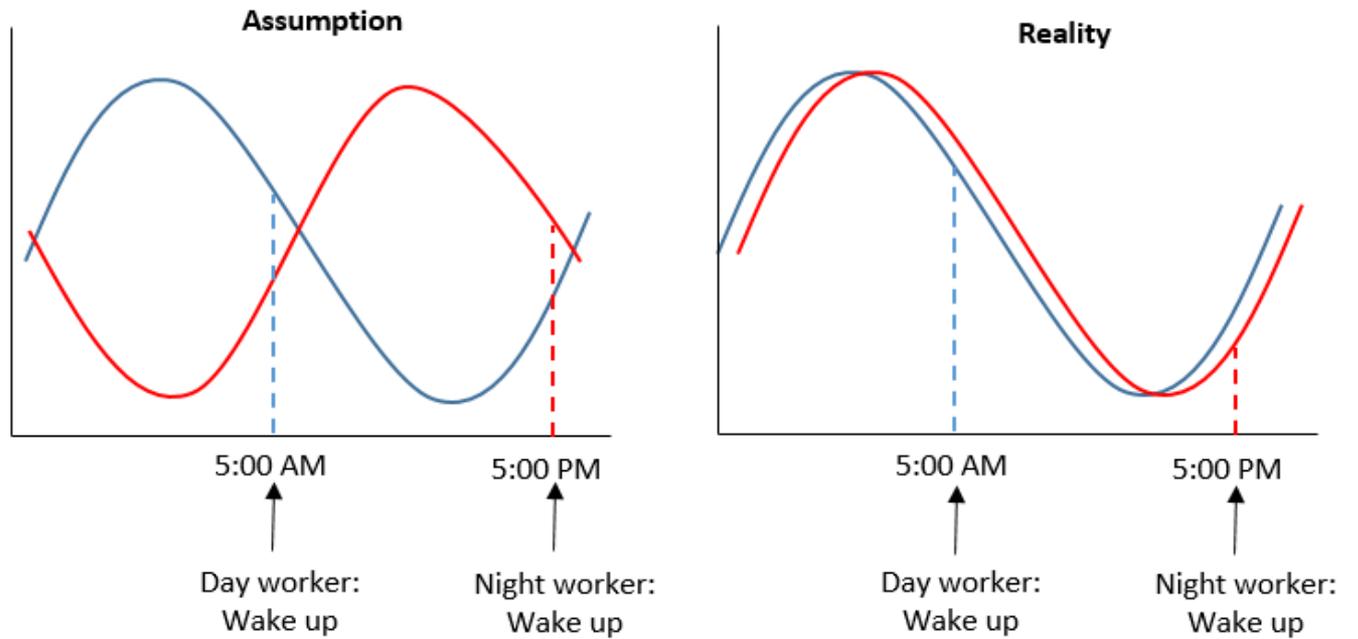


- Several laboratory studies suggest increased light leads to decreased melatonin
- Epidemiologic (observational) studies: few, some concordance
 - Limitations: confounding by circadian rhythm – i.e., measuring at the wrong chronological time

EVIDENCE

Shift work and melatonin

— Day worker
— Shift worker



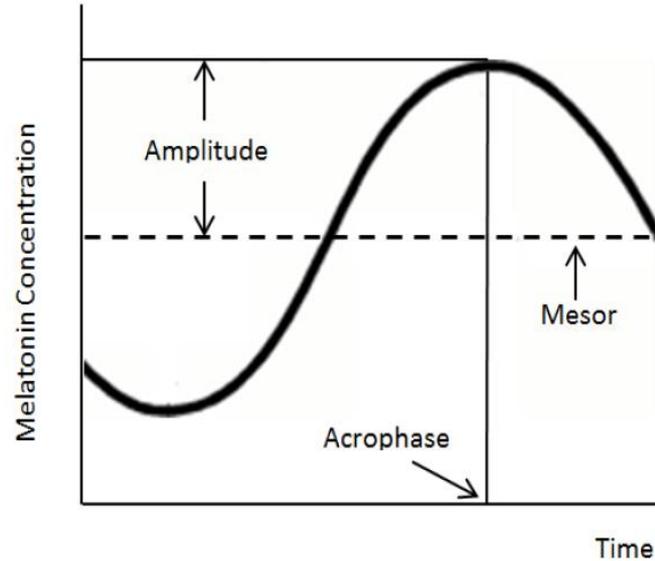
EVIDENCE

Shift work and melatonin

Light at night
• Shift Work

Melatonin pattern
• mesor, amplitude,
acrophase

Cancer



EVIDENCE

Shift work and melatonin

Research Article

Cancer
Epidemiology,
Biomarkers
& Prevention

Shift Work, Chronotype, and Melatonin Patterns among Female Hospital Employees on Day and Night Shifts

Michael Leung^{1,2}, Joan Tranmer^{1,3}, Eleanor Hung¹, Jill Korsiak^{1,2}, Andrew G. Day^{1,4}, and Kristan J. Aronson^{1,2}

Objective

1. Evaluate the relationship between shift work and melatonin pattern
2. Evaluate effect modification by chronotype

Participants

- n=328
- September 2011- February 2014
- 168 shift workers, 160 day workers
- 48-hour urine samples



EVIDENCE

Shift work and melatonin

Chronotype

- Chronobiologic propensity for sleep and activity
- Hypothesized effect modifier, may help explain why among shift workers some develop cancers and others not
- Adaptability and tolerance to working at night



EVIDENCE

Shift work and melatonin

Chronotype

- Munich Chronotype Questionnaire to characterize people based on their mid sleep time
- Sleep 12-6, mid sleep time is 3

| <u>Chronotype</u> | |
|-------------------|---------------------|
| 0-<1 | Extreme early type |
| 1-<2 | Moderate early type |
| 2-<3 | Slight early type |
| 3-<4 | normal |
| 4-<5 | Slight late type |
| 5- <6 | Moderate late type |
| 6-≥7 | Extreme late type |

EVIDENCE

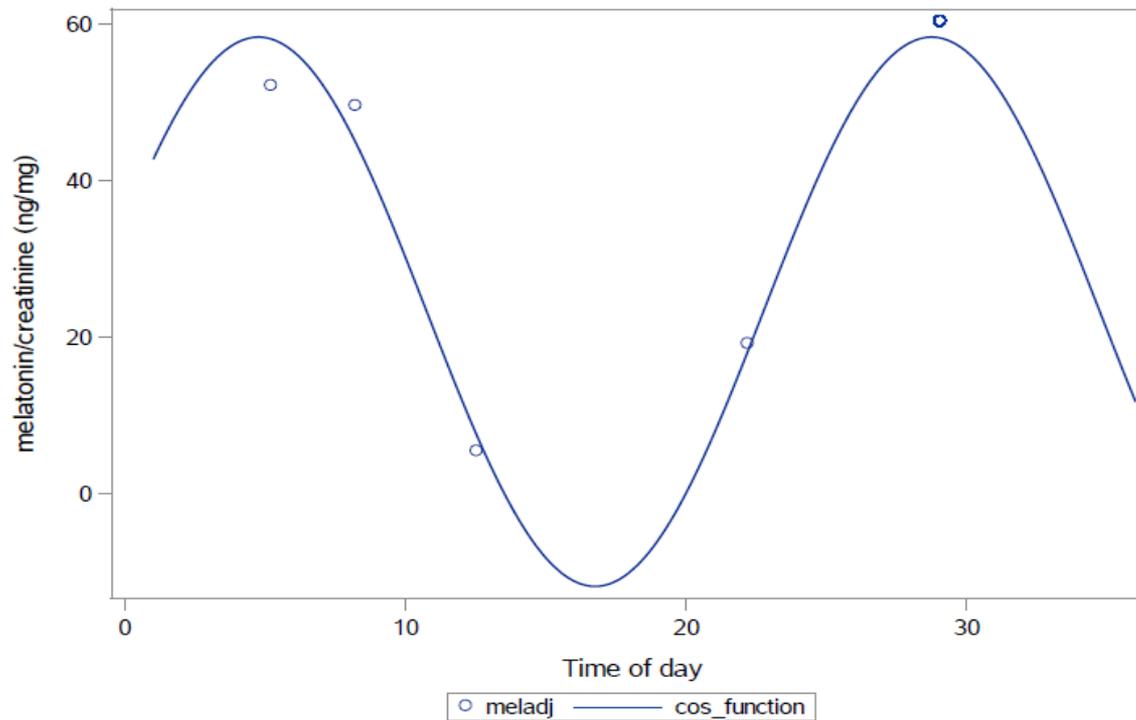
Shift work and melatonin

| | Sleeping at night at home | Working on night shift |
|---|----------------------------------|-------------------------------|
| | Mean | Mean |
| Log-transformed mean light intensity between 12AM and 5AM in log lumens/m ² (SD) | -2.14 (0.06) “Dark” | -0.06 (0.06) “Dim” |

EVIDENCE

Shift work and melatonin

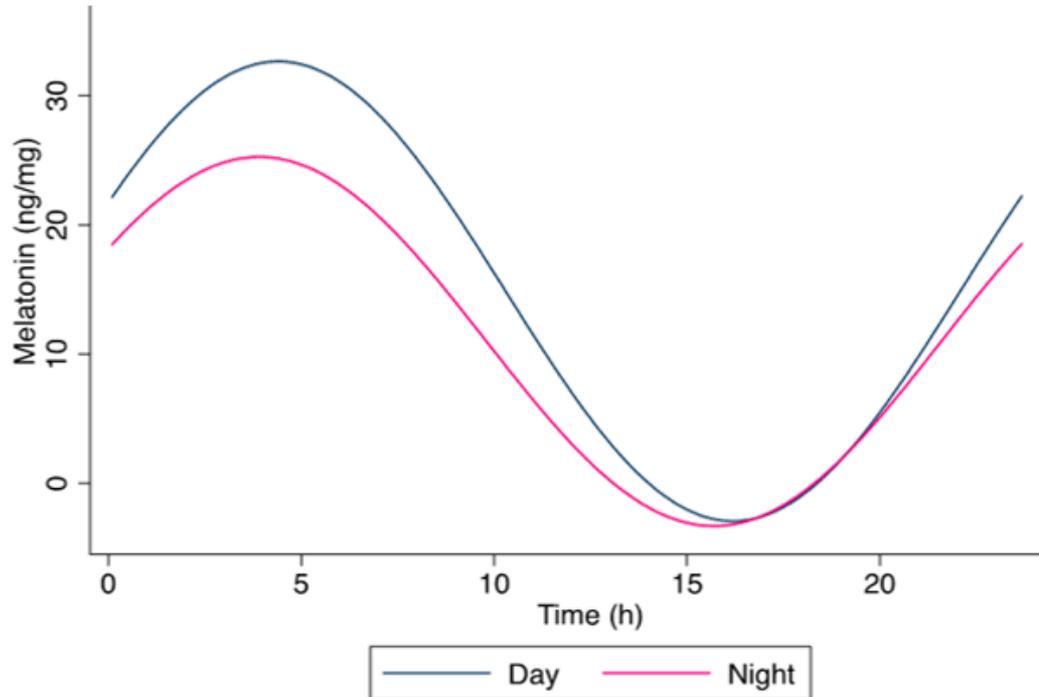
Cosinor analysis



EVIDENCE

Shift work and melatonin

Shift work



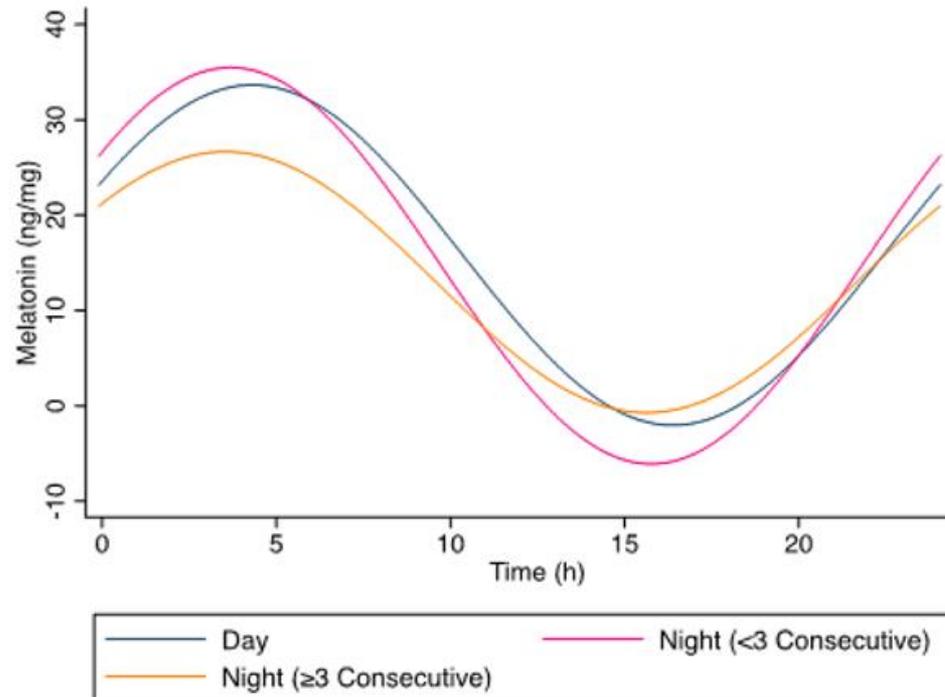
Shift workers on night rotations had a lower mean ($p < 0.05$) and earlier peak ($p < 0.05$) melatonin compared to day only workers.

Leung M, Tranmer J, Hung E, Korsiak J, Day A, Aronson KJ. Shift work, chronotype and melatonin patterns among female hospital employees on day and night shifts. Cancer Epidemiology, Biomarkers and Prevention 2016; doi:10.1158/1055-9965.EPI-15-1178.

EVIDENCE

Shift work and melatonin

Number of consecutive nights



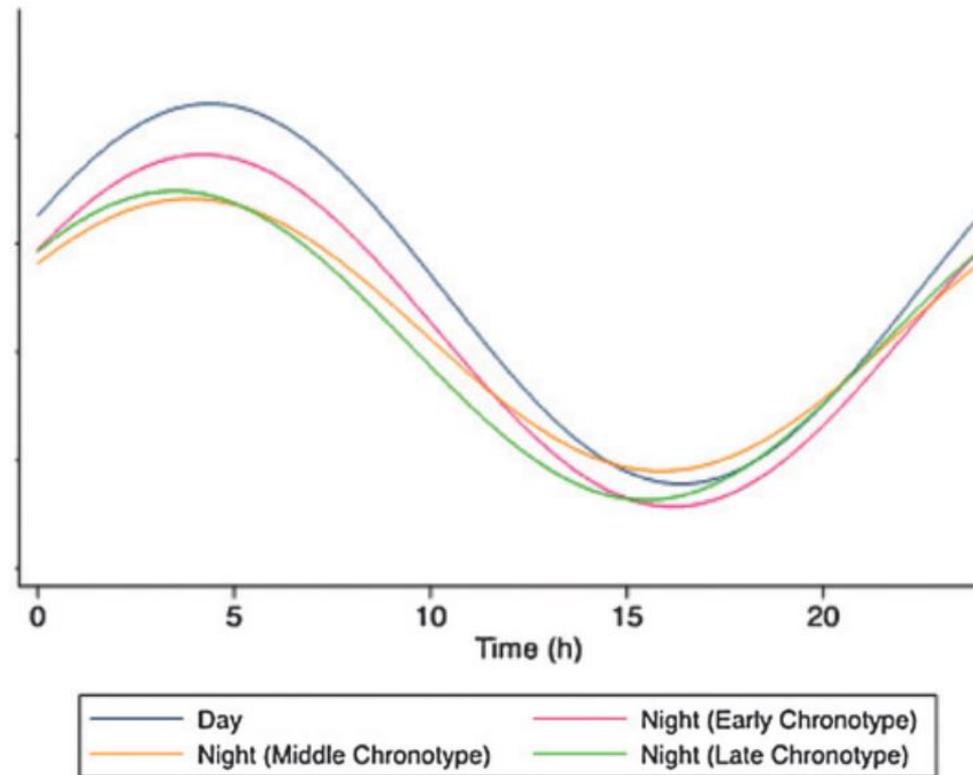
Among those working at night, ≥ 3 consecutive nights: lowest mean melatonin.

Leung M, Tranmer J, Hung E, Korsiak J, Day A, Aronson KJ. Shift work, chronotype and melatonin patterns among female hospital employees on day and night shifts. Cancer Epidemiology, Biomarkers and Prevention 2016; doi:10.1158/1055-9965.EPI-15-1178.

EVIDENCE

Shift work and melatonin

Chronotype



Late chronotype are more susceptible to light-at-night effects

Leung M, Tranmer J, Hung E, Korsiak J, Day A, Aronson KJ. Shift work, chronotype and melatonin patterns among female hospital employees on day and night shifts. Cancer Epidemiology, Biomarkers and Prevention 2016; doi:10.1158/1055-9965.EPI-15-1178.

EVIDENCE

Shift work and melatonin

Chronotype

| | | Mesor (95% CI) | |
|----------------------------|----------|--------------------------------|-------------------------------------|
| | <i>N</i> | Crude geometric mean (ng/mg) | Adjusted mean % change ^a |
| Day only, shift work night | | | |
| Day (only) ^b | 147 | 15.4 (14.1, 16.7) | Ref |
| Night (rotation) | 114 | 13.6 (11.3, 15.9) ^c | -25.0 (-37.7, -9.8) ^d |
| Chronotype (MSF) | | | |
| Early | 38 | 14.4 (9.9, 18.9) | -22.1 (-39.3, -0.6) ^d |
| Middle | 38 | 12.1 (9.7, 14.4) | -24.7 (-40.6, -4.7) ^d |
| Late | 38 | 14.4 (9.5, 19.2) | -30.6 (-46.8, -9.2) ^d |

Late chronotype are more susceptible to light-at-night effects

Leung M, Tranmer J, Hung E, Korsiak J, Day A, Aronson KJ. Shift work, chronotype and melatonin patterns among female hospital employees on day and night shifts. Cancer Epidemiology, Biomarkers and Prevention 2016; doi:10.1158/1055-9965.EPI-15-1178.

EVIDENCE

Shift work and melatonin

Findings

- Setting: dim light at night on hospital wards
- Current shift work is associated with lower mean and earlier peak time
- More consecutive nights is associated with lower mean and smaller amplitude
- Effect modification by chronotype

Strengths

- Use of different exposure metrics
- Longitudinal data – 48 hour melatonin collection
- No confounding by circadian rhythm

Limitations

- Not generalizable



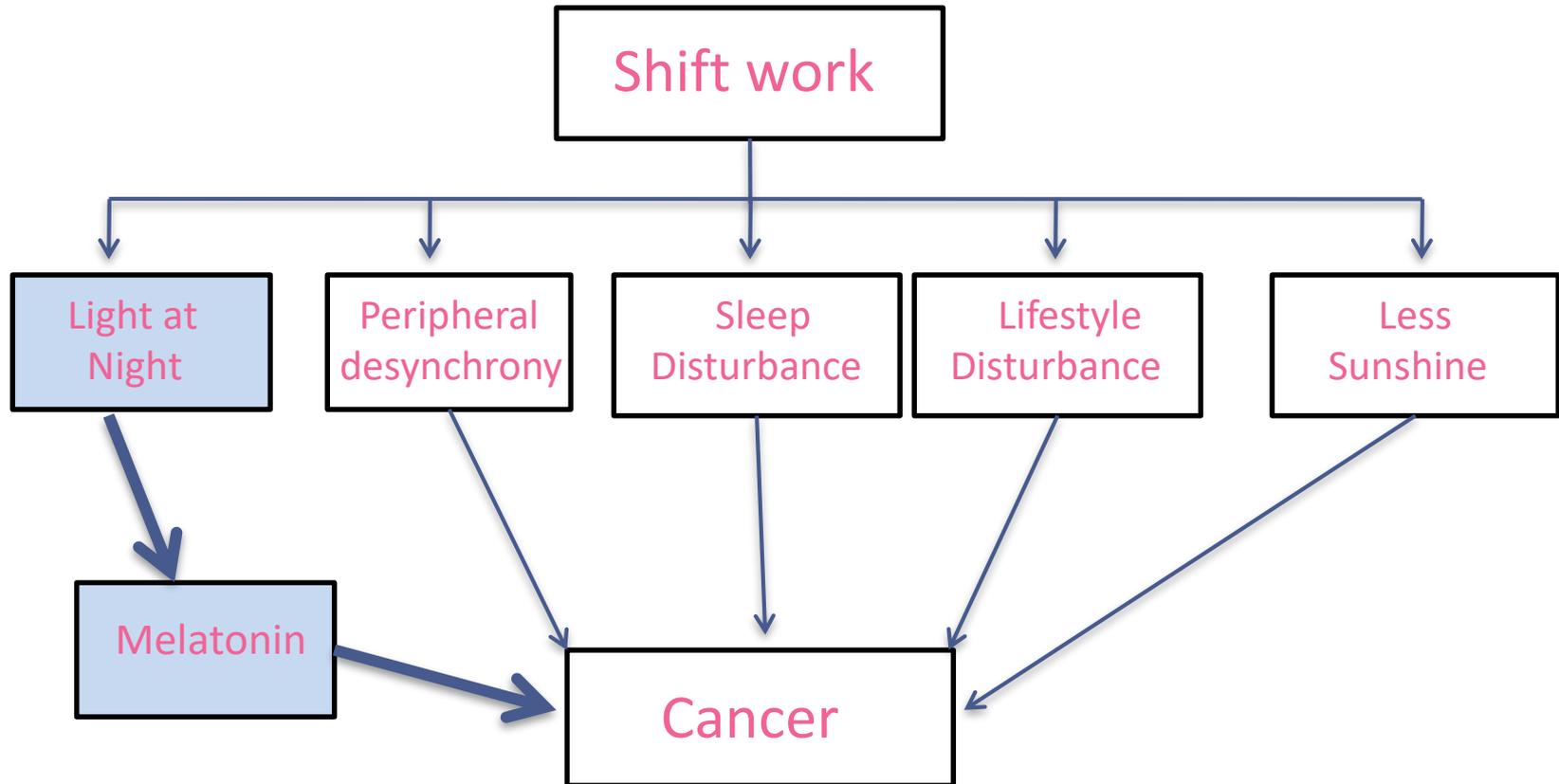
EVIDENCE

Solutions

- Limit lifetime duration of shift work to 20 years
- No more than 2 nights in a row
- Dim lighting if possible

(Some of these solutions are not possible in manufacturing and other settings...)

FUTURE DIRECTIONS



Adapted from: Fritschi L, Glass DC, Heyworth JS, Aronson KJ, Girschik J, Boyle T et al. Hypotheses for mechanisms linking shift work and cancer. *Med Hypotheses* 2011; 77:430-436.



FUTURE DIRECTIONS

- More extreme shift patterns
- Workers with brighter light levels on night shifts
- Parallel pathways: sleep quality, vitamin D etc.
- Genetic pathways
- Various ethnicities
- Direct comparisons between different shift patterns
- Ambient outdoor light seeping indoors
- Different lighting types

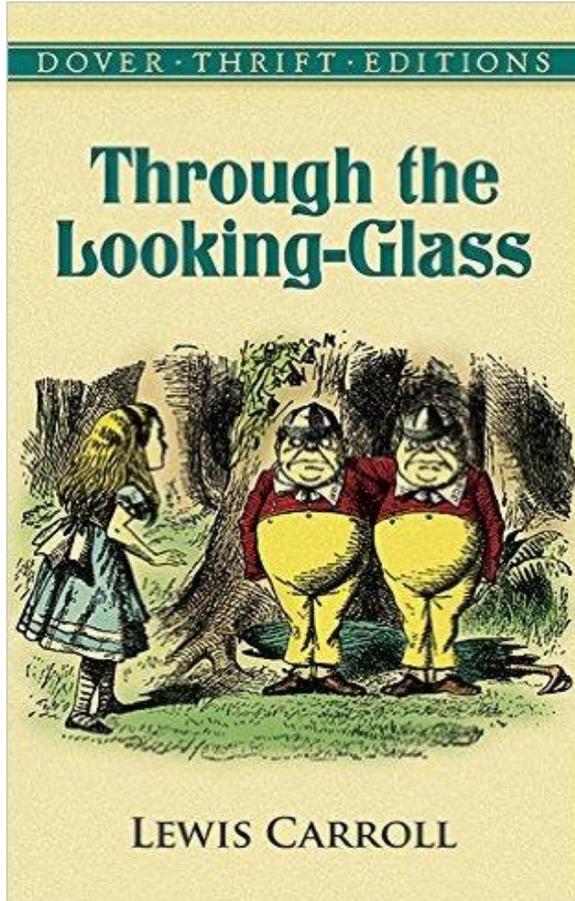


FUTURE DIRECTIONS

Ongoing Studies

- Collaboration: Prevention of ovarian cancer in Quebec (PROVAQ) study
 - Shift work, vitamin D, physical activity etc. general life style
- Shift work and sleep – cardiovascular disease, cancer
- Shift work and cortisol – cardiovascular disease
- Combining shift work study with others from Germany, France, Spain and Australia for a pooled analysis

FUTURE DIRECTIONS



Alice:

“In our country, you’d generally get to somewhere else – if you ran very fast for a long time”

Queen:

“A slow sort of country! Now, here you see, it takes all the running you can do, to keep in the same place”

Lewis Carroll, *Through the Looking Glass*

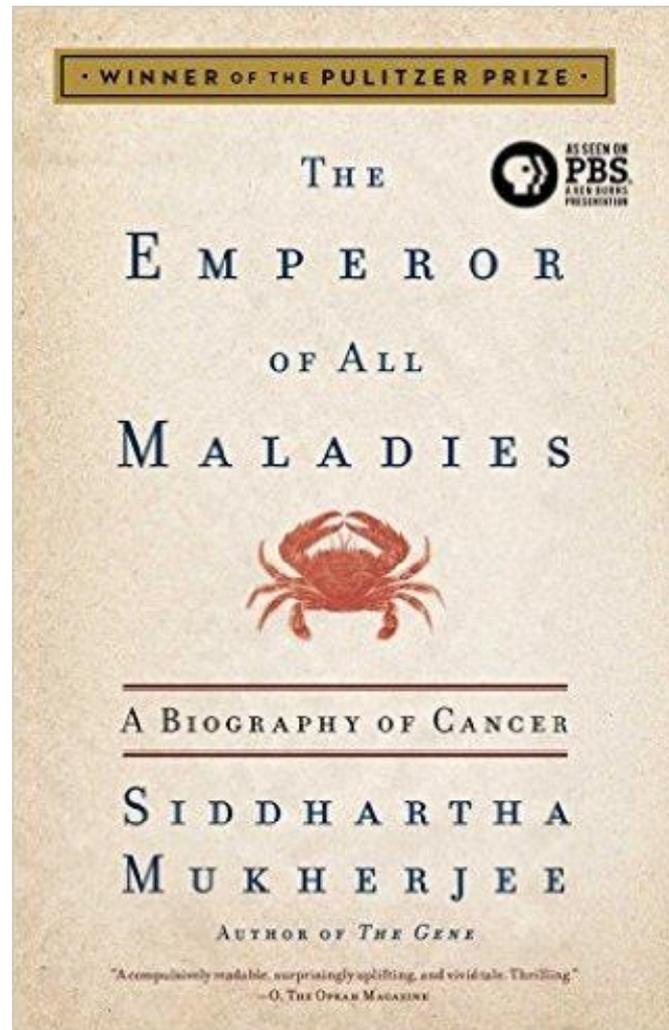
ACKNOWLEDGEMENTS

- All study participants
- Kristan Aronson – Supervisor and Investigator
- Anne Grundy – Research Associate (University of Montreal and CRCHUM)
- Students and staff: Jill Korsiak, Eleanor Hung, Renee Corbin
- Co-investigators: Joan Tranmer, John Spinelli, Harriet Richardson, Igor Burstyn, Angela Brooks-Wilson, Johanna Schuetz, Agnes Lai, Caroline Lohrisch, Sandip Sengupta, Rozmin Janoo-Gilani, Stephen Leach, Ian Janssen, Andrew Day, Christine Collier, Chris Kyba
- Funding: Canadian Institutes of Health Research; Workplace Safety and Insurance Board of Ontario; Breast Cancer Action Kingston; Ontario/Baden-Württemberg Faculty Research Exchange
- CIHR Graduate Scholarship – Doctoral Award to Anne Grundy; Master’s Award to Michael Leung



Breast
Cancer
Action
Kingston

ACKNOWLEDGEMENTS



QUESTIONS?



michael.leung@sickkids.ca