Scientific Symposium

The Health Effects of Shift Work

Toronto, April 12, 2010

Shift Work and Breast Cancer: need for mechanisms

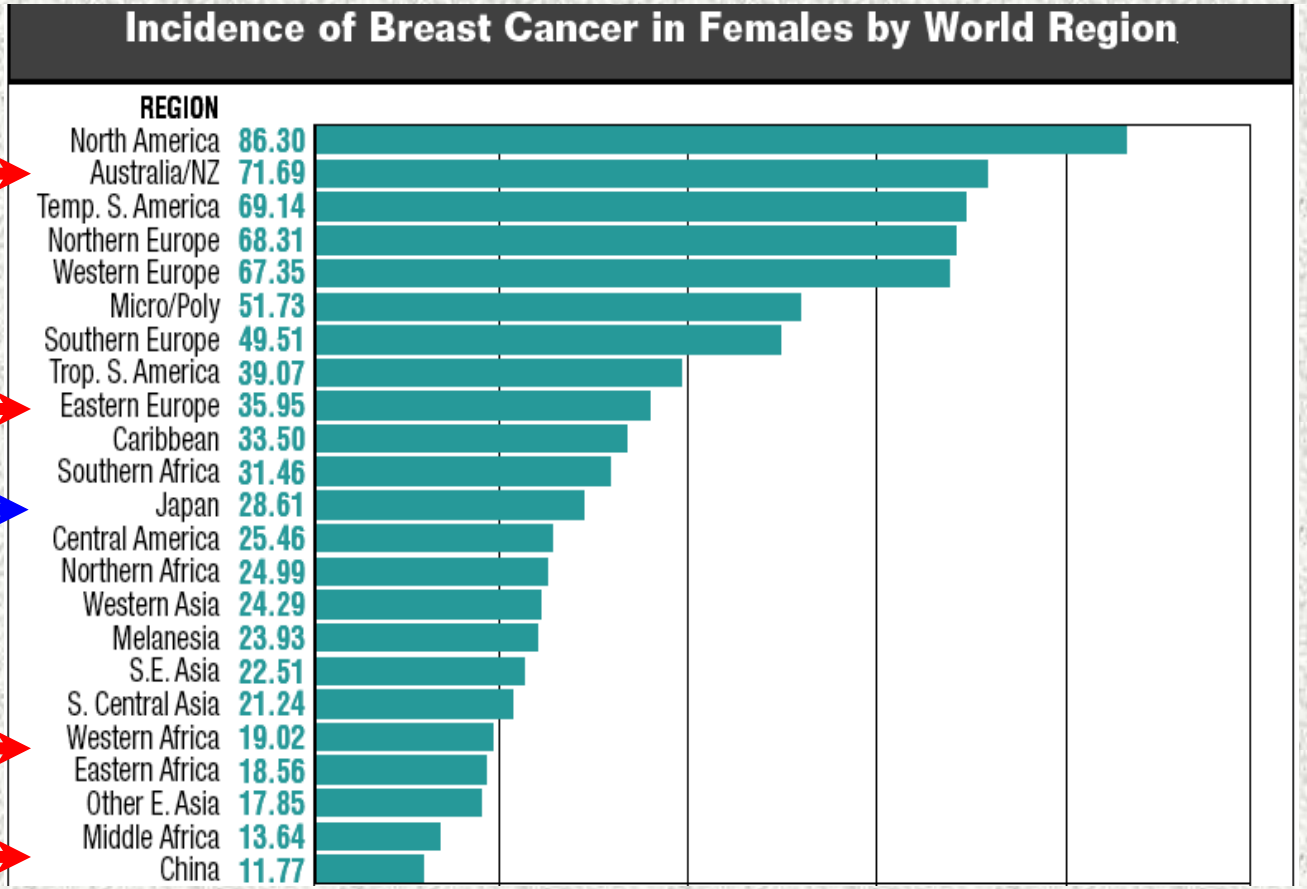
R Stevens
University of Connecticut

Institute for Work & Health | Research Excellence Advancing Employee Health

Occupational Cancer Research Centre

Breast Cancer Incidence/100,000 women/year

age-adjusted



U.S. & W. Europe

Eastern Europe

Japan

Africa

Japan, 1950s

China

From the IARC, Lyon: Parkin, DM, et al. *CA Cancer J Clin*, 49:33-64, 199

25 years ago we knew more about the causes of breast cancer than we do today

at that time, most of us believed the high-fat ‘Western’ diet explained the high risk

but decades of intense research has so far failed to find an obvious connection

so where are we now?

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')

Light at Night - U.S. - the Present

Light at Night - U.S. - the Past

http://www.earthview.mars/safe/

Human Studies

Breast Cancer and 'Light-at-Night'

- Theory: light-at-night alters hormones, increasing risk, and thereby explains some of the high risk in industrialized societies
- Predictions (i.e., 'hypotheses'):
  - shift workers at higher risk
  - blind women at lower risk
  - lighted bedrooms at night increase risk
  - long sleep lowers risk

Battelle
Pacific Northwest Laboratories
P.O. Box 999
Richland, Washington U.S.A. 99352
Telephone (509) 376-4761
Telex 15-2874

November 13, 1987

Walter Willett, M.D.
Channing Laboratory
180 Longwood Avenue
Boston, MA 02115

Dear Walter:

We met once about 4 years ago when I was applying for a job in the department of Epidemiology. I admire your work, and appreciate your efforts in understanding the tools of epidemiology (e.g. food frequency questionnaires) as well as making advances in understanding disease causation.

My purpose in writing is to suggest a look at shift work and breast cancer in your nurse cohort. I wrote a little thing about electric power and breast cancer (Am J Epi, 1987;125:556), and a letter with Bob Hiatt about your alcohol study that is supposed to appear in New Engl J Med soon. The underlying notion to both is that disruption of pineal function, and consequent reduction in melatonin production might increase the turnover of the normal breast epithelial stem cells at risk, and result in the reduction of an oncostatic agent in serum and tissue (i.e. melatonin). Disruption of circadian rhythms by exposure to shift work might also have this effect. Your cohort of nurses undoubtedly offers a powerful data set for investigating this possibility. Such analyses would be complicated, I suspect, by association of shift work with age, parity, marital status, and the like.

Anyway, I hope to meet you again in the future.

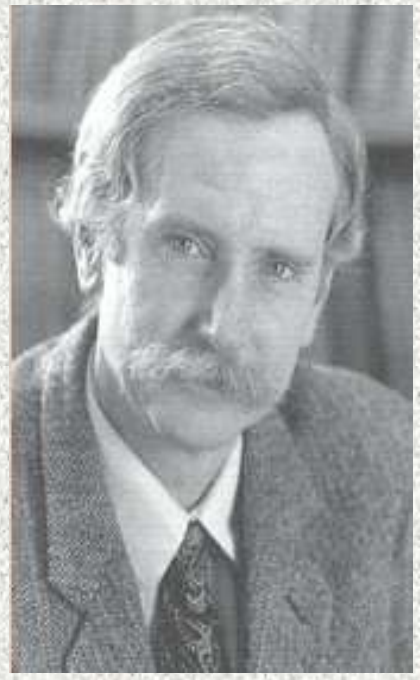
Sincerely,

Richard Stevens

Richard Stevens

Nurses' Health Study

letter to Walt Willett suggesting shift work question



IARC: shift workers at higher risk

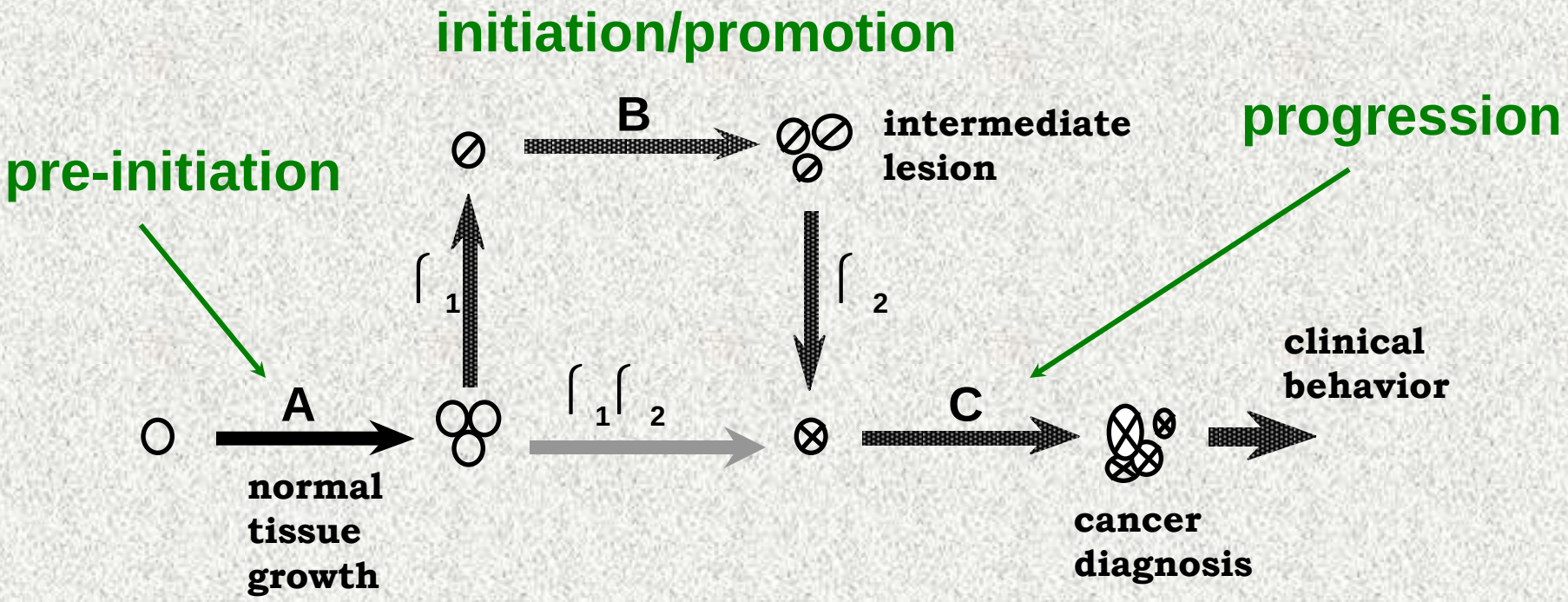
Straif K, et al. Lancet Oncology, December 2007 page 1065

“On the basis of ‘limited evidence in humans for the carcinogenicity of shift-work that involves nightwork’, and ‘sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)’, the Working Group concluded that ‘shift-work that involves circadian disruption is probably carcinogenic to humans’ (group 2A).”

Circadian Disruption and Cancer: Genes & Mechanisms

understanding will be crucial for intervention and mitigation

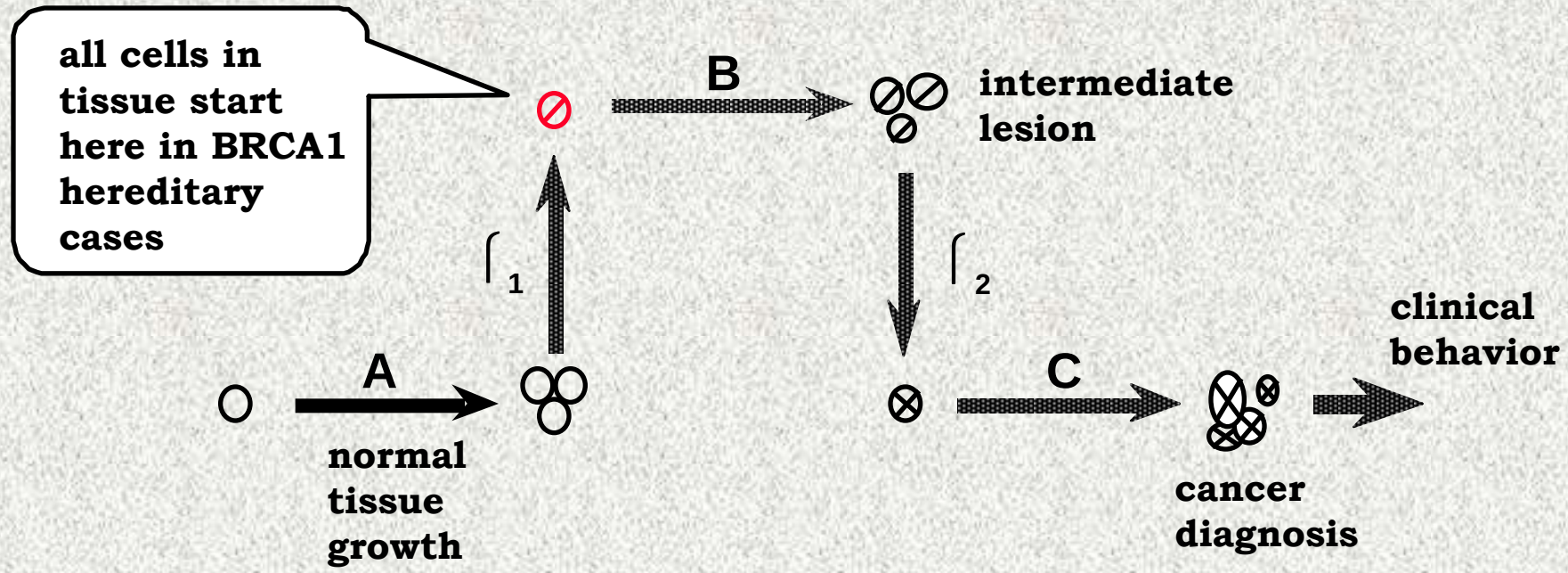
points of impact of CD



pre-initiation	e.g., early effects on mammary tissue development
initiation/promotion	e.g., CD affects on cyclin D1 expression
progression	e.g., oncostatic effects of melatonin

Moolgavkar, Day, Stevens, *JNCI*, 65:559-569, 1980

Circadian Disruption Example



○ normal cell

⊘ intermediate cell

⊗ cancer cell

$\int_1$ = oxidative stress

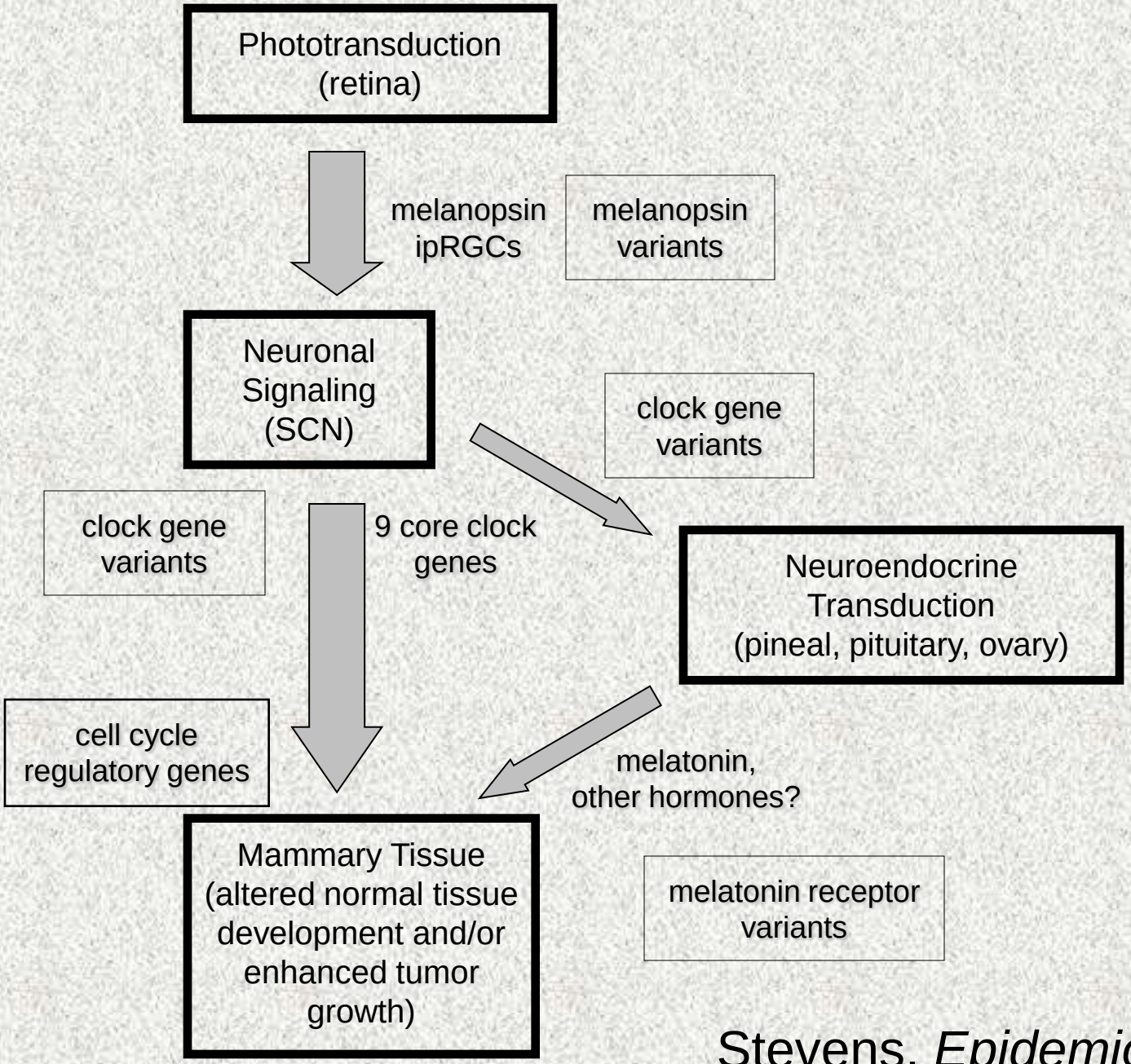
$\int_2$ = DNA repair

A = altered reproductive endocrinology

B = altered cell cycle regulation (CLOCK)

C = depleted melatonin

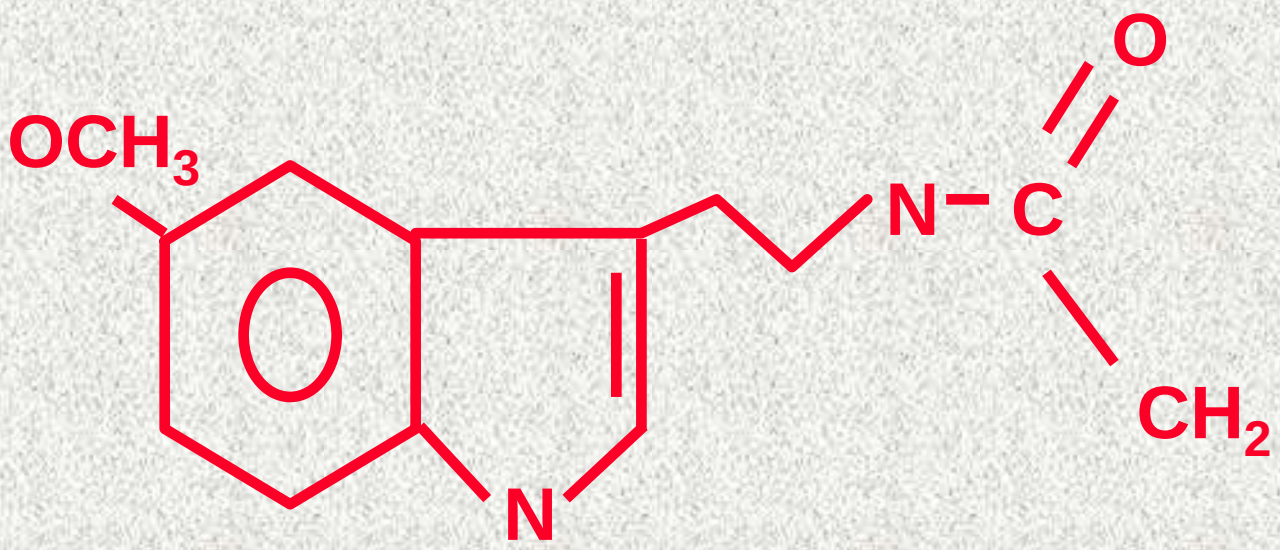
Moolgavkar, Day, Stevens, *JNCI*, 65:559-569, 1980



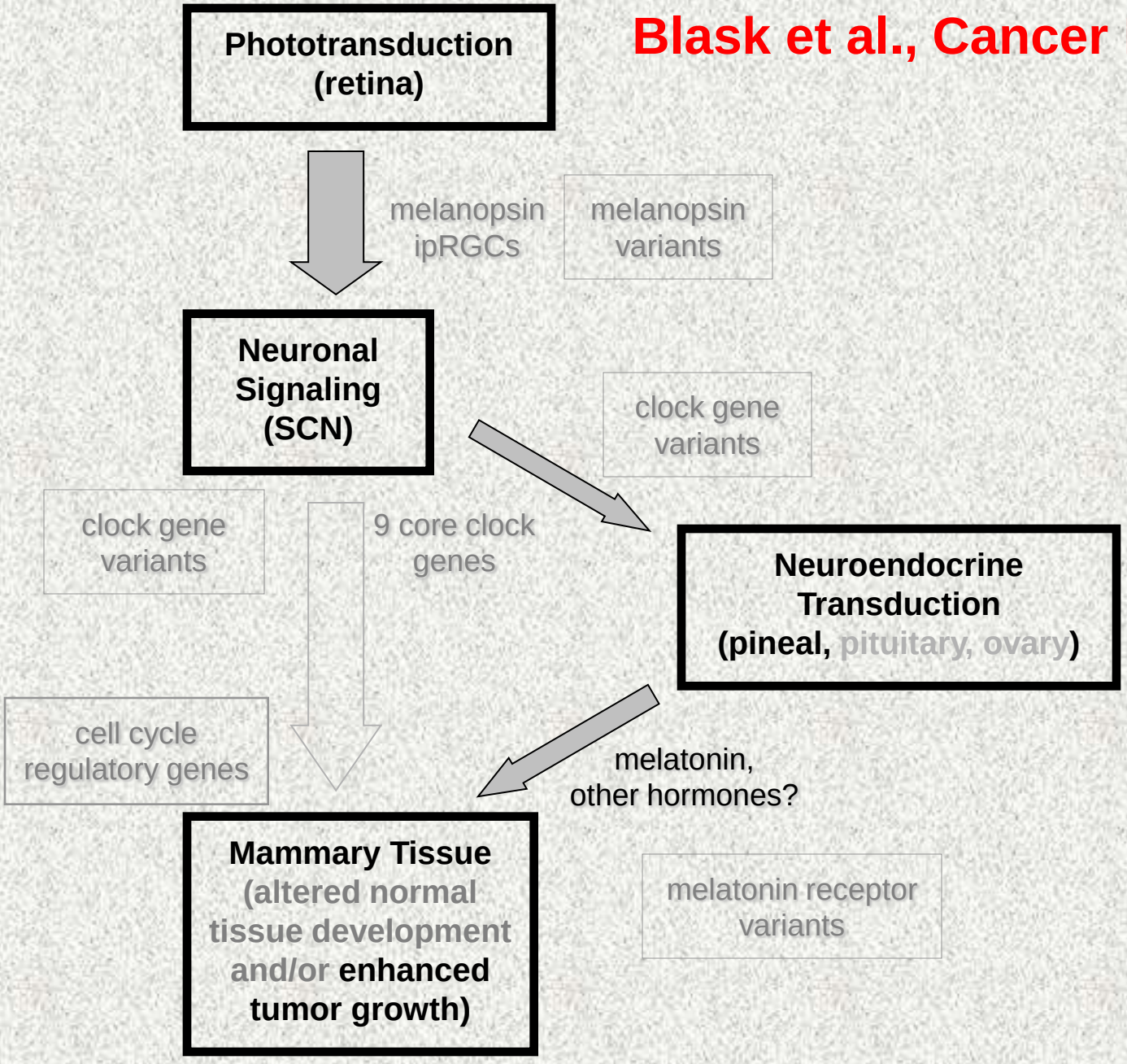
Stevens, *Epidemiology*, 2005

Mechanism:

Progression


OCH3
O
N
N
C
O
CH2

Blask et al., Cancer Res, 2005



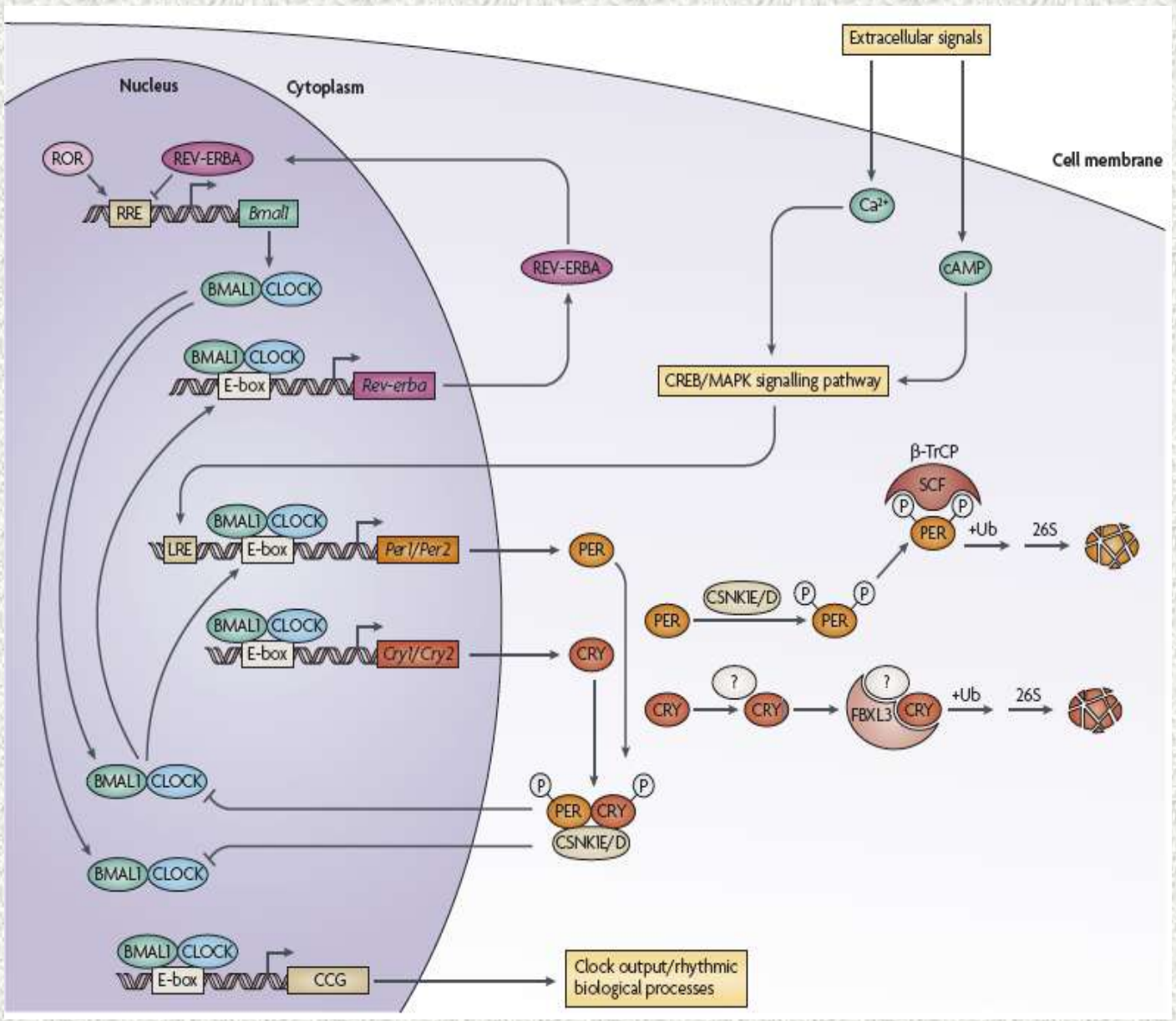
The Circadian Clock: clock-controlled genes

- 5-10% of all mammalian genes are clock controlled
- among these are genes for the key regulators of cell-cycle progression and apoptosis (e.g., cyclins and caspases)

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



map of NYC subway system; tough for an out-of-towner

Circadian Loop

Positive (transcriptional activators?): CLOCK (or NPAS2) and BMAL1 are basic helix-loop-helix PAS-domain containing transcription factors that activate transcription of the Per and Cry genes.

Negative (transcriptional repressors?): The resulting PER and CRY proteins heterodimerize, translocate to the nucleus and interact with the CLOCK–BMAL1 complex to inhibit their own transcription. After a period of time, the PER–CRY repressor complex is degraded and CLOCK–BMAL1 can then activate a new cycle of transcription.

The entire cycle takes approximately 24 hours to complete

Takahashi et al., *Nat Rev: Genet*, October, 2008

Epidemiology of Cancer and Circadian Gene Polymorphisms

(Yong Zhu and his student Aaron Hoffman, Yale)

gene	cancer	finding	role in feedback loop; comment
PER3 length (Zhu 2005)	breast	structural variants 5-peat/4-peat OR = 1.7	negative; predicted due to lark/owl
NPAS2 Ala394Thr (Zhu 2008)	breast	heteros/wt homozygotes OR = 0.61	positive; hetero advantage? role in DNA repair (Hoffman et al., Mol Cancer Res, 2008)
CRY2, 140147:G>C NPAS2, Per1, Per3 (Chu 2008)	prostate	for CRY2, OR = 1.7 NS for others including Per3 structural	CRY2, negative;

Yong Zhu and his student Aaron Hoffman, Yale

gene	cancer	finding	comment
CRY2 3 SNPs (Hoffman 2009)	NHL	ORs of 2.3, 2.4, and 3.0	MCF-7 functional analysis affects on immune function
NPAS2 Ala394Thr (Zhu 2006)	NHL	heteros/wt homozygotes OR = 0.69	differs from BrCa result in that homozygote variant also at reduced risk
CLOCK several variants (Hoffman et al., 2010a)	breast	ORs range from 0.78 to2.25	stronger in ER-/PR- cancers
CRY2 several variants (Hoffman et al., 2010b)	breast	ORs range from 0.27 to 2.49	stronger for ER-/PR- cancers

Are these gene findings replicable, and if so, what do they mean?

as with the larger area of GWAS looking for common but low penetrance SNPs for cancer causation, there is as yet no clear message for screening, treatment, or prevention

e.g., Easton (Nature 2007) GWASed 227,876 SNPs and found 5 to be highly significantly associated with breast cancer in a two stage case control study design: 4,398 cases in first stage and 21,860 in the second

odds ratios ranged from 1.08 to 1.23

Mechanism:

circadian gene function

Cyclin D1

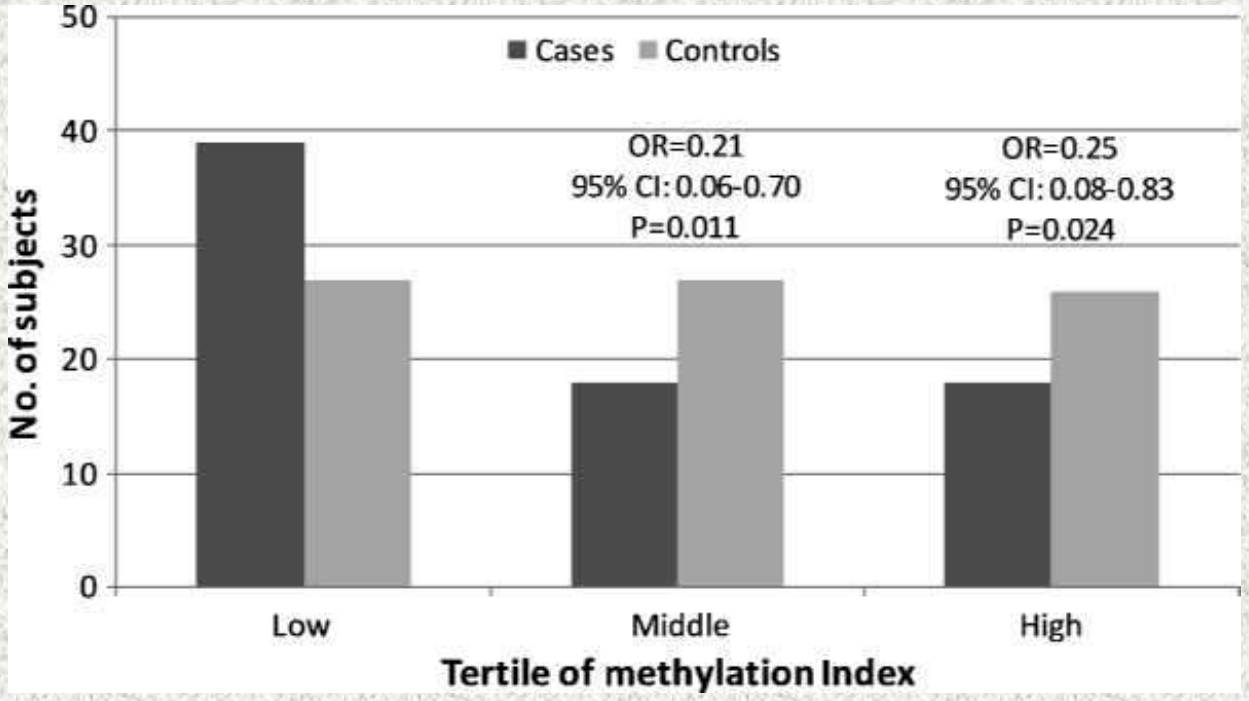
(one tenuous thread; Stevens & Rea, 2001)

- Cyclin D1 over expressed in breast cancer (Arnold and Papanikolaou, 2005)
- maybe the *CLOCK* gene product affects cyclin D1 function and thereby risk (Stevens and Rea, 2001)
- *CLOCK* is also an enzyme that has histone acetyltransferase (HAT) activity and might affect cyclin D1 (Sahar and Sassone-Corsi, 2007)
- disruption and over-expression of *CLOCK* might increase breast cancer risk
- many other possibilities (Matsuo et al., Science, 2003; Haus & Smolensky, Cancer Cause Control, 2006)

"CLOCK in Breast Tumorigenesis"

(Hoffman 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



Thank You