hello

Electric light, circadian disruption and cancer risk

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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; 1–4.* ©2012 AACR.

Acknowledgments

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Electric Light
a hallmark of modern life

- Our Evolutionary Past
  - bright, full-spectrum days
  - dark nights
- Modern Life
  - dim, spectrum-restricted days inside buildings
  - lighted nights ('light pollution')

Electric light:
the World increasingly glowing around the clock

The Past

3 billion years ago to
~120 years ago

~12 hours sunlight
~12 hours dark
season and latitude permitting

The Present

~120 years ago to now

Electricity

shift work (evening, night, rotating)

late-night reading or TV

dimly-lit bedrooms during sleep

short sleep duration

bright bathroom light during night

night glow over cities (no Milky Way)

day work inside buildings (no Sun)

- dim days inside buildings
- lighted nights

leading to:

"circadian disruption"

Biology

Properties of a Circadian Rhythm

- An endogenous, self-sustained ~24-hour oscillation in biochemistry, physiology, or behavior under constant environmental conditions (e.g., constant dark or constant light)
- Entrainment by environmental cycles of light
- Molecular mechanism to maintain ~24-hour cycle at different temperatures (important for ectotherms)

Takahashi, *Annu Rev Neurosci*, 18:531, 1995

Elements of a Circadian System

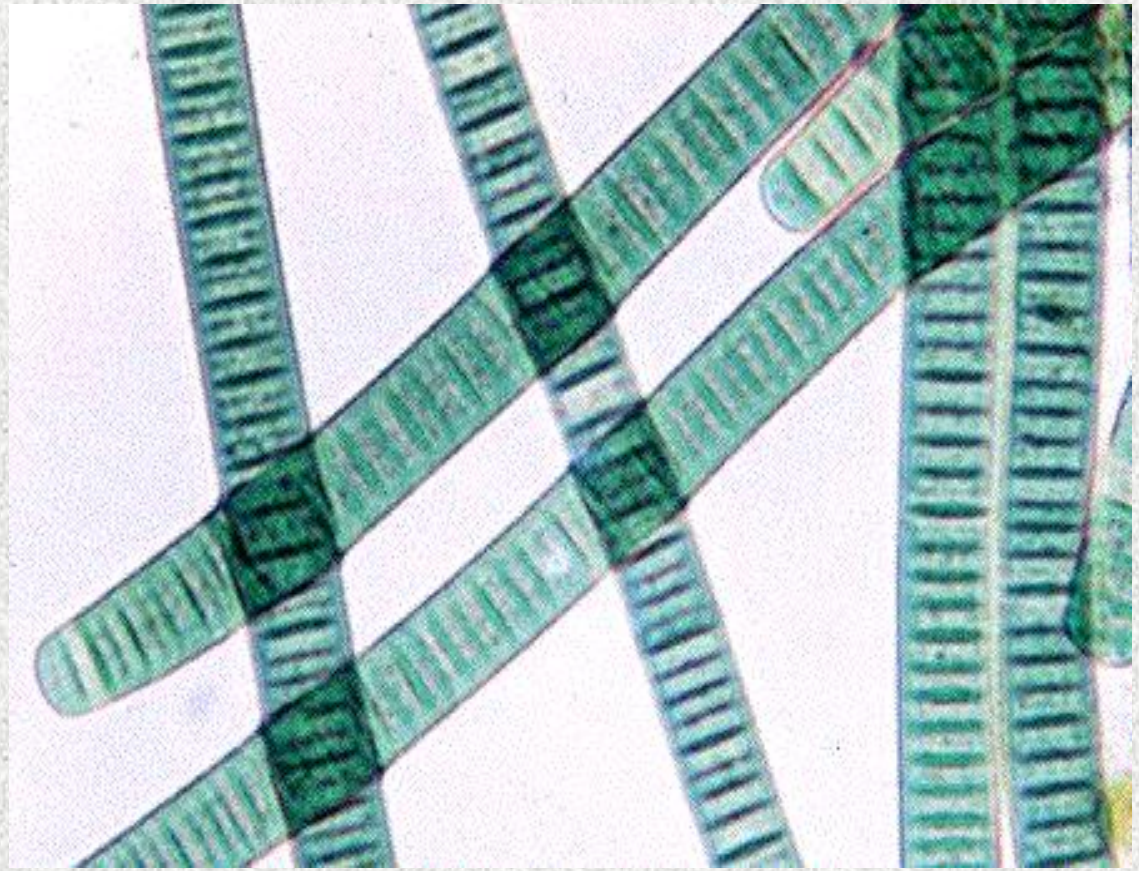
- **Environmental input**
  - phototransduction to entrain the clock
- **Molecular mechanism of the clock itself**
  - clock genes and feedback loops
- **Physiological output**
  - transduce 'molecular time' of the endogenous 24-hour clock into behavioral changes in the cell and organism

    e.g., rhythms of gene expression

    timing of hormone production and release

Takahashi, *Annu Rev Neurosci*, 18:531, 1995

Ancient aspect of biology
- Cyanobacteria -



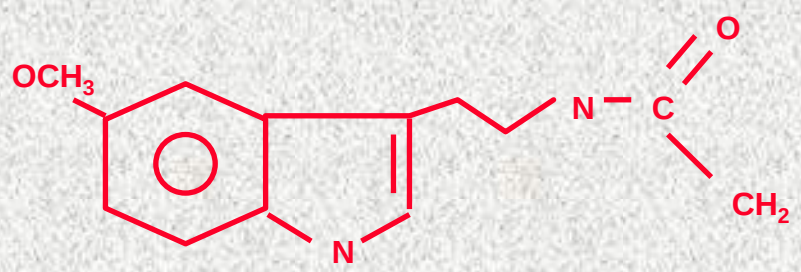
contributions: oxygen in the atmosphere, and plant-life

Mammals

- Mammals exhibit an endogenous 24-hour circadian rhythm
  - melatonin production
  - core body temperature
- Suprachiasmatic nucleus is master circadian pacemaker
- Light can reset the circadian rhythm

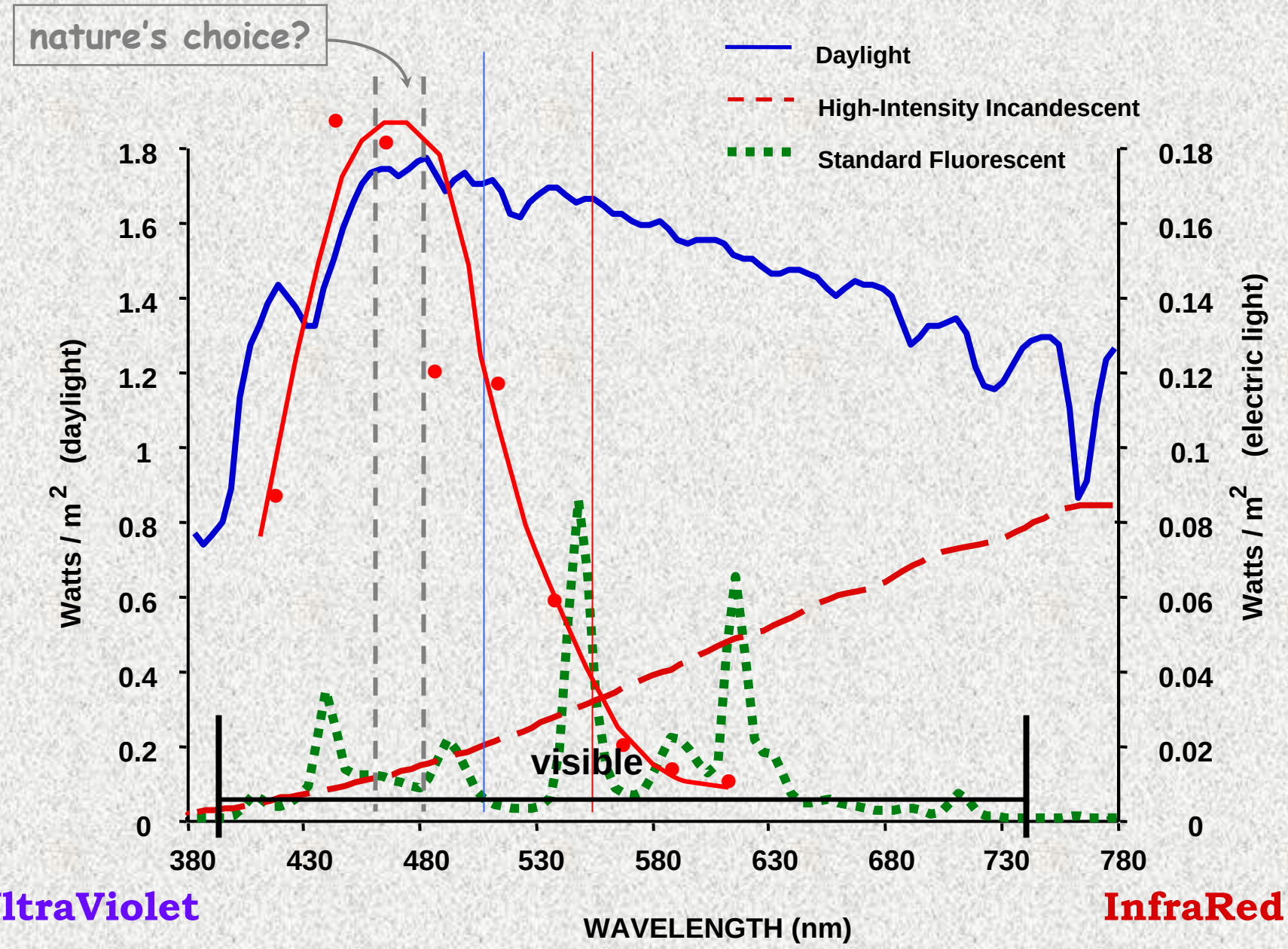
Melatonin

- monoamine hormone
  - pineal gland
  - strong daily rhythm
    - low during day
    - high at night



- robust marker of circadian rhythmicity
- oncostatic to breast cancer cells
- protective against cancer in general?

Spectra of Natural and Artificial Light

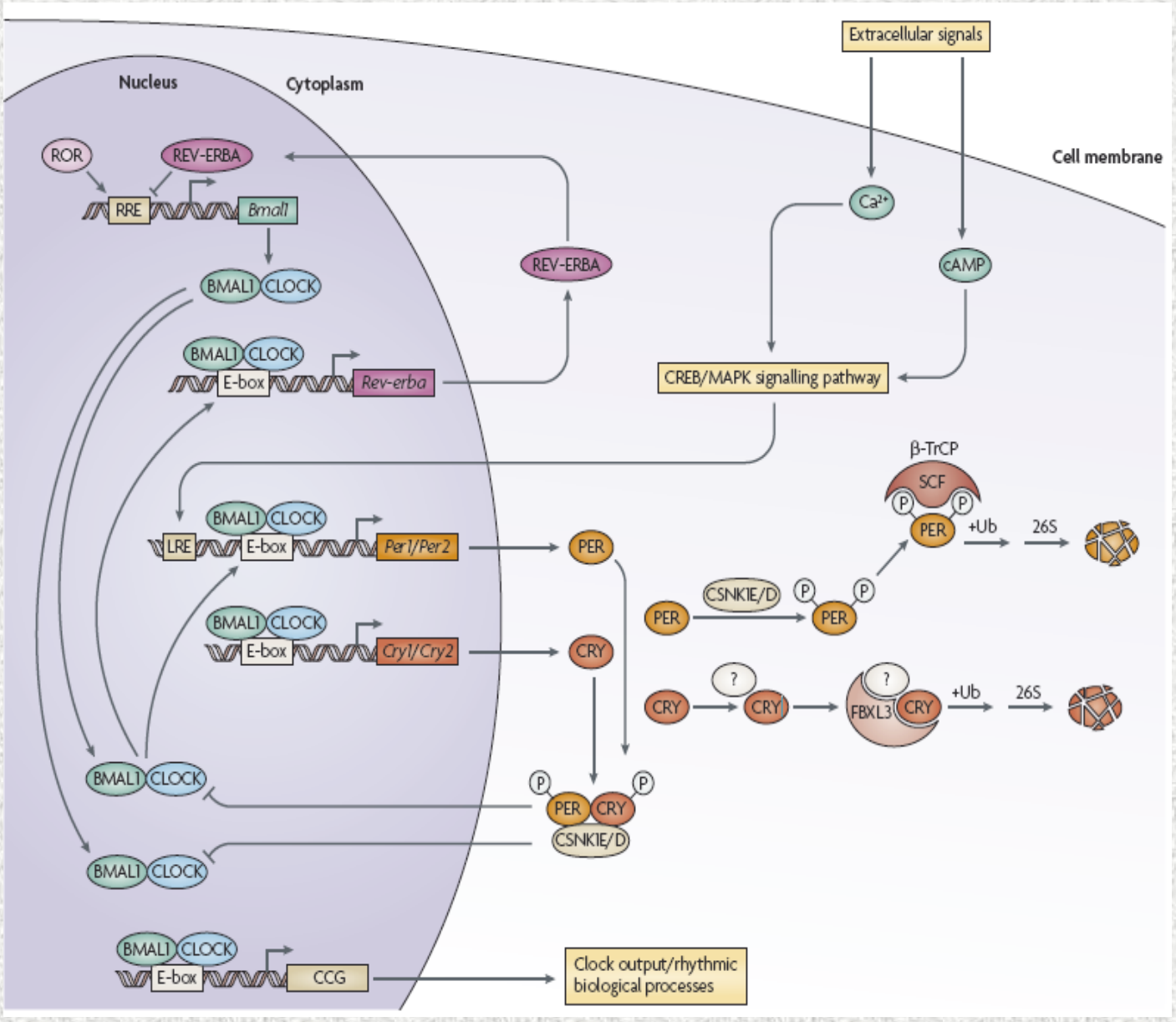


Circadian Genes and Cancer

"When you're thinking about something that you don't understand, you have a terrible, uncomfortable feeling called confusion."

– Richard Feynman, 1963

[Nobel prize in Physics, 1965]



map of the London Tube? tough for an out-of-towner

The Circadian Mechanism: circadian-controlled genes

- 5-10% of all mammalian genes are under circadian control
- among these are genes for the key regulators of cell-cycle progression and apoptosis (e.g., cyclins and caspases)
- cell cycle regulation crucial to normal and malignant cell growth (e.g., cyclin D1)
- DNA damage repair (Aziz Sancar, UNC)
- metabolism (Paolo Sassone-Corsi, UCI)

Circadian Disruption: e.g., ill-timed electric light

- compromised DNA damage response?
- altered metabolism; increased obesity and inflammatory response?
- dis-regulated cell cycles and thereby increased mutation potential?
- suppressed 'oncostatic' melatonin?

Circadian genes

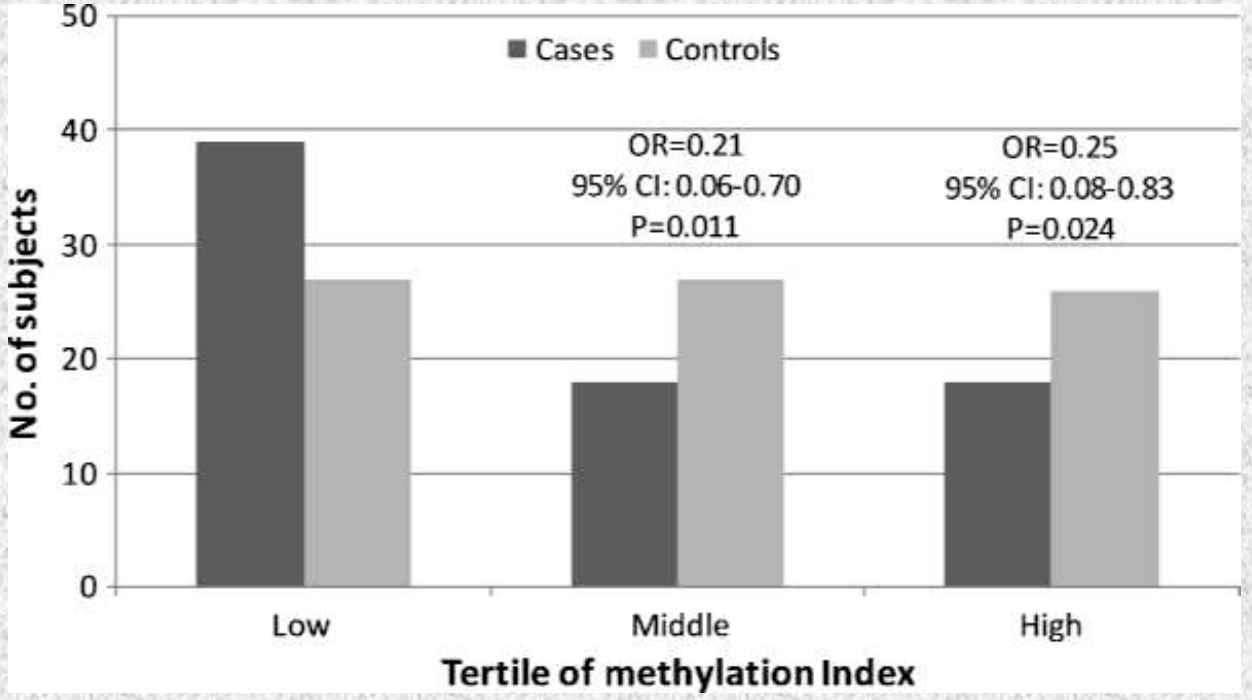
epigenetic modification by environmental factors:

electric light

CLOCK in Breast Tumorigenesis

(Hoffman A, et al., Cancer Research, 2010;70:1459-68)

- case-control study in CT (441 cases)
- 80 cases before adjuvant therapy
- hypomethylation strongly associated with risk

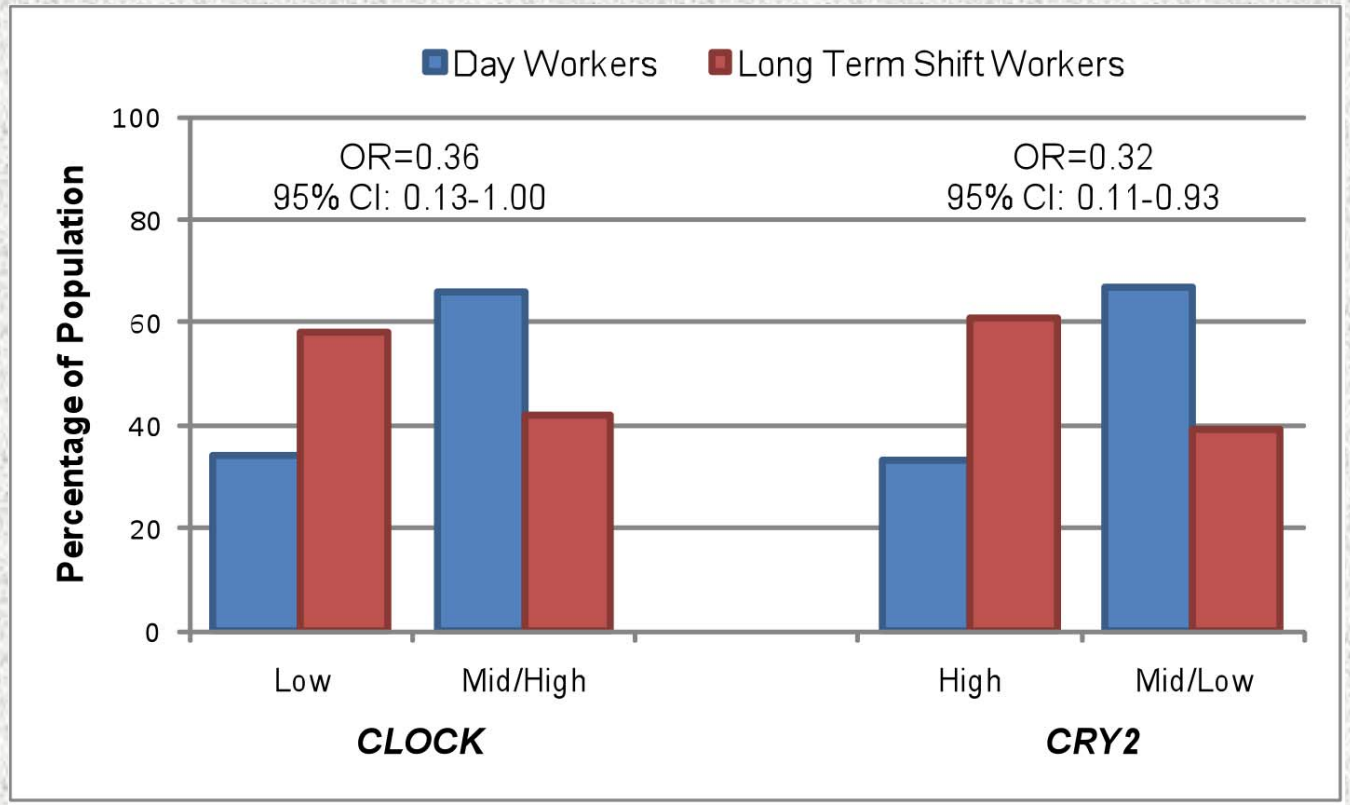


methylation in night workers

(Zhu Y, et al., Chronobiology International, 2011;28:852-61)

- Danish members of the 'Diet, Cancer, and Health' cohort, enrolled 1993 to 1997
- 19 long term night workers, 98 day workers, all disease free at blood draw

CLOCK and CRY2



Cancer in Children:

specific predictions amenable to epidemiologic testing

predictions

Maternal circadian disruption by light at night during pregnancy (e.g., from shift work), increases subsequent risk of cancer in her child.

predictions

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.

predictions

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.

minimizing

Circadian Disruption

from use of electric lighting

Pregnant mother: get dark at night and some sun in the morning; avoid night work

Hospital: maintain as nearly as possible a diurnal rhythm of lighting in the wards

At home: avoid night lights; for attending to a child at night, use dim red light sources

Thank You