Epidemiological evidence in relation to the IARC 2b classification

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Radio frequency fields

- Electromagnetic fields - 30 kHz–300 GHz
- Workers: high power sources (induction heaters, radars) can have higher cumulative whole body exposure
- Mobile phone users: higher brain exposures
- Base stations: exposure orders of magnitude lower

Epidemiological studies on cancer risk and RF

- Occupational studies
- Mobile phone studies (brain tumours and acoustic neuromas)
  - Incidence time trends studies
  - Cohort studies (Danish cohort)
 - Case control studies (Interphone and "Hardell" studies for brain tumours)

Incidence time trends studies

- Yearly description of number of new cancer cases (after age standardisation to a reference population) occurring in a population
- Based on cancer registry data
- Informative for effects occurring at population scale
  - Screening programmes, introduction of new diagnostic tools, impact of tobacco epidemic
- Not informative for effects occurring in small subgroups of populations, or if other factors are also changing at population scale
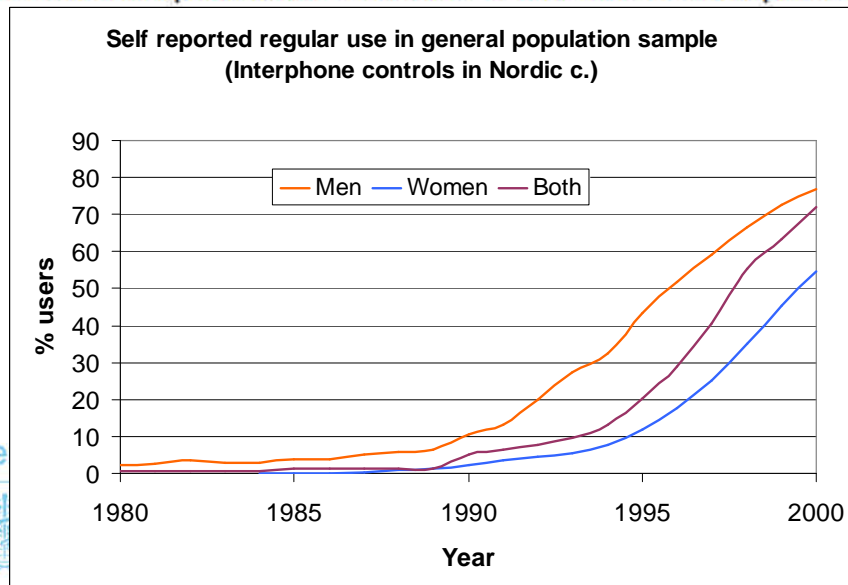
  => If mobile phone causes gliomas or other cancers, it will ultimately show up in incidence rates of these diseases

Prevalence of use of mobile phones in Nordic countries

Mobile subscriptions[1] per capita
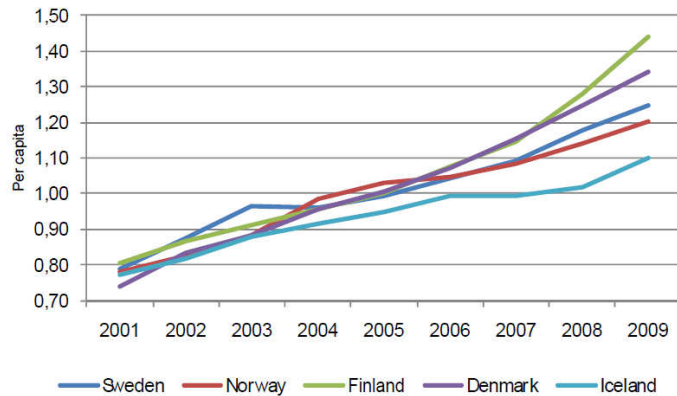
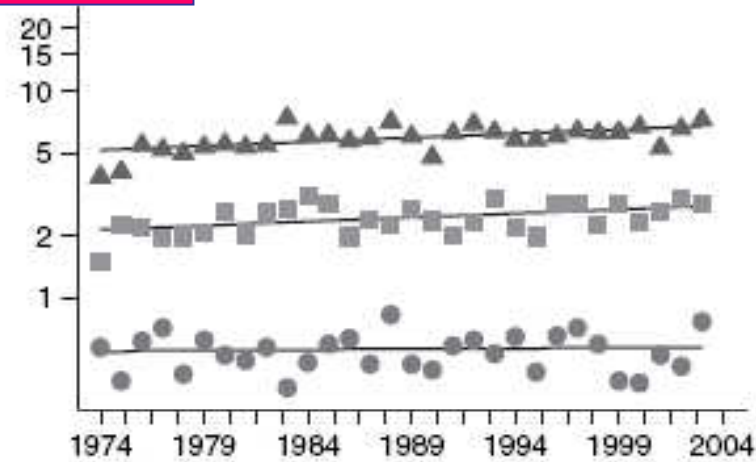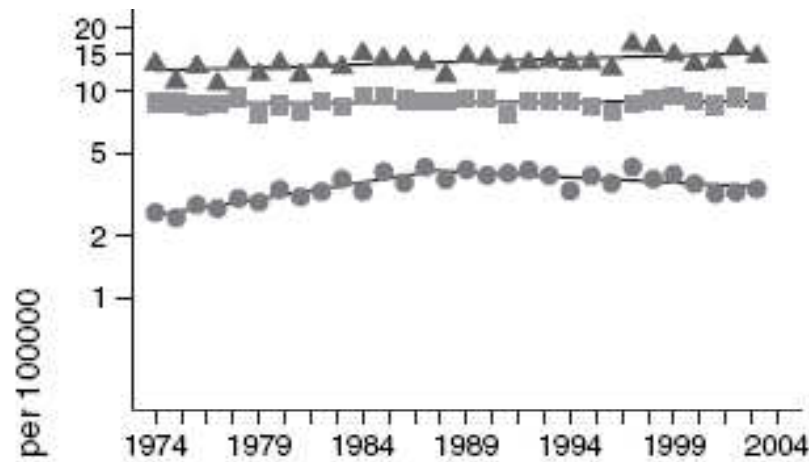[1]Includes both private and business GSM/UMTS subscriptions.

- Very similar between Nordic countries
- Differences in prevalence of use at given time between age and gender groups
- Men aged 40-60 yrs first to adopt mobile phones

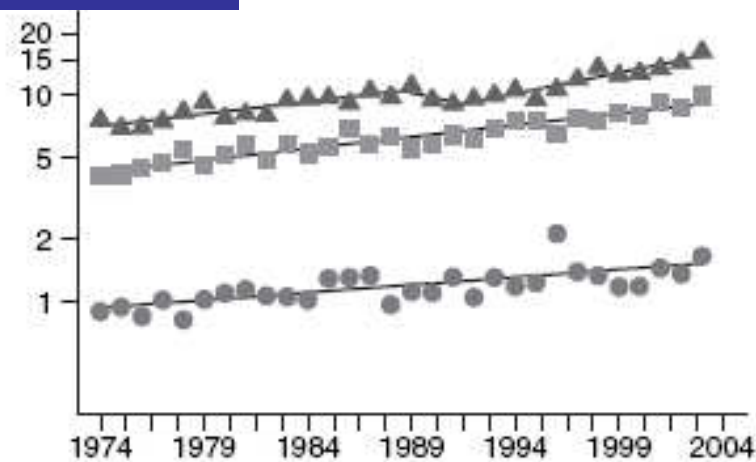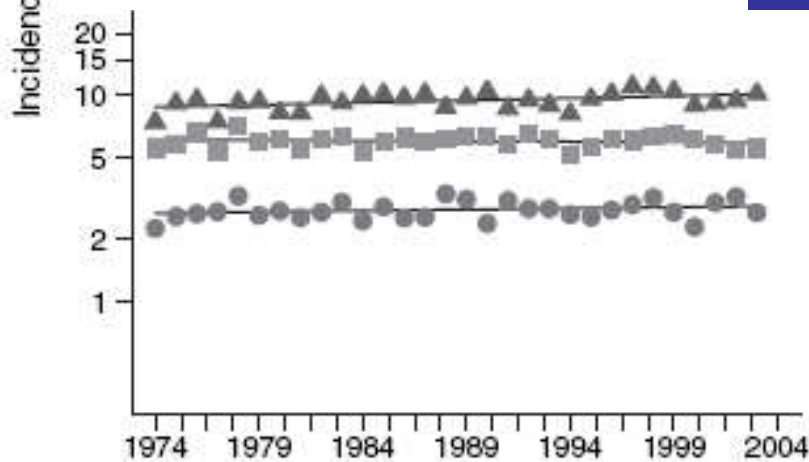# Incidence rates of brain tumors
(Nordic countries - 2003)

Deltour et al., J Natl Cancer Inst, 2009

Incidence time trends of malignant brain tumours

In 2006, 220 Million subscribers in USA
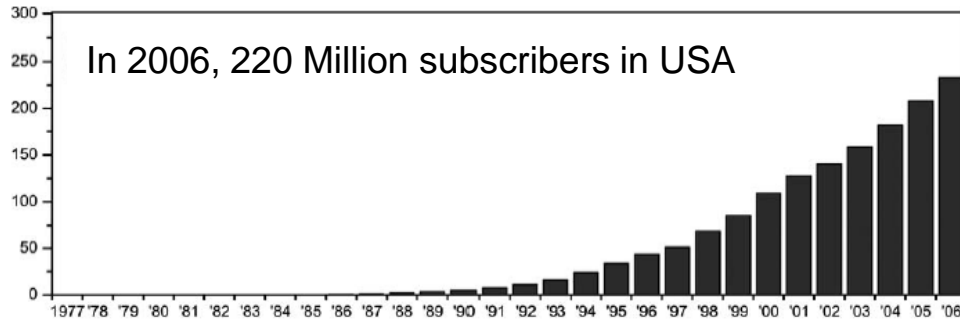
England,
1998-2007

Fig. 1. Brain cancer incidence rates between 1998 and 2007 per 100,000 people in England and number of mobile phone subscribers in the UK between 1985 and 2003 [ITU, 2010].

USA,1977-2006
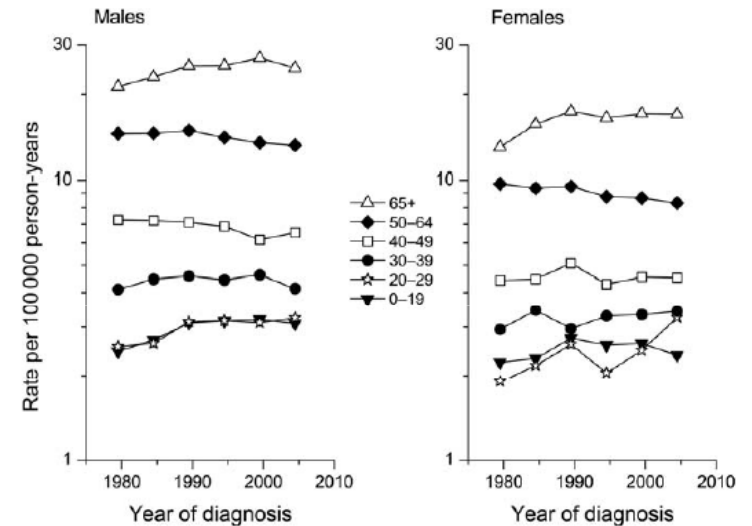
Brain cancer incidence trends among whites by age, SEER 9, 1977–1981 to 2002–2006.

Inskip et al, Neurology, 2010

de Vocht et al, Bioelectromagnetics, 2011

International

World Health Organization

Incidence studies

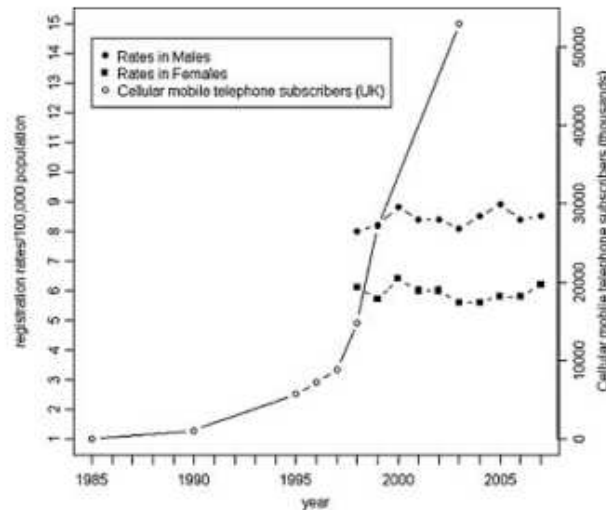- Provide evidence that there is no observable effect of mobile phones at the population scale on glioma in 3 different studies (6 countries) so far
- Could miss an effect if effect is small, limited to small subgroups (highest users, temporal lobe tumors) or occurs at the population scale after longer time than observed so far

Stresses the importance of high quality cancer registration for epidemiological studies

Cohort studies

- Follow a group of people over time
- Compare the occurrence of disease among exposed individuals to non exposed individuals

Danish cohort of early mobile phone subscribers: design

From the 2 danish mobile telephone companies , Sonofon and TeleDanmarkMobil,
<u>all numbers</u> issued between 1982 and 1995 were obtained,
name and address of subscription holder (person or company), date of subscription

Unexposed (no subscription bef. 1996)
Approximately 4,130,000 persons

Exp.

Early subscribers maximum 720,000 persons

Danish cohort study: analysis

Exclusions:

200 000 corporate subscriptions (no individual user identified)

100 000 subscriptions (mismatches -names or addresses, 2 subscriptions for same name,…)

<u>Identification of 420 095 persons</u> who were early subscribers of mobile phones and their date of subscription (1982-1995)

Unexposed (no subscription bef. 1996)
Approximately 4,130,000 persons

Exp.

Early subscribers identified 420,000

Not identified subscribers 300,000
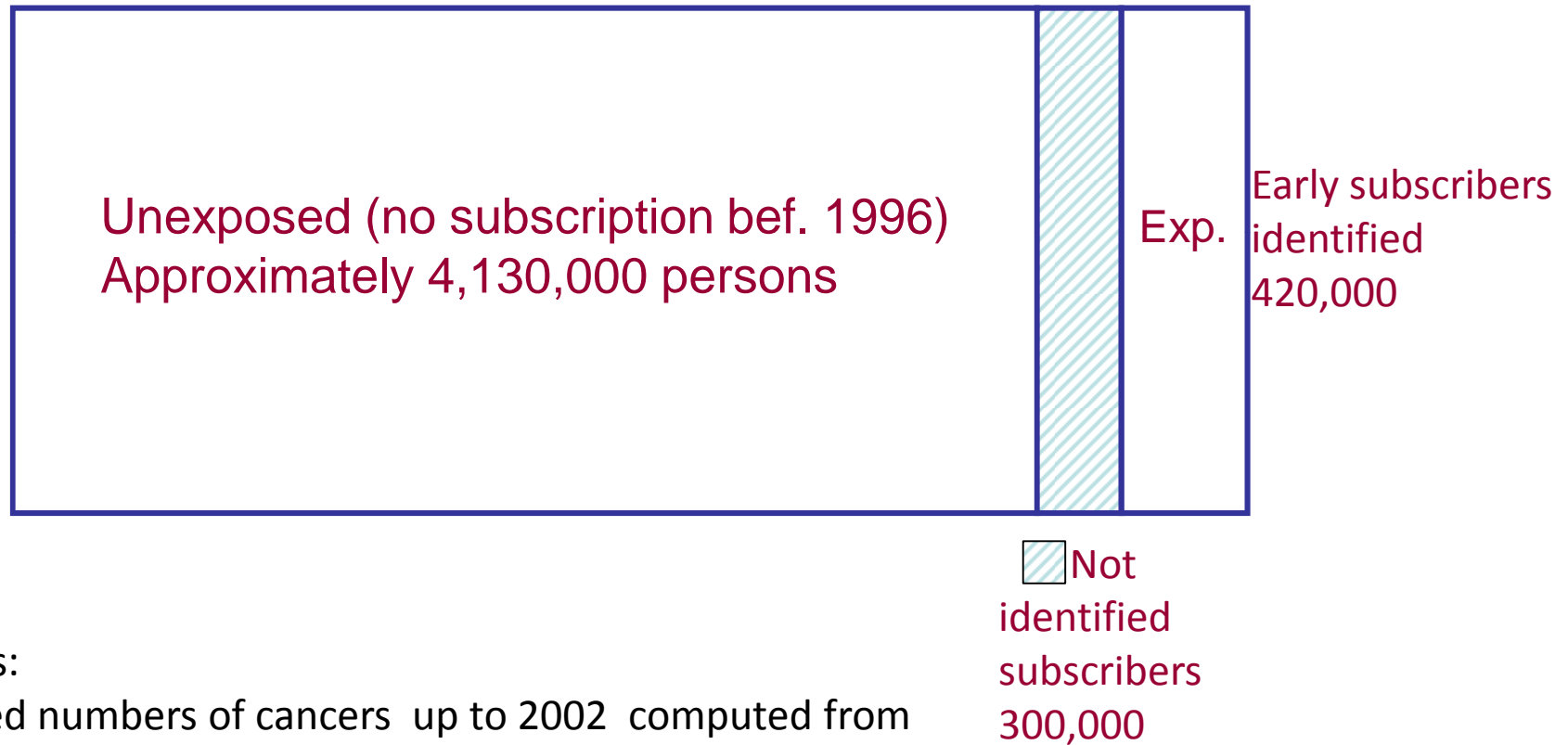
Analysis:

Expected numbers of cancers up to 2002 computed from rates in unexposed and unidentified subscribers, compared to observed numbers of cases in the identified subscribers

Danish cohort study: results for follow up to 2002

(*Schuz et al, JNCI, 2006*)

- Mean exposure duration: 8.5 years
- Number of cases : glioma 257, meningioma 68
- Results :
  – Entire follow up, gliomas: SIR=1.01 (0.89-1.14)
  – 5-9 years, all CNS, men : SIR= 0.96 (0.84-1.09)
  – 10+ years all CNS, men : SIR= 0.66 (0.44-0.95)
- But number of cases small,
- No information on level of use

Maria Feychting

Case-control studies

- Principle: comparison of past exposures of
  - Individual with disease (cases)
  - Random sample of population (controls)
- Quality of case-control study
  - High participation ensures selection bias (cases and controls representative of the same source population)
  - Assessment of exposure is important
    - Random error in exposure -> underestimation of association exposure - disease
    - Recall bias is a concern (cases report differently than controls)

Case-control studies

Case-control studies based on cases diagnosed before 2000:

Brain tumours:

Sweden	> 5 years
US	≥ 4 years
US	≥ 5 years
Finland	> 2 years

0.1   1   10

RR
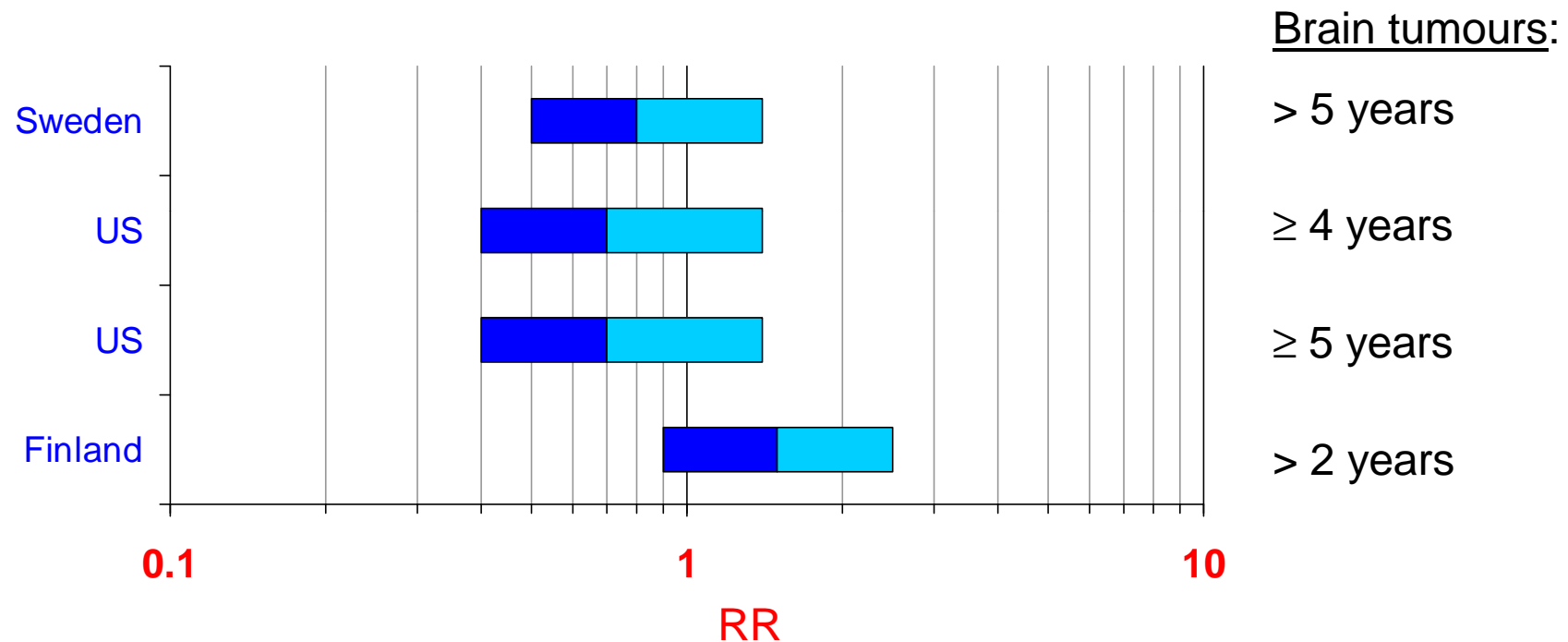
Hardell et al., Int J Oncol, 1999
Muscat et al., JAMA, 2000
Inskip et al., N Engl J Med, 2001
Auvinen et al., Epidemiology, 2002

Case-control studies

Case-control study in Sweden, by Hardell and team:

> 10 years analogue

> 10 years digital

Astrocytoma III/IV
by amount of use
of NMT phone
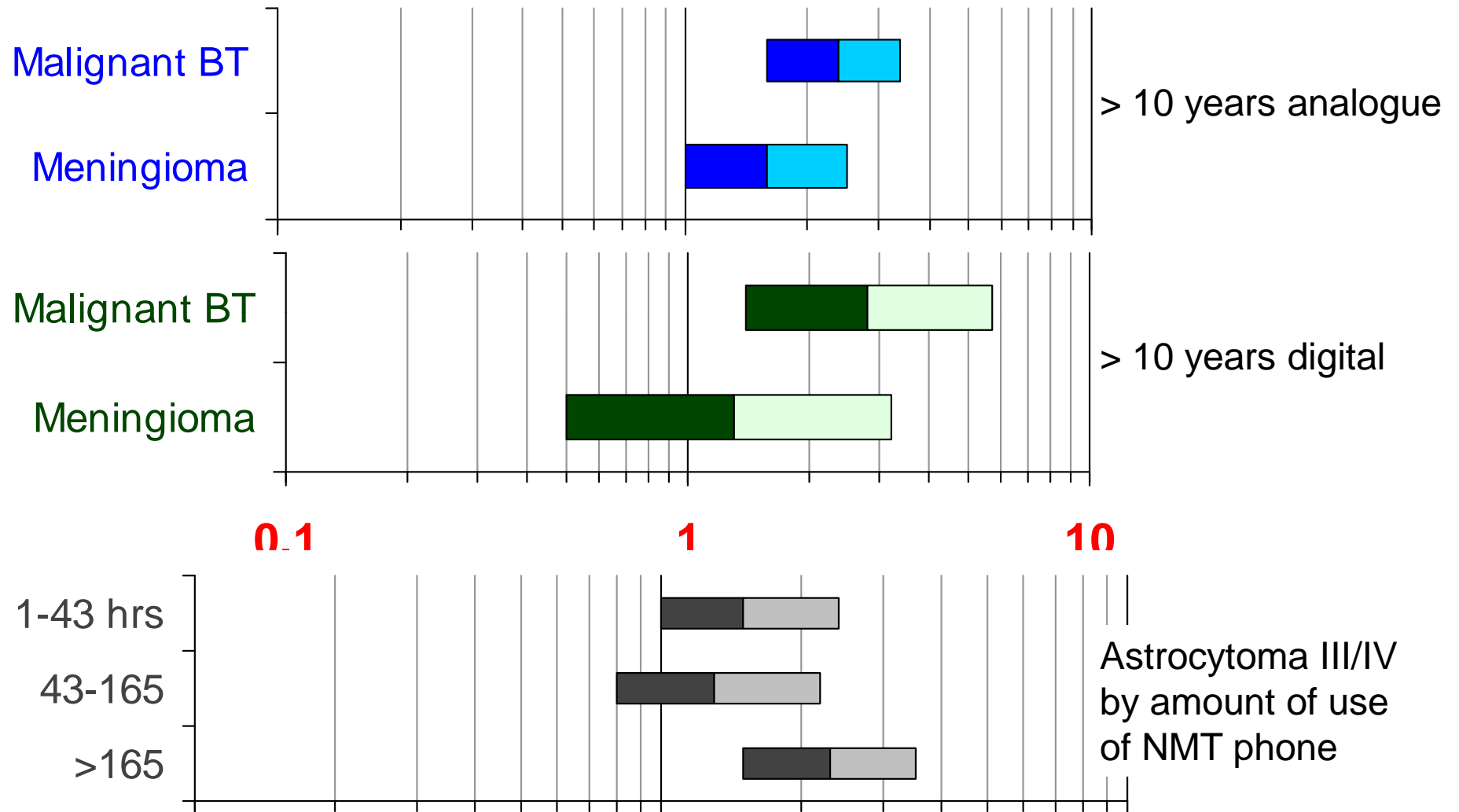
Hardell et al., World J Surg Oncol, 2006

Interphone Study

16 centers in 13 countries
European centers
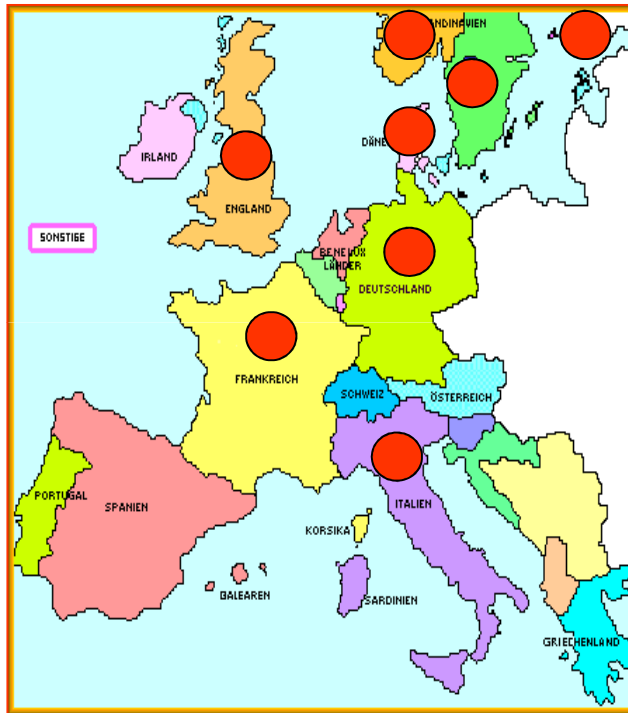
+ Australia, Canada, Israel,
Japan, New Zealand

**Study of mobile phone use and risk of brain tumours and acoustic neuroma among adults (30-59 years old).
Characteristics:**

Personal interviews with:
- 2708 patients with glioma
- 2409 patients with meningioma
- 1105 patients with ac. neuroma
- similar number of controls
or their proxies

Ascertainment: 2000-2003

Representativity of the control population

Study center	Controls			
	Interviewed subjects		NRQ respondents*	
	Total (n)	Phone users (%)	Total (n)†	Phone users (%)
Australia	669	82	418	55
Canada - Montreal	234	49	39	26
Canada - Vancouver	239	64	115	46
Finland	559	89	190	82
France	472	69	109	54
Germany	1,190	46	368	39
Israel	599	85	180	72
Italy	340	79	23	83
Japan	287	73	131	60
New Zealand	172	65	20	60
Norway	278	71	42	69
Sweden	407	73	64	56
All combined	5,446	69	1,699	56

Vrijheid et al., Ann Epidemiol 2008

- Low response rate, particularly among controls
- More mobile phone users among participants
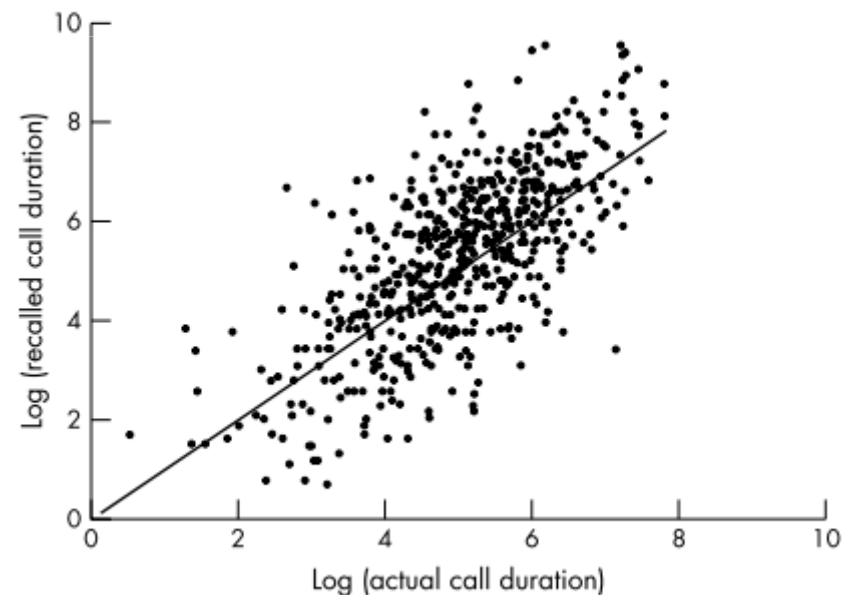
Recall of mobile phone use

672 volunteers in 11 countries

Actual duration of use: Operators or Software Modified Ph.

Recalled use: questionnaire 6 -12 months after

Recalled to actual monthly
duration of calls
mean ratio = 1.4

95% of subjects 0.12-17

Vrijheid et al, OEM, 2006

Evaluation of recall bias: operators' records compared to questionnaire

In Australia, Canada and Italy, all major operators provided mobile phone records for cases and controls of the main Interphone study

	Cases (N=212)	Controls (N=296)
Mean period of evaluation (months)	29 m. , gap 6 m.	34 m., gap 8 m.
Ratio of recalled to actual monthly duration of calls		
Overall *(95% limits of agreement)*	1.39 *(0.10-18.8)*	1.40 *(0.12 – 16.1)*
By period of use		
<1 year	1.4	1.4
1-2 years	1.5	1.4
2-3 years	1.8	1.4
3-4 years	2.1	1.4
> 4 years	2.2	1.6

Vrijheid M, et al. J Expo Sci Environ Epidemiol. (2009)

World Health Organization

Interphone: results (all countries)

- For meningiomas, no increased risks
- For gliomas and acoustic neuromas:
  - No increased risk for the majority of users
  - Increased risks for the 10 % highest user group
    glioma -   OR = 1.40 (95%CI 1.03 - 1.89),
    ac. neuroma- OR = 2.79 (95%CI 1.51 - 5.16)

    (5 year latency)

Biases and errors prevent a causal
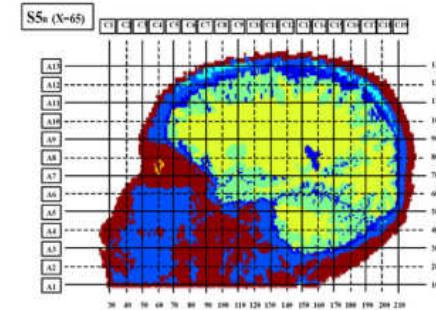 interpretation

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World Health
Organization

Interphone study: OR by cumulative call time
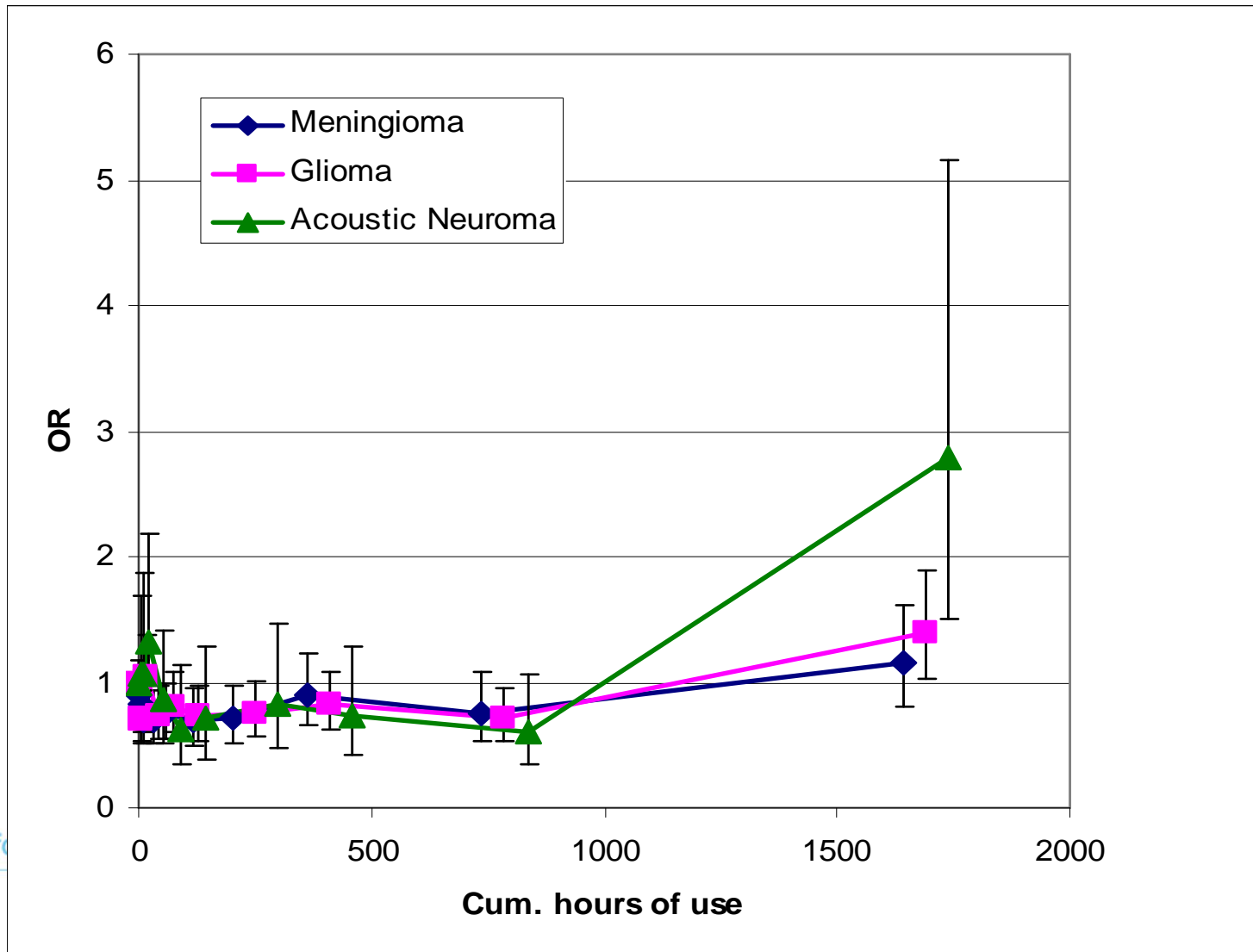
Interphone –localisation of tumour within head

- Neuro-radiologists localised origin of tumour within brain

- Analysis of distance of glioma from ear (7 countries)

  Larjavaraa et al, Am J. Epi, 2011

  – distance ear – tumour = 6.3 cm, same in >10 years group

- Analysis of cumulative specific energy at tumour site (5 countries)

  – Highest quintile (>3123 J/kg): OR 1.7 (1.0 to 2.7) (57 cases with tumour localised by neuroradiologist)

International Agency for Research on Cancer

World Health Organization

Cardis et al, Occ Env Med, 2011

IARC Monograph program

2 to 3 times per year, ad hoc group of expert convenes for 1 week

- Review published literature
  - Sources and Exposure mechanisms
  - Studies of carcinogenicity in humans (epidemiology)
  - Studies of carcinogenicity in animals (in vivo)
  - Other relevant data (in vitro, …)

Classification scheme

1 – carcinogenic to humans (tobacco, HPV virus type 16, ionising radiation, benzene, ethanol in alcoholic beverages…)
Sufficient evidence in humans: causal relationship has been established, in which chance, bias and coufounding could be ruled out

2a – probably carcinogenic to humans: limited evidence in humans, sufficient evidence in animals (emission from high temperature frying, shift work,…)
Epidemiological studies: causal interpretation is credible, but chance, bias and confounding could not be ruled out as possible explanations.

2b – possibly carcinogenic to humans: limited evidence in humans, not sufficient evidence in animals (chloroform, dry cleaning, naphtalene,…)
Epidemiological studies: causal interpretation is credible, but chance, bias and confounding could not be ruled out as possible explanations.

3 – not classifiable: inadequate data (aciclovir, eosin, haematite, personal use of hair colouring products,…)

4 – evidence of lack of carcinogenicity (1 agent)

Conclusions

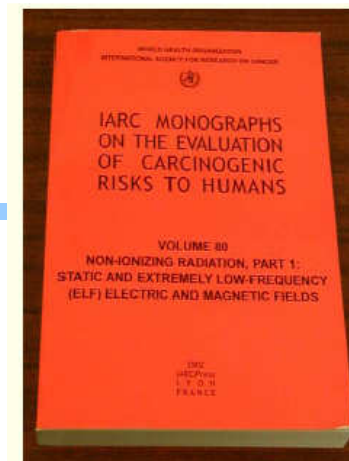**Time trends in incidence rates of brain tumours**
... show no increase suggesting a mobile phone-related effect
... would not show small effect in longer term heavy users yet

Cohort study
... does not show an increased brain tumour risk
... did not allow any investigation by amount of use

24-31 May 2011
IARC Monograph

Case-control studies
"Although both INTERPHONE and Swedish pooled analysis are susceptible to bias—due to recall error and selection for participation— the Working Group concluded that the fi ndings could not be dismissed as refl ecting bias alone, and that a causal interpretation between mobile phone RF-EMF exposure and glioma is possible. A similar conclusion was drawn from these two studies for acoustic neuroma,..."   -> limited evidence from epi studies

Few members: inadequate evidence from epi studies
(lack of dose response in Interphone, inconsistencies between C-C studies, lack of effect in other epidemiological studies)

New publications since May 2011

- Cefalo study: Brain tumours in children and adolescents (July 2011)

- Update of Danish cohort study with cancer cases occurring up to 2007 (Nov 2011)
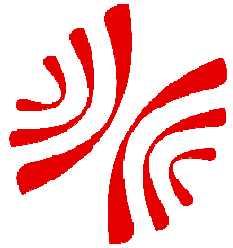
Cefalo: Children & Teenagers Brain Tumor

Aydin et al, Journal of the National Cancer Institute, 2011

- International case – control study among 7-19 year in Denmark, Norway, Sweden and Switzerland (352 cases-646 controls)

- Use of mobile phones : Self reported + operators records if available

- Results:
  - OR (user/non user)= 1.36; (95% CI = 0.92 to 2.02)
  - Significant trend with increasing time based on Operators records (163 subjects). OR (>2.8 y) = 2.15 (1.07 to 4.29)
  - Inconsistent results with laterality, tumor location

- Need for further studies with good exposure information
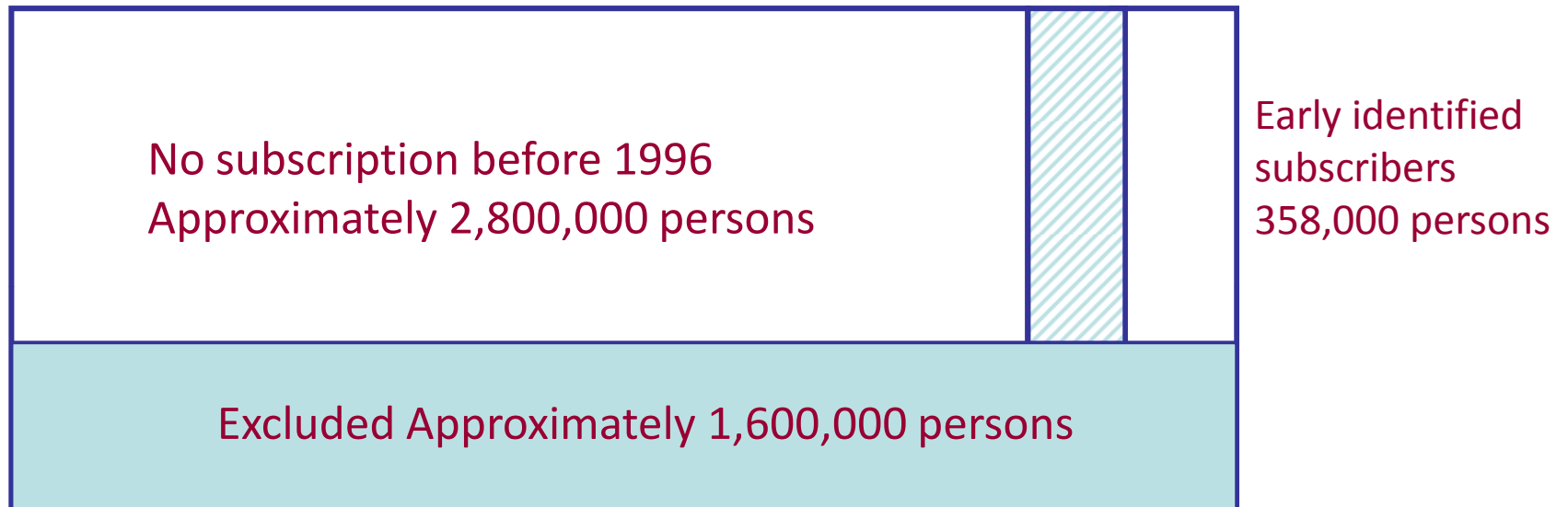
- Need of monitoring of incidence time trends

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World Health Organization

Danish cohort: updated analyses to 2007

Frei et al, BMJ, 2011

Exclusion of subscriptions contracted prior to 1987 (mainly car phones)
Link with individual data on income, education available for all Danes born after 1925, older than 30, after 1990.

No subscription before 1996
Approximately 2,800,000 persons

Early identified subscribers
358,000 persons

Excluded Approximately 1,600,000 persons

Not identified subscribers

Analysis: observed versus expected cases Stratified by sex, age, calendar period, education, income
Results: 356 glioma cases among early subscribers,
 Men gliomas - 10-12 years: IRR=1.06 (0.85-1.34)
 Men gliomas $\geq$13 years: IRR=0.98 (0.70-1.36)

- Thank you for your attention

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