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## **Epidemiology and shift work**

### **- Chronobiological fallacies**

## The example of cancer

- 1 Starting point: IARC2007
- 2 Post-IARC epidemiology
- 3 Did epidemiology do it “chronobiologically” right?
- 4 „Next generation“ studies
- 5 Challenges

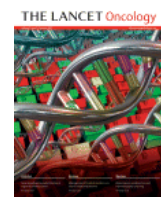
22 Experts



- after diligent review and discussion of published scientific results:

**Shiftwork**  
that involves **circadian disruption**  
is **probably carcinogenic to humans**  
**[Group 2A].**

„... sufficient evidence in experimental animals  
for the carcinogenicity of light  
during the daily dark period (**biological night**) ....“



„.... **limited evidence in humans**  
**for the carcinogenicity of**  
**shift-work that involves nightwork“**

-Straif et al.  
Lancet Oncol 2007

Epidemiological research between 2008 & 2016 into shift work and cancer

Study results compatible with significantly increased cancer risks

Yes  
No

breast	breast	ovary	pros- tate	lung	colon	rectum	bladder	panc- reas	NHL	cancer mort.	mort.
Pesch 2010	Pronk 2010		Pukkala 2009						Lahti 2008		Ober- linner 2009
Lie 2011	Grundy 2013	Poole 2011	Kubo 2011								
Hansen 2012	Fritschi 2013										
Meneg. 2012	Ramin 2013										
Knutsso. 2012	Koppes 2014										
Hansen 2012	Wang 2015		Parent 2012	Parent 2012	Parent 2012	Parent 2012	Parent 2012	Parent 2012	Parent 2012		Nätti 2012
Rabstein 2013	Akerstedt 2015	Bhatti 2013	Gapstur 2014	Schernh. 2013				Lin 2013			
Rabstein 2014	Papanto. 2016	Carter 2014	Pukkala 2014							Yong 2014	Yong 2014
Li 2015	Travis 2016		Papanto. 2015	Kwon 2015					Costas 2016	Gu 2015	Gu 2015



ARTICLE

## Night Shift Work and Breast Cancer Incidence: Three Prospective Studies and Meta-analysis of Published Studies

Ruth C. Travis, Angela Balkwill, Georgina K. Fensom, Paul N. Appleby,  
Gillian K. Reeves, Xiao-Si Wang, Andrew W. Roddam, Toral Gathani,  
Richard Peto, Jane Green, Timothy J. Key, Valerie Beral

-Travis et al.  
JNCI 2016

<b>Question 1</b>	Are incidence risks for breast cancer in women with or without night distinguishable from 1 ?	<b>No</b>
<b>Question 2</b>	Are results of meta-analyzing 10 prospective studies distinguishable from 1 ?	<b>No</b>
<b>Methods</b>	-3 new prospective studies Million Women Study & EPIC Oxford & UK Biobank -meta-analyses of 10 prospective studies	
<b>Conclusion</b>	<b>“The prospective evidence now available shows that classification of night shift work as a probable human (breast) carcinogen is no longer justified“</b>	<b>1.4 million women</b>

Can we close the book on  
shift work and cancer ?

**No**

Did post-IARC epidemiology  
focus appropriately on  
**circadian disruption**



-NEL 2013

Thought experiment

Consider scientists sitting on the edge of a hill overlooking a large Factory A:

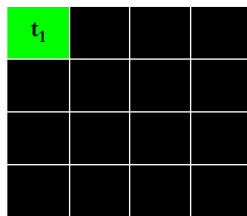
- A 2-fold risk of cancer is observed in A.



**H1** workers in A are exposed to doses of some carcinogen

The scientists could get key information from the workers

$t_1$  At certain times,  
individuals are provided with protective gear to shield them from exposures.

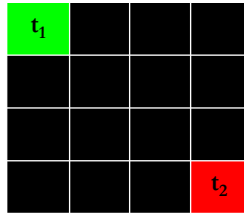




The scientists could get key information from the workers

$t_1$  At certain times,  
individuals are provided with protective gear to shield them from exposures.

$t_2$  At certain times,  
exposures are carcinogenic but otherwise not.

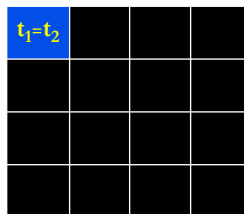


**H2** when  $t_1 \neq t_2$ , workers in  $t_2$  are at increased cancer risks

The scientists could get key information from the workers

$t_1$  At certain times,  
individuals are provided with protective gear to shield them from exposures.

$t_2$  At certain times,  
exposures are carcinogenic but otherwise not.



**H3** when  $t_1 = t_2$ , workers in  $t_2$  are not at increased cancer risks


	thought experiment	real life scenario
$t_1$	protective gear	biological day
$t_2$	carcinogenic exposure	„shift-work associated times“
$t_1 = t_2$	cancer risk: no	CD: no
$t_1 \neq t_2$	cancer risk: yes	CD: yes

-NEL 2013  
 -Naturwissenschaften 2013

How can we quantify ....  
 disruptions of biological nights



-NEL 2013  
-Naturwissenschaften 2013

How can we assess **chronodisruption**   
= disruption of the physiological nexus  
or overlap of internal & external times

2013 **Chrono**marker of exposure

-Naturwissenschaften 2013

2014 **Internal time** [=chronotype] vs.  
**External time** [=shift-work associated time]

-Chronobiology International  
2014

A genetically (co-)determined  
 „temporal variation“ of ....

**Biological night & biological day**

18:00

19	20	21	22
23	24	1	2
3	4	5	6
7	8	9	10
11	12	13	14
15	16	17	18

civil  
 night

Ignoring chronotype

18:00

19	20	21	22
23	24	1	2
3	4	5	6
7	8	9	10
11	12	13	14
15	16	17	18

biological  
 night

Early

18:00

19	20	21	22
23	24	1	2
3	4	5	6
7	8	9	10
11	12	13	14
15	16	17	18

biological  
 night

Intermediate

18:00

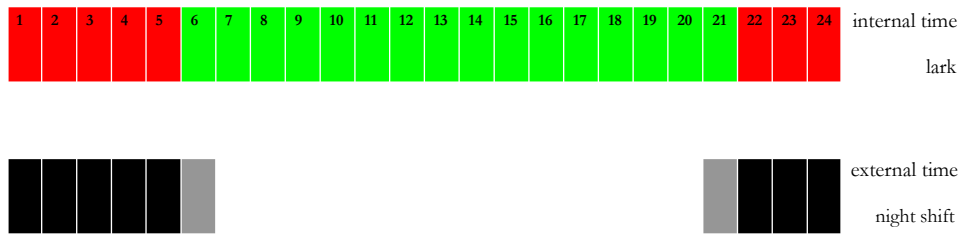
19	20	21	22
23	24	1	2
3	4	5	6
7	8	9	10
11	12	13	14
15	16	17	18

biological  
 night

Late

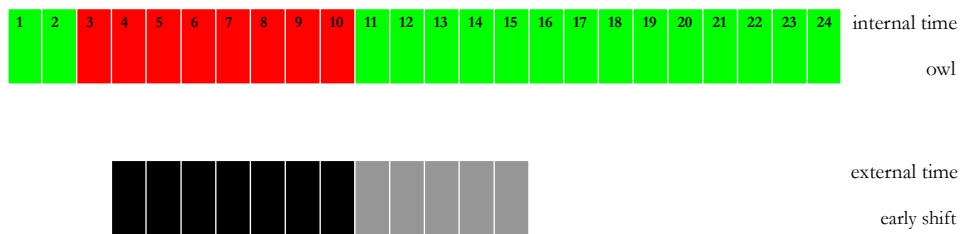
**Chronodisruption** 8/8

Disruption of internal & external times



**Chronodisruption** 7/8

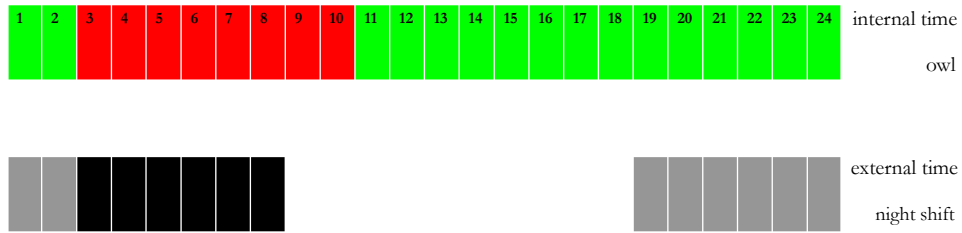
Disruption of internal & external times



**Chronodisruption**

6/8

Disruption of internal & external times



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 Article

ARTICLE

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0	2400
<del>2400</del>	<del>7200</del>
2400	9600
4800	9600
<del>0000</del>	<del>0000</del>
4800	9600
9600	14400
<del>0000</del>	<del>0000</del>
9600	14400
0	1600
1600	4800
<del>7680</del>	<del>7680</del>
9280	14080
3200	6400
0	0
<del>6720</del>	<del>7680</del>
9920	14080
6400	9600
0	0
<del>3840</del>	<del>5760</del>
10240	15360



## Chronobiological fallacies

-Chronobiology International 2014

### Ignoring “internal time” information

When is the individual’s biological night?

Internal time error

### Truncating “external time” information

What is the individual’s “shift work associated time”?

External time error

Activities at chronobiologically unusual times  
may start before and do not end with the shift

-Travis et al.  
JNCI 2016

**The prospective evidence now available shows that  
classification of night shift work  
as a probable human (breast) carcinogen  
is no longer justified**

**“Chronobiology”**

**To interpret their & other work before & after IARC 2007,  
future research should avoid internal & external time errors  
as a basis to attempt to falsify  
the hypothesized role of individual biological nights**

“Next generation” studies

Shift-work epidemiologists: How should we work?

cancer risks in **biological night**-workers /  
cancer risks in **biological day**-workers

Practical challenges

		Prospective		Retrospective
	Nurses Health Study USA	Million Women Study UK	EPIC Oxford Study UK	BCEE Study Australia
Chronotype	„yes“	„yes“	„yes“	„yes“
Shift times	no	no	„yes“	„yes“



**Practical challenges**

**Chronotype**

Workshop invitation:

In the presence of circadian disruption,  
chronotypes prove more difficult to establish  
and chronotype-questionnaires may be poorly suited for this task



**Practical challenges**

**Chronotype**

Ultimately, obtaining necessary details  
regarding chronotype  
may only be possible  
in cohort studies which collect data over time

**Shift times**

Ultimately, only industry- or community-based studies  
may provide shift details  
of appropriate completeness and accuracy  
over years or decades in an independent fashion



**Time for Questions?**

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