Essential problems in the interpretation of epidemiologic evidence

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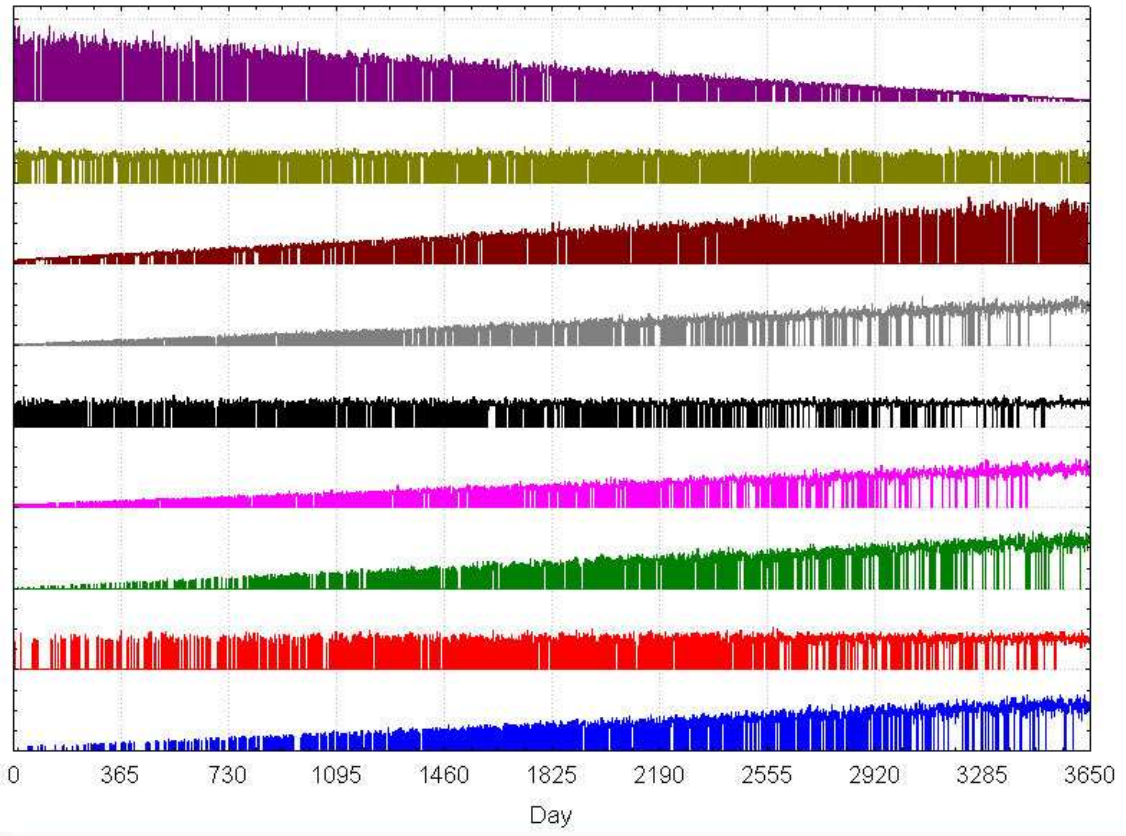
Methodological Difficulties

- If correctly applied, analytical epidemiology is able to detect a risk from an exposure provided the following conditions are met:
  - There is a reliable exposure metric
  - There is an evidence based selection of a disease
  - Exposure duration is compatible with the natural history of the disease

None of these conditions are at present ideally met for the study of mobile phone use and tumors in the head region.

Problem 1: Exposure Metric

Fundamental problems of exposure assessment



All these patterns have the same cumulative hours of use!

Are they equivalent?

Problem 1: Exposure Metric

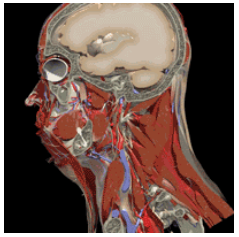
It is unknown which aspect of exposure is responsible for the increased risk.

Cumulative hours of use, cumulative number of calls, specific absorption rate in the area of the tumor and other parameters may or may not reflect essential aspects of exposure.

The mechanism of interaction between the EMF and cells and tissues must be the basis for the definition of exposure!

Problem 2: Selection of Disease

Intracranial Tumors



Exposure for traditional MP use is predominantly to the head. Therefore, studies were almost exclusively about tumors in the head region.

Nervous System Tumors

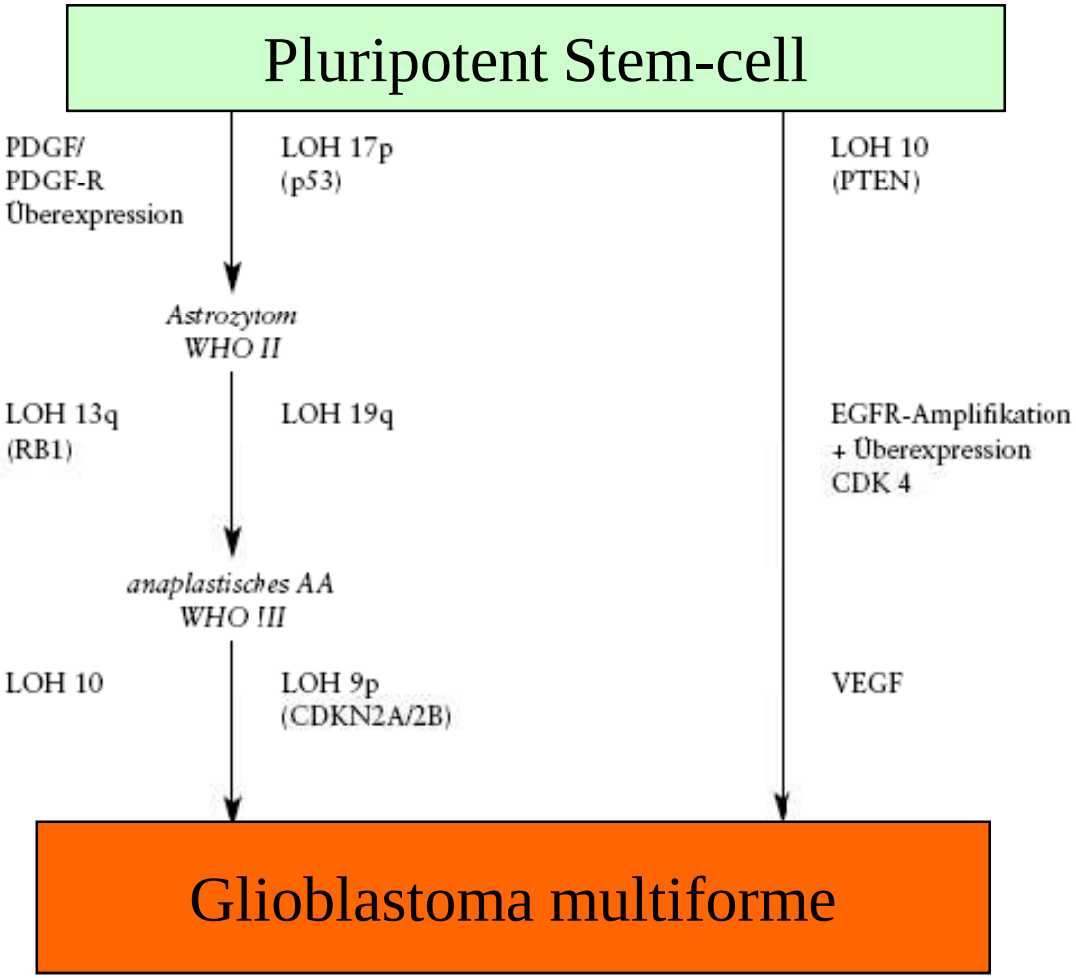
Neuroepithelial tissue
Astrocytic tumors (11)
Oligodendroglial tumors (2)
Mixed glioma (2)
Ependymal tumors (8)
Choroid plexus (2)
Neuronal and mixed (12)
Embryonal tumors (11)
Others (5)

Peripheral nerves
Schwannoma (4)
Neurofibroma
Perineuroma
MPNST (5)

Meningial Tumors
Meningioma (16)
Mesenchymal (21)

Lymphoma &
Haematopoietic
Neoplasms (3)
Germ cell (8)
Sellar region (4)

Molecular histopathology

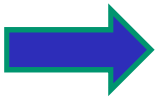


One and the same histopathologic type may be distinctly different with respect to molecular histopathology

Problem 2: Selection of Disease

Are all types of brain tumors associated with an increased risk from mobile phone use?

It is impossible to differentiate all types of tumors with respect to this risk based on epidemiology!



It is important to work on potential mechanisms of action of low intensities of EMF in biological systems!

Problem 3: Exposure Duration

Mobile phone use and risk of glioma in adults: case-control study

Sarah J Hepworth, Minouk J Schoemaker, Kenneth R Muir, Anthony J Swerdlow, Martie J A van Tongeren, Patricia A McKinney

What this study adds

This large case-control study found no increased risk of developing a glioma associated with mobile phone use either in the short or medium term

Mobile phone use does not raise the risk of cancer, at least in the first 10 years of use, the largest investigation to date shows. **BBC News**

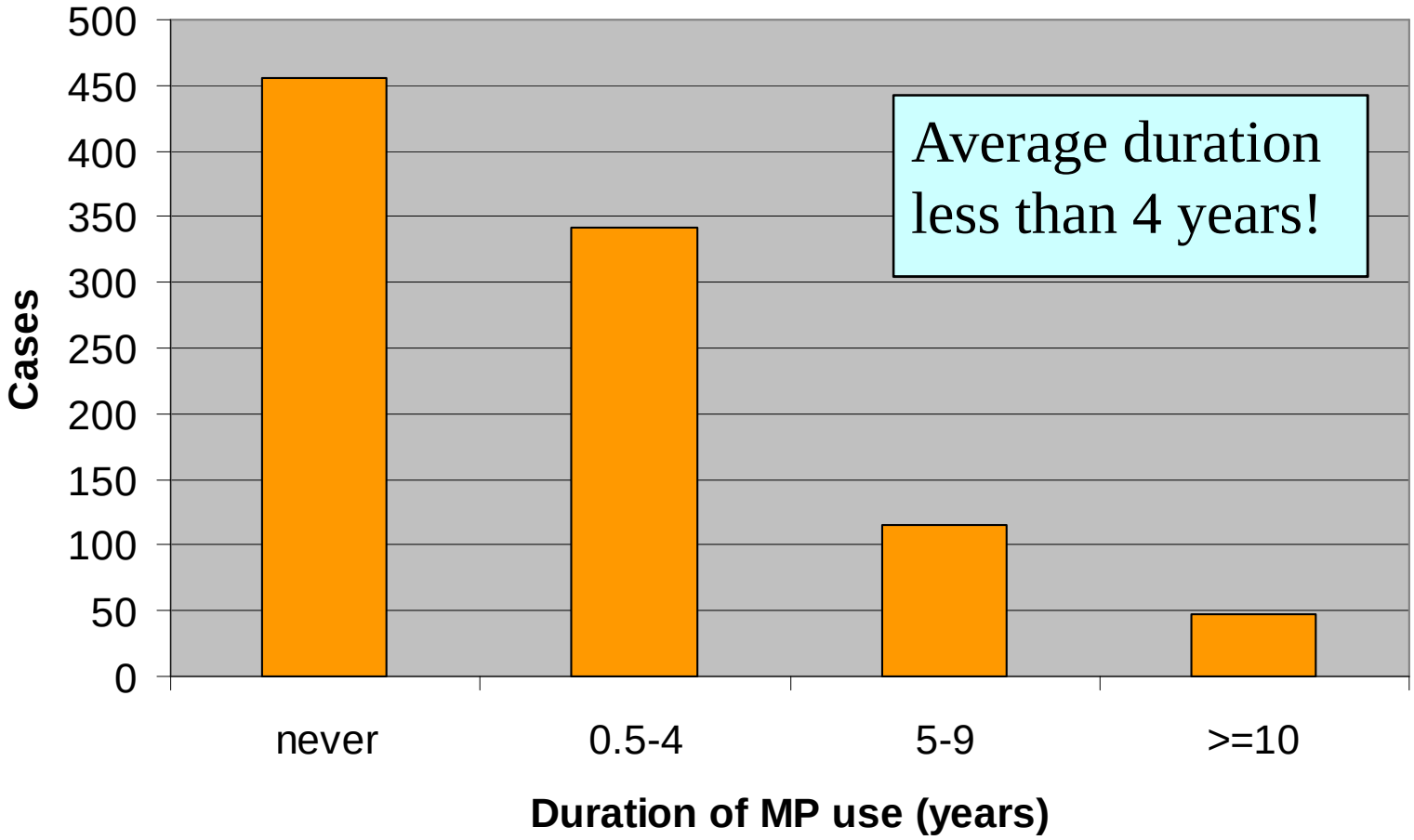
"Whether there are longer-term risks remains unknown"

Senior investigator Professor Anthony Swedlow

Latency of Brain Tumors

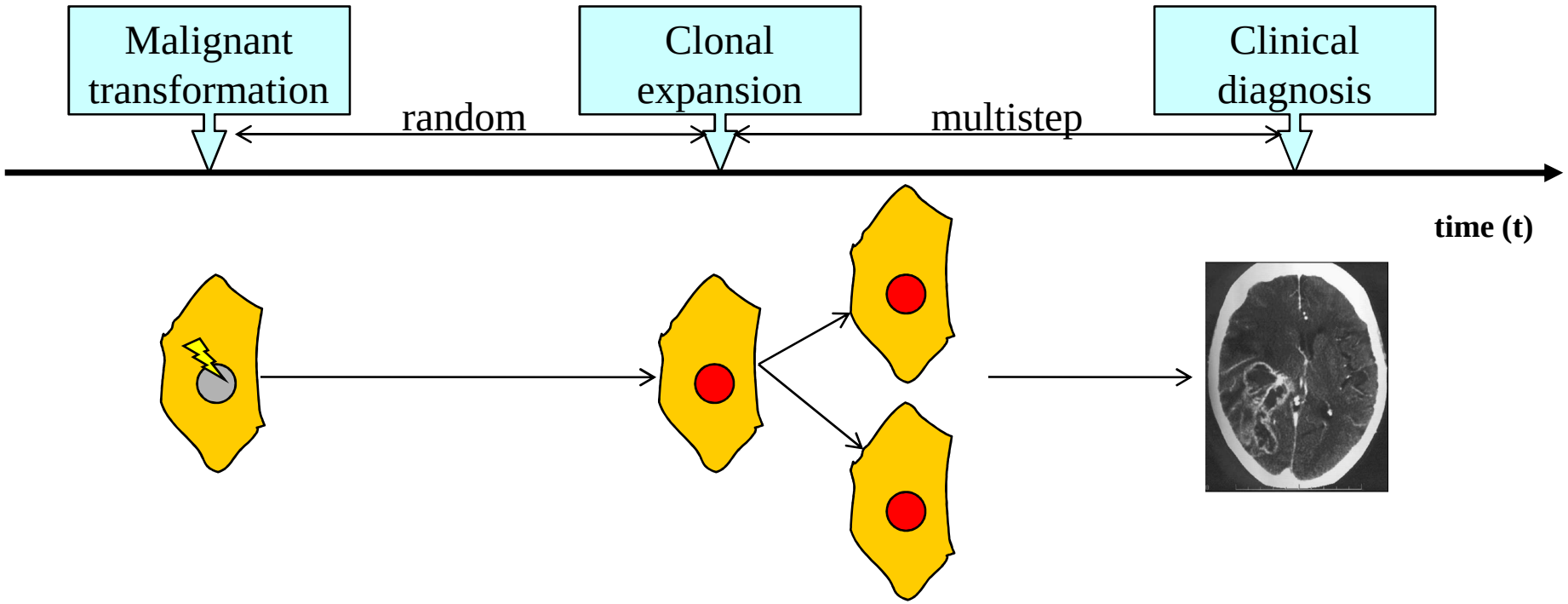
- Glioma:
  - 20-30 years average (Kranzinger et al. 2001; Sadetzki et al. 2005)
- Meningioma
  - 20-40 years average (Umansky et al. 2008)
- Acoustic Neuroma
  - Average doubling time ~1.7 years -> 25 years Latency (Mohyuddin et al. 2003)

Interphone Study – Exposure Duration



Source: Hepworth et al. BMJ 2006; 332(7546):883-887

It follows that it is impossible to study tumor initiation for the time being. Virtually all MP users must have already the disease in the latent phase when they started MP use!



From animal experiments and retrospective CT/MRI analysis it follows that tumor growth is a complex process and in the worst case exponential. In some tumors (e.g. primary glioblastoma) exponential growth is seen in the last phase only.

"…, if RF exposure is assumed to act by promoting the growth of an underlying brain lesion, then the **intense recent use**, as currently experienced by large numbers in our cohort, might be **of more importance** than latency or long-term use considerations." (Johansen et al. 2001)

This completely wrong assumption has influenced many authors and led to a lot of misinterpretations of results of epidemiological studies.

In contrast, it is virtually impossible to detect a substantial increase of the growth rate of brain tumors if the duration of mobile phone use is less than about 10 years!!

Derivation of the effect of growth promotion on time to diagnosis

- We assume as a worst case an exponential tumor growth with a growth constant of ß
- Let MP use increase growth rate by a factor f
- Assume that tumor growth starts at t_o and MP use at t_1 ($t_1 > t_o$)
- Clinical diagnosis is assumed to occur if the tumor volume has reached V_d ml, which we assume to occur at time t_d without mobile phone use

WITHOUT MP USE

$$V_t = V_o e^{ß(t-t_o)} \Rightarrow V_d = V_o e^{ß(t_d-t_o)}$$

t_d-t_o is the tumor latency

WITH MP USE

$$V_t = V_o e^{ß(t-t_o)} \quad t < t_1$$

$$V_t = V_o e^{ß(t_1-t_o)+fß(t-t_1)} \quad t \geq t_1$$

$$V_d = V_o e^{ß(t_1-t_o)+fßt_{mp}}$$

$$t_d - t_o = t_1 - t_o + ft_{mp}$$

$$\text{Shift} = (f-1)t_{mp}$$

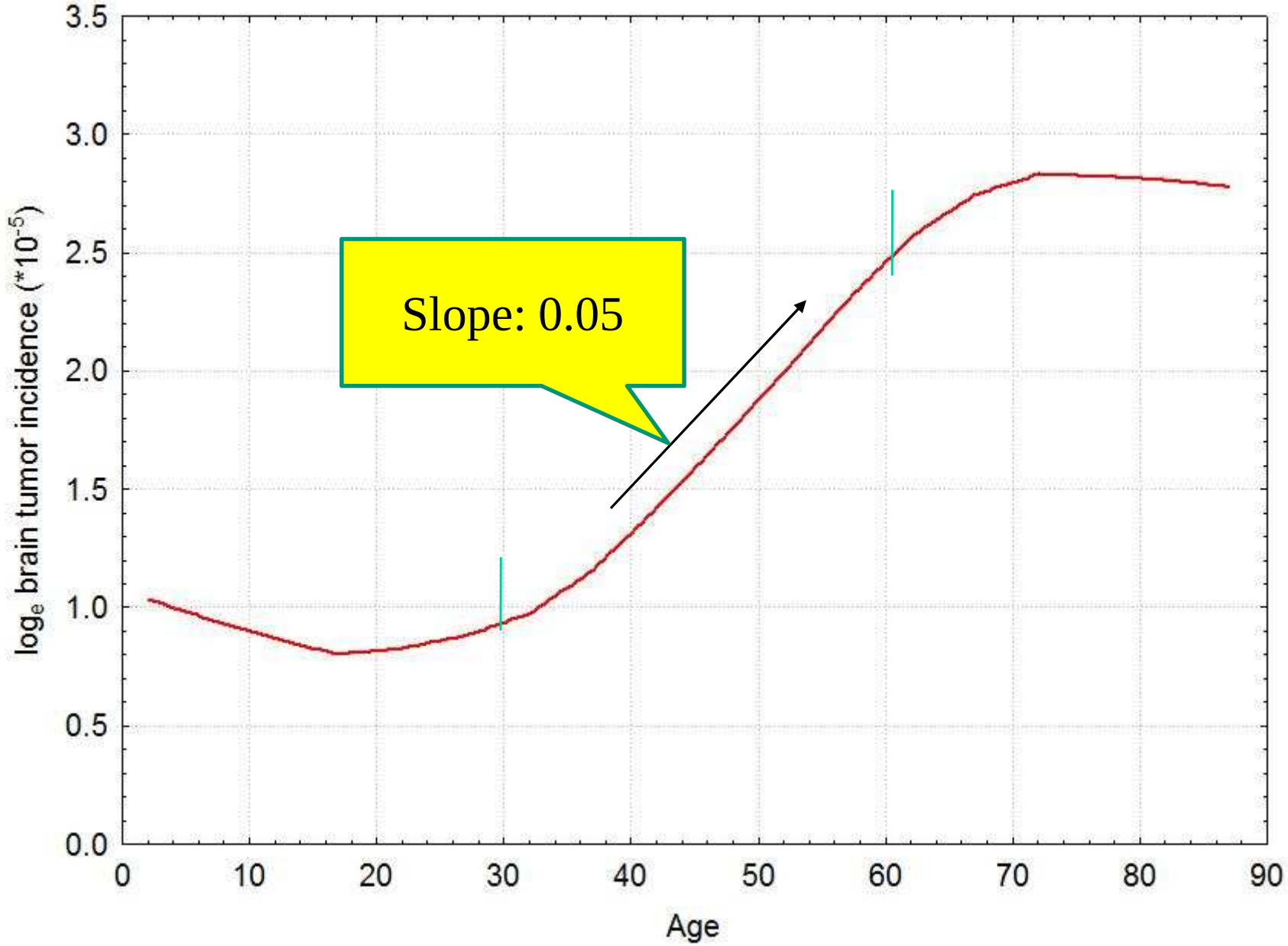
If e.g. MP use increases the growth rate by 50% then the shift of latency is 50% of the duration of MP use

Derivation of the effect of growth promotion on the odds ratio

- Assume that growth rate is increased by 50% due to MP use
- This results in at most a shift of time to diagnosis by 50% of the duration of MP use
- Average duration of MP use was less than 4 years
- Hence we assume a shift of time to diagnosis by 2 years

Derivation of the effect of growth promotion on the odds ratio

- Let the fraction of MP users in the population be π
- Then the estimated odds for MP use in controls is $\pi/(1-\pi)$
- For brain tumors there is a log-linear age incidence function with a slope for malignant brain tumors of 0.05 ($\log_e$ units per year).
- If this function is shifted by t_s years, then the incidence at all ages increases by a factor $e^{0.05ts}$


Slope: 0.05
log$_e$ brain tumor incidence (*10^{-5})
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
Age

Derivation of the effect of growth promotion on the odds ratio

$$\Pr(bt, a \mid noMP) = e^{\alpha+\gamma a}$$

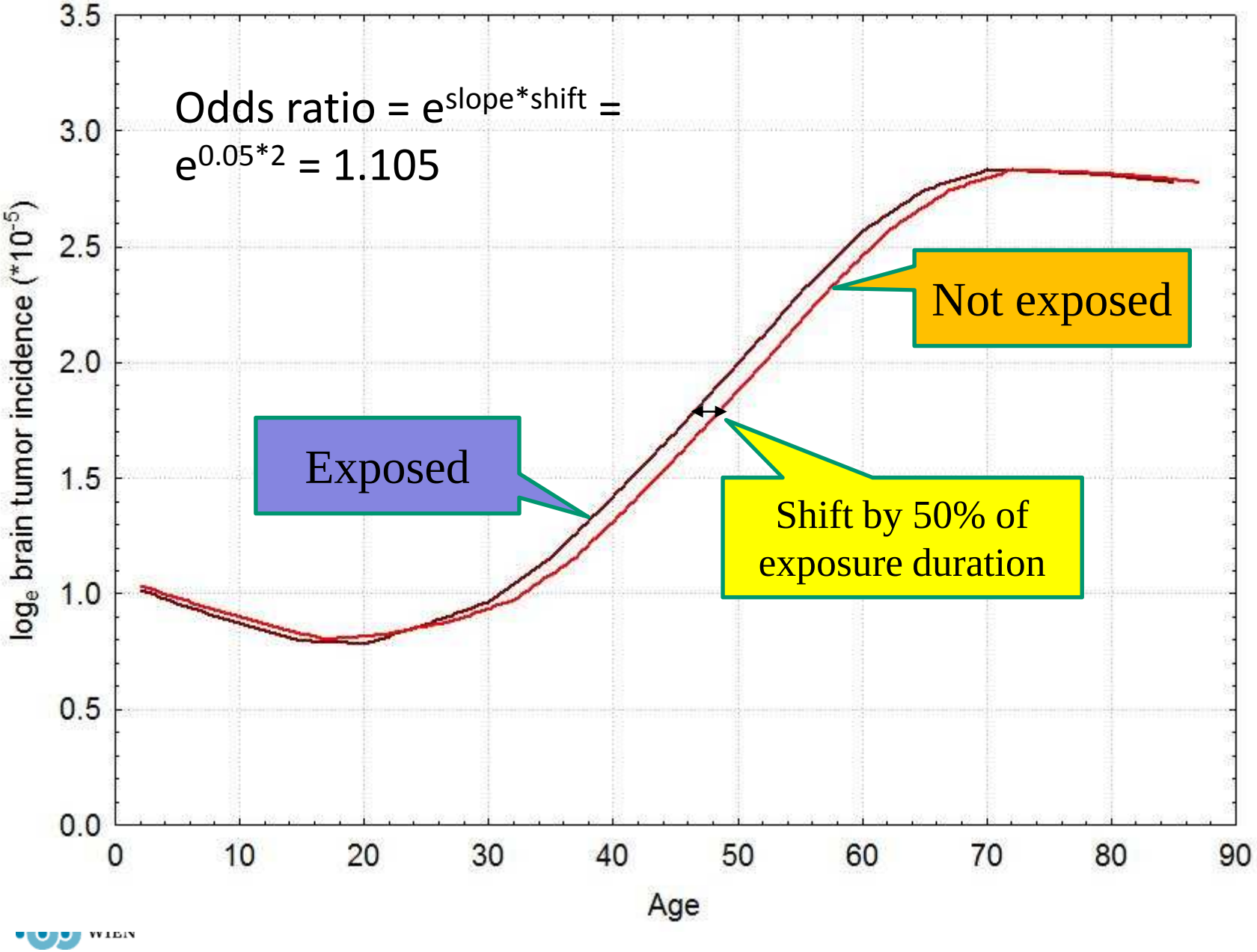
$$\Pr(bt, a \mid MP) = e^{\alpha+\gamma(a+t_s)}$$

$$\Pr(MP \mid bt, a) = \frac{\Pr(bt, a \mid MP)\pi}{\Pr(bt, a \mid MP)\pi + \Pr(bt, a \mid noMP)(1-\pi)} = \frac{e^{\gamma t_s}\pi}{1+\pi(e^{\gamma t_s}-1)}$$

$$Odds = \frac{\Pr(MP \mid bt, a)}{1-\Pr(MP \mid bt, a)} = \frac{\pi}{1-\pi} e^{\gamma t_s}$$

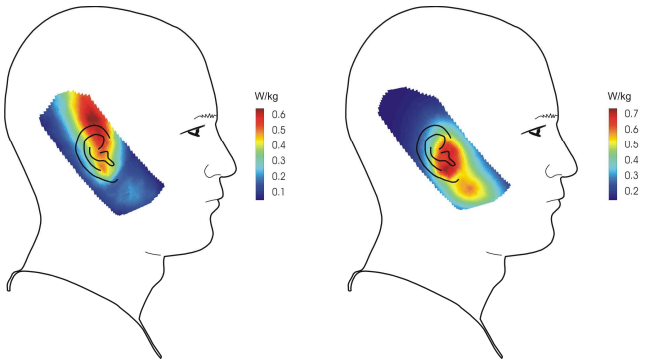
$$\Rightarrow OR = e^{\gamma t_s} = e^{0.05 \cdot 2} = 1.105$$

To have a 80% chance to detect such a low risk a sample of ~6500 brain tumor cases and an equal number of controls is necessary.


Odds ratio = e^slope*shift =
e^0.05*2 = 1.105
Not exposed
Exposed
Shift by 50% of
exposure duration
log_e brain tumor incidence (*10^-5)
Age
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
10
20
30
40
50
60
70
80
90

It follows that it is virtually impossible to find an increased risk in the overall results if duration of MP use is short and an effect of MP use on tumor growth is assumed!

Exposure is predominantly unilateral!



97%-99% of absorbed power from mobile phone use is absorbed in the hemisphere corresponding to the side of the head the mobile phone is held during calls

Only the side of the head the phone is held to during calls can be considered exposed!

Conclusions

- It is impossible at present to study an effect of MP use on tumor initiation
- It is virtually impossible to detect an effect of MP use on tumor growth if duration of MP use is short
- Only the subgroup of long-term users give informative results
- Since we study effects on tumor growth, only ipsilateral exposure counts

From these considerations it follows that reporting overall results from short average exposure duration of MP use is misleading and deceiving the public since from lack of an increased risk the public will erroneously conclude that there is no risk.

All results from short exposure duration must completely be dismissed in risk analysis. Only data from long-term users (~10 years MP use) should be considered and predominantly those from ipsilateral MP use.