Cell phones and cancer risk

Professor Anssi Auvinen, MD, PhD
Tampere University, Tampere, Finland
STUK – Radiation and Nuclear Safety Authority
Helsinki, Finland

DCEG Radiation Epidemiology and Dosimetry Course 2019
Declaration of interests

- Member of INTERPHONE study group, PI of the Finnish Interphone study
- Member of COSMOS study group, PI of the Finnish COSMOS study
- Former member of the SCENIHR committee, ICNIRP PG, and SSM Expert Group
- Research funding through governmental research program and/or firewall from Nokia, network operator Telia and Mobile Manufacturers’ Forum (currently MWFAI)
Outline

- Background: Introduction to RF-EMF and cellular phones
- Issues in epidemiological studies of cellular phones
- Results of major epidemiological studies
- Analysis by location
- Incidence trends
- Overall assessment
Background
Electromagnetic field
Radiofrequency fields

<table>
<thead>
<tr>
<th>CLASS</th>
<th>FREQUENCY</th>
<th>WAVELENGTH</th>
<th>ENERGY</th>
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<tbody>
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<td>300 Hz</td>
<td>1 pm</td>
<td>1.24 MeV</td>
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<td>30 Hz</td>
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<td>124 μeV</td>
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<td>1 Mm</td>
<td>1.24 peV</td>
<td></td>
</tr>
<tr>
<td>30 Hz</td>
<td>10 Mm</td>
<td>124 feV</td>
<td></td>
</tr>
</tbody>
</table>

From 3 kHz to 300 GHz
The Electromagnetic Spectrum
Sources of radiofrequency fields
RF field from various sources

Energy absorbed, SAR (W/kg)

- GSM
- WLAN
- Baby monitor
- DECT
- Microwave oven
- Base station
Field strength (SAR) from a mobile phone
How do cellular phones work?
Why is it ‘cellular’?

- Area covered by a base station is a ‘cell’
- Base stations linked to each other to form a network
Issues in epidemiological studies of cellular phones
Introduction

- Health risks from exposure to radiofrequency electromagnetic fields a topic of ‘epidemiology wars’
- Highly contested interpretation of the evidence
- Some researchers unfailingly report major increases in risks that are not replicated in other studies
- Are mobile phones the ‘new tobacco’? An emerging major threat to public health?
- Comprehensive review of expert panels by IARC, AGNIR, SCENIHR, SSM and others
Major challenges

- Exposure assessment
- Recall bias in case-control studies
- Possible interference of brain tumor on recall and cognitive function
- Lack of identified biological mechanism, and hence a proper concept of dose (or even identification of the main aspect relevant for risk)
- Unclear latency
Exposure assessment for mobile phone use

- Questionnaire or interview
  - Retrospective
  - Inaccurate, possibility of bias

- Network operator records
  - Usually only ownership of a subscription
  - Who is the actual user?
  - Corporate subscriptions?
  - Amount and mode of use?

- Output power best proxy indicator of SAR
  - Not available in any epidemiological study
Determinants of cell phone output power

- Network/phone technology
  - Increasing efficacy, lower output with each generation
    NMT >> GSM >> UMTS >> LTE
  - Automatic power control: Minimal power needed for proper transmission
- Proximity to base station
  - If heavy traffic, a call can be referred to a more distant base station
- Calling while in transport
  - Wave-like increases and decreases in output power (first decreasing and then increasing distance)
- Rural area with higher power
- Hands-free devices minimise the exposure to the head (do not affect power)

How accurate is recalled usage data? (1)

- Number of calls underestimated and **duration overestimated**
- Agreement between reported and recorded **diminished with time**
- **Kappa** 0.66 - 0.51 - 0.31** for quintiles of call duration**
  - Kiyohara JESEE 2018: Comparison of recorded (SMP phone) and reported, N=94
  - Reported after the 1-month study period, at 1 year and at 4 years
- **Kappa for call duration** 0.50, **number of calls** 0.39
- **Overreporting** x1.7 for call numbers, x2.8 for all duration
  - Parslow Radiat Prot Dosim 2003 questionnaire vs operator data for 6-mo period, N=93
How accurate is recalled usage data? (2)

- Mireku et al. *Environ Res* 2018
- 350 participants with self-reported vs. operator-recorded call data
- Call duration overestimated by 45-59% of participants (underestimated by 11-16%)
- Weighted kappa 0.08-0.10 for call duration (7 categories)
- Sensitivity for identifying heavy use 13%

- Toledano *Int J Hyg Environ Health* 2018, 67,947 participants of COSMOS study
- Self-reported vs. operator-recorded call data
- Weighted kappa 0.50 for call duration (six categories)
Issues in recall and reporting in cases: Recall bias

- A form of information bias
- Typical for case-control studies with self-reported exposure
  - Cases interviewed after dg about exposure prior to dg
- Classically, cases are highly motivated, want find an explanation for their disease, attribute it to a specific factor
- Therefore, provide a more complete and comprehensive account of their exposures than controls
  - Root cause is under-reporting of exposure in cases
- In addition, possible over-reporting (exaggeration) of exposures in cases
  - Not classical form of recall bias
  - A case knows side of brain tumor, which could affect reported laterality of use
Issues in recall and reporting in cases (2)

- Cognitive and memory function may be affected by the tumor
- Physiological effect depending on the anatomic site
- Psychological impact of severe major disease, a life-changing effect
- Lower quality of data in cases??
- Mainly for malignant tumors, less of an issue for meningioma, schwannoma/neuroma
Is there recall bias in reporting?

Overreporting of use in distant past more pronounced in cases than controls


Mean difference in year of start between reported and recorded

- Cases  +0.25
- Controls -0.51

- 96 vestibular schwannoma cases and 111 controls
- Pettersson et al. 2015
Epidemiological findings
Evidence from epidemiology

- Glioma, meningioma, schwannoma/neurinoma
- Case-control studies: Interphone, Hardell, CEFALO, CERENAT
- Cohort studies: Danish subscribers, UK Million Women
  - Less prone to recall bias
- Case-case studies: Within Interphone (Larjavaara, Cardis, Grell)
- Time trend analyses: Nordic countries, UK, US, other populations
# Early studies of cellular phones and cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Dg years</th>
<th>Duration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscat 2000</td>
<td>469 brain cancers</td>
<td>1994-1998</td>
<td>Max 4+ yrs (mean 2.8 yrs)</td>
</tr>
<tr>
<td>Inskip 2001</td>
<td>489 gliomas, 197 meningiomas, 96 neurinoma</td>
<td>1994-1998</td>
<td>Max 5+ years (22 cases)</td>
</tr>
<tr>
<td>Auvinen 2002</td>
<td>398 brain cancer, 34 salivary gland tumors</td>
<td>1996</td>
<td>Max &gt;2 years (17 cases)</td>
</tr>
<tr>
<td>Lönn 2006</td>
<td>Salivary gland</td>
<td>2000-2002</td>
<td>Max &gt;10 yrs (6 cases)</td>
</tr>
<tr>
<td>Sadetzki</td>
<td>Salivary gland (parotid)</td>
<td>2001-2003</td>
<td>Max &gt;10 years (13 cases)</td>
</tr>
</tbody>
</table>

U.S. Cohort of 255,868 subscribers with 6 brain cancer deaths in 1-year follow-up (Dreyer et al. 1999)
## Major studies of cellular phones and cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Glioma</th>
<th>Meningioma</th>
<th>Acoustic neurinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardell</td>
<td>382/1844</td>
<td>346/1625</td>
<td>58/316</td>
</tr>
<tr>
<td>Interphone</td>
<td>252/2708</td>
<td>110/2409</td>
<td>68/1105</td>
</tr>
<tr>
<td>Yoon</td>
<td>-/285</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coureau</td>
<td>22/757</td>
<td>10/582</td>
<td>-</td>
</tr>
<tr>
<td>Han</td>
<td>-</td>
<td>-</td>
<td>92/343</td>
</tr>
<tr>
<td>Pettersson</td>
<td>-</td>
<td>-</td>
<td>103/422</td>
</tr>
<tr>
<td>Frei</td>
<td>117/356</td>
<td>29/80</td>
<td>15/404</td>
</tr>
<tr>
<td>Benson</td>
<td>135/571</td>
<td>63/251</td>
<td>14/96</td>
</tr>
</tbody>
</table>

Aydin et al. JNCI 2011: Childhood and adolescent brain tumors, no long term use
Glioma risk with any mobile phone use in Hardell studies

![Bar chart showing glioma risk with mobile phone use by year and type (Analog (NMT) and Digital (GSM)). The chart indicates higher risk from 2000 to 2003 compared to 1994 to 1996.]
Glioma risk with duration of use in Hardell studies
Acoustic neuroma in Hardell studies

Hardell et al. 2013
Meningioma risk in Hardell studies

Time since start of use

- Mobile
- Cordless

Categories: <5, 5-10, 10-15, 15-20, 20-25
Interphone study

- International collaborative study in 13 countries
- Glioma, meningioma, acoustic neuroma (vestibular schwannoma)
- Cases diagnosed 2000-2004
- Cases enrolled prospectively with interview an average 3 mo from dg
- Participation 65% cases and 53% controls
  - Proxy interviews for 13% of glioma cases
“Apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use”

Interphone study group, Int J Epid 2010
Cumulative call-time and meningioma risk

Ever regular use OR=0.79 (0.68-0.91)

Call hours

Interphone study group, *Int J Epid* 2010
Cumulative call-time and acoustic neuroma

Ever regular use OR=0.95 (95% CI 0.77-1.17)

Schuz et al, Cancer Epidemiol 2011
Danish cohort study

- Exposed group: 358,403 subjects with private subscription in 1982-1995
  - Excluding 28% with corporate-owned subscription
- Poisson regression analysis
  - Confounders: Income, education
- Follow-up 1990-2007 (mean length 10.6 yrs)
  - 10,729 CNS tumors
Duration of use and brain tumor incidence

Frei et al. 2011
Duration of use and CNS cancers

Frei P et al. *BMJ* 2011;343:bmj.d6387
UK cohort study – Million Women Study

- Benson et al. *Int J Epid* 2013
- 791,710 women recruited 1996-2001 at mammography screening
- Questionnaire for collection of exposure data
  - At baseline and a re-survey in 2009
  - 500,000 ever users and 300,000 never-users
- Follow-up on average for 7 years
  - 1261 incident cases
Mobile phone use in the Million Women Study
Duration of use and risk of brain tumors

Benson et al. *Int J Epid* 2011
Million women study extended follow-up (up to 2011)
Meta-analyses of mobile phone use

- Röösli et al. *Annu Rev Public Health* 2019: Focus on long-term use
  - "Epidemiological studies do not suggest increased brain tumor risk with mobile phone use, although some uncertainty remains about long latency periods, rare subtypes and usage in childhood"

- Wang et al. *World Neurosurg* 2018: Wireless phone (DECT), glioma only
  - "Ever use of wireless phones was not significantly associated with adult glioma, but there could be risk in long-term users"

- Bortkiewicz et al. *Int J Occup Med Environ Health* 2017: Overlap between studies??
  - "The results support the hypothesis that long-term use of mobile phone increases risk of intracranial tumors, especially ipsilateral exposure"
## Meta-analysis - glioma

**Glioma (long-term use)**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SEX</th>
<th>CASES</th>
<th>RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frei et al. 2011</td>
<td>M</td>
<td>117</td>
<td>1.04 (0.85, 1.26)</td>
</tr>
<tr>
<td>Frei et al. 2011</td>
<td>F</td>
<td>10</td>
<td>1.04 (0.56, 1.95)</td>
</tr>
<tr>
<td>Benson et al. 2014</td>
<td>F</td>
<td>135</td>
<td>0.77 (0.62, 0.96)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>0.92 (0.72, 1.16)</td>
</tr>
<tr>
<td><strong>I^2 = 52.2%, p = 0.124</strong></td>
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</tbody>
</table>

| **Case control** |     |       |               |
| Interphone 2010  | M+F | 252   | 0.98 (0.76, 1.26) |
| Coureau et al. 2014 | M+F | 22    | 1.61 (0.85, 3.09) |
| Yoon et al. 2015 | M+F | 100   | 1.04 (0.52, 2.09) |
| Hardell & Carlberg 2015b | M+F | 382   | 1.69 (1.40, 2.03) |
| **Subtotal**   |     |       | 1.30 (0.90, 1.87) |
| **I^2 = 76.0%, p = 0.006** |     |       |               |

| **Overall**     |     |       | 1.11 (0.85, 1.46) |
| **I^2 = 82.0%, p < 0.001** |     |       |               |
# Meta-analysis - meningioma

## Meningioma (long-term use)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SEX</th>
<th>CASES</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Frei et al. 2011</td>
<td>M</td>
<td>21</td>
<td>0.90 (0.57, 1.42)</td>
</tr>
<tr>
<td>Frei et al. 2011</td>
<td>F</td>
<td>8</td>
<td>0.93 (0.46, 1.87)</td>
</tr>
<tr>
<td>Benson et al. 2014</td>
<td>F</td>
<td>63</td>
<td>1.08 (0.78, 1.49)</td>
</tr>
<tr>
<td><strong>Subtotal (I² = 0.0%, p = 0.794)</strong></td>
<td></td>
<td></td>
<td>1.00 (0.78, 1.29)</td>
</tr>
<tr>
<td><strong>Case control</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Interphone 2010</td>
<td>M + F</td>
<td>110</td>
<td>0.83 (0.61, 1.14)</td>
</tr>
<tr>
<td>Coureau et al. 2014</td>
<td>M + F</td>
<td>10</td>
<td>1.57 (0.64, 3.86)</td>
</tr>
<tr>
<td>Carlberg &amp; Hardell 2015</td>
<td>M + F</td>
<td>346</td>
<td>1.10 (0.92, 1.32)</td>
</tr>
<tr>
<td><strong>Subtotal (I² = 37.0%, p = 0.204)</strong></td>
<td></td>
<td></td>
<td>1.02 (0.80, 1.30)</td>
</tr>
<tr>
<td><strong>Overall (I² = 0.0%, p = 0.596)</strong></td>
<td></td>
<td></td>
<td>1.03 (0.90, 1.17)</td>
</tr>
</tbody>
</table>

Röösli et al. 2019
# Meta-analysis – acoustic neuroma

## Neuroma (long-term use)

<table>
<thead>
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<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schütz et al. 2011b</td>
<td>M</td>
<td>15</td>
<td>0.88 (0.52, 1.48)</td>
</tr>
<tr>
<td>Benson et al. 2014</td>
<td>F</td>
<td>14</td>
<td>1.17 (0.60, 2.27)</td>
</tr>
<tr>
<td><strong>Subtotal ((I^2 = 0.0%), (p = 0.509))</strong></td>
<td></td>
<td></td>
<td><strong>0.98 (0.65, 1.48)</strong></td>
</tr>
<tr>
<td><strong>Case control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interphone 2011</td>
<td>M + F</td>
<td>68</td>
<td>0.76 (0.52, 1.11)</td>
</tr>
<tr>
<td>Han et al. 2012</td>
<td>M + F</td>
<td>92</td>
<td>1.29 (0.69, 2.43)</td>
</tr>
<tr>
<td>Hardell et al. 2013b</td>
<td>M + F</td>
<td>58</td>
<td>2.49 (1.74, 3.56)</td>
</tr>
<tr>
<td>Pettersson et al. 2014</td>
<td>M + F</td>
<td>103</td>
<td>1.11 (0.76, 1.61)</td>
</tr>
<tr>
<td><strong>Subtotal ((I^2 = 85.8%), (p &lt; 0.001))</strong></td>
<td></td>
<td></td>
<td><strong>1.29 (0.74, 2.23)</strong></td>
</tr>
<tr>
<td><strong>Overall ((I^2 = 78.3%), (p &lt; 0.001))</strong></td>
<td></td>
<td></td>
<td><strong>1.19 (0.80, 1.79)</strong></td>
</tr>
</tbody>
</table>

Relative risk

Röösli et al. 2019
Analyses of tumor location
Local field – local effect?
Glioma location

888 cases from 7 Interphone centers

Larjavaara *Am J Epid* 2011
Distribution of gliomas among cellular phone users vs non-users

In users, 22% within 5 cm of external meatus of the ear, among non-users 24% (OR=0.90, 95% CI 0.65-1.26)
Gloma location by cell phone usage

Grell AJE 2016
792 cases, 13 Interphone centers

Distance

<55 55-75 75-95 95-115 >115

<6 yrs use >6 yrs use <200 hrs use >200 hrs use
Danish cohort: RR by location

Frontal 1.13 (0.89-1.45)

Parietal 0.73 (0.50-1.05)

Temporal 1.13 (0.86-1.48)

Occipital 1.47 (0.87-2.48)

Cerebrum 0.90 (0.67-1.22)

Frei et al. BMJ 2011
Incidence trends
Reality check

- If use of mobile phones increases brain tumor risk, we should be able to observe increasing trends in incidence at some point
  - Population coverage ~100%, widely adopted since late 1990’s
- How large effect?
- What amount of cellular phone use?
- When does it occur (induction period or lag/latency)?
Observed and predicted incidence, Nordic countries

Deltour et al. *Epidemiology* 2012
Observed and expected glioma incidence in the U.S.

Little et al. *BMJ* 2012
Incidence of adult glioma in Finland

Incidence 7.7/100,000
Men: 9.3, women: 6.5

No obvious trend
APC: +0.1% (95% CI: -0.5, +0.7)
For 2007-2016, APC -0.5%

For temporal tumors,
APC -0.6% (-1.8, +0.5)

Natukka et al. *Acta Oncol* 2019
Latest incidence trends, children, Nordic countries
Summary and conclusions
IARC carcinogenicity review

- Radiofrequency EMF classified in 2102 as 2B – possibly carcinogenic to humans
  - Limited evidence in humans and experimental animals
  - Similar assessment as for ELF-EMF
- Based on epidemiological studies of glioma and acoustic neuroma
  - Interphone: Highest amount of cumulative use, ipsilateral use, temporal lobe tumors
  - Hardell studies and a Japanese case-control study
- Minority opinion suggested ‘inadequate evidence’ due to null findings in cohort studies and temporal trends
Summary

- Case-control studies have not shown strong evidence for increased brain tumor risk in relation to mobile phone use
  - Some indications of increased risk, but with an inconsistent pattern
  - Location of gliomas not affected by mobile phone use, though some discrepancy in results
- Real world data do not show increases in brain tumor incidence trends <20 years after large-scale adoption of mobile phones
- Cohort studies show little indication of increased risks
  - COSMOS substantially larger, with quantitative call-time data
- There are still uncertainties but the balance of evidence post-IARC weighs toward no major health impact
Developments awaited

- MobiKids study
- COSMOS Cohort Study of Mobile Phone Use and Health
  - Swe-Fin-Den-UK-NL-Fra
  - 260,000 participants
  - Follow-up from 2009-2010
  - Analyses of tumor risks pending
- IARC carcinogenicity review to be revised
ICNIRP summary

- Extensive research has been undertaken in relation to exposure to HF fields used specifically in mobile telephony.
- Risk of tumors in close proximity to the ear where the phone is held, e.g. brain tumors, has been a key focus, some studies reporting a slight increase in risk for long-term and heavy mobile phone users.
- Reporting biases and weaknesses of the studies may explain the observed findings.
- Several studies have not reported any increase in brain tumors with mobile phone use.
- The increased risk observed in some of the epidemiological studies is inconsistent with the stable frequency of occurrence of these cancers in the population.
- **The overall evaluation of all the research on HF fields leads to the conclusion that HF exposure below the thermal threshold is unlikely to be associated with adverse health effects.**
Quiz (1)

Exposure assessment in studies of cancer risk associated with mobile phone use need to overcome methodological challenges related to:

A. Recall bias
B. Random error/misclassification in self-reported usage
C. Lack of a physical dose concept
D. All of the above
Quiz (1)

Exposure assessment in studies of cancer risk associated with mobile phone use need to overcome methodological challenges related to:

A. Recall bias
B. Random error/misclassification in self-reported usage
C. Lack of a physical dose concept
D. All of the above
Evidence supporting an increased risk of brain tumors is mainly

A. Increasing incidence trends
B. Positive results from cohort studies
C. Increased risks found for meningioma
D. None of the above
Evidence supporting an increased risk of brain tumors is mainly

A. Increasing incidence trends
B. Positive results from cohort studies
C. Increased risks found for meningioma
D. None of the above