Should we Hang Up on the Debate about Cell Phones and Cancer Risk?

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Overview

• Cell phones (mobile phones) and cancer risks:
  > rationale for studies
  > characteristics of exposure
  > biological effects
  > results of epidemiologic studies
  > strategies for reducing exposure
• Other radiofrequency radiation exposures & cancer risks
• Methodologic & other challenges in studying cancer risks associated with cell phone use
• Scientific gaps
• Ongoing research
How risky is cell-phone radiation?

The Food and Drug Administration says the "weight of scientific evidence has not linked cell phones with any health problems," including brain tumors from the low-level radiation that phones emit in normal use. Yet in the past year San Francisco lawmakers have enacted an ordinance requiring that cell phones disclose the amount of radiation emitted, and Rep. Dennis Kucinich (D-Ohio) announced plans to push for radiation warnings on all cell phones.

Phone manufacturers are required by federal law to package every cell phone with information about its specific values only to ensure that maximum radiation exposure falls below the level at which experts agree there could be adverse health effects.

Still, consumers are caught in the middle, trying to resolve conflicting messages from regulators and legislators. (The latter include those in the European Parliament who have called for stricter limits on exposure to cell-phone radiation, which have been criticized by many scientists.)

Consumers Union believes a number of measures would benefit consumers:

• The U.S. needs a national research
Cell Phones & Brain Tumors: Rationale

- Radiation & cancer: long-standing concern
- Electromagnetic fields and cancer: passionate & polarized views
- Rapid increase in cell phone use since 1990s

Cell Phone Subscribers in U.S. (1985-2010)*

*Cellular Telephone Industry Association (CTIA)
Early analog phones (450 & 900 MHz)

Digital phones (1800-1900 MHz)

Universal mobile telecommunications system (1900-2200 Mhz)
Population Radiofrequency Exposures

- Exposures ubiquitous, but limited measurements
- Exposures decline notably with increased distance
- Residential sources & levels:
  - cell phones: ≤ 0.25 watt
  - Wi-Fi, microwave ovens and others: indoor levels 1-100 times lower than outdoor levels
- Outdoor exposures to general population:
  - radio & TV transmitters: up to 1 megawatt
  - cell phone base stations: ≥ 1 watt
- Occupational maximum permissible exposure limits:
  - vary with frequency range
  - measured in mW/cm² time-averaged
Biological Effects of Radiofrequency Radiation

• Radiofrequency radiation energy:
  - insufficient for breaking molecular bonds
  - most exposures are orders of magnitude less energy than x-rays

• Primary biological effects:
  - thermal
    > measurable at high power levels
    > minimal at low power levels (cell phones)
  - non-thermal
    > activation of proteins and genes; unclear relevance to long-term effects

• Conundrum for animal studies:
  - exposures need to be higher than typical exposures experienced by humans
  - need to avoid thermal effects
Early Epidemiological Studies

• 1993: anecdotal TV report
  — Congressional hearings
  — trade industry (CTIA) commits $25 million

• 1994: 4 studies launched
  — 3 case-control studies
  — 1 cohort study Denmark
Summary: Early Studies of Gliomas

- Exposure assessment:
  - case-control studies: questionnaires
  - cohort study: subscriber listings

- Case-control studies: No associations

- Cohort study: No excess in subscribers vs non-subscribers
Unresolved Issues following Initial Studies

• No information on long-duration, heavy users

• Relevant surrogate exposure metric unknown:
  - years of regular use?
  - cumulative numbers of phone calls?
  - cumulative hours of use?
  - other?

• Biological and mechanistic issues in carcinogenesis
Next Generation of Epidemiologic Studies

• Extended follow-up of Danish Cohort Study (2006; 2011)

• INTERPHONE case-control studies (13 countries pooled data)
  - individual study publications (2002-2008)
  - pooled study (2010)
Extended Danish Cohort Study*

- 358,403 persons with first cell phone subscriptions in 1987-1995 and followed up through 2007
- Compared incidence >10 yrs use vs. non-subscribers

<table>
<thead>
<tr>
<th>CNS tumor type</th>
<th>Sex</th>
<th>IRR</th>
<th>(95%CI)</th>
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<tbody>
<tr>
<td>Glioma</td>
<td>Men</td>
<td>1.04</td>
<td>(0.85 – 1.26)</td>
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<tr>
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<td>Women</td>
<td>1.04</td>
<td>(0.56 – 1.95)</td>
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<tr>
<td>Meningioma</td>
<td>Men</td>
<td>0.90</td>
<td>(0.57 – 1.43)</td>
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<td>Women</td>
<td>0.93</td>
<td>(0.46 – 1.87)</td>
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- No increase in risk among subscribers with >10 years use

*Frei et al. BMJ, 2011
<table>
<thead>
<tr>
<th>INTERPHONE* Study of Brain &amp; Other Tumors*</th>
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<tbody>
<tr>
<td>• Denmark</td>
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<td>• Japan</td>
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<td>• Canada</td>
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*13 countries where cell phones used earlier than in U.S.
Glioma – INTERPHONE Study

- 2,708 glioma patients (64% participation); 2,972 controls (53% participation)
- Reduced risks for years since 1st use, duration of use, cumulative number of calls, and for digital phone use
- ↑ risks for highest decile of call time: OR = 1.40, 95%CI = 1.03-1.89)
- ↑ risk for use on same side of head as tumor, but ↓ risk on opposite side of head, BUT risks highest for short-term users

Meningioma – INTERPHONE Study

- ORs < 1.0 in lowest 9 deciles of cumulative call time, and OR=1.15, 95%CI=0.81-1.62) in highest decile
  - No excess risk among medium and long-term users, but ↑ risk in short-term users
- Reduced risks for temporal lobe tumors for regular use and for all metrics; same for other anatomic sites
- Borderline elevated risk for tumors on same side as phone use (OR=1.07, 95%CI=1.00-1.16)

*INTERPHONE Study Group. Int J Epidemiol (2010)*
Acoustic Neuroma – INTERPHONE Study*

- 1,105 cases, 2,145 controls
- Risk estimate: [OR (regular use = 0.85; (CI:0.69-1.04)]
- No overall increase in risk for cumulative hours of use, duration of use
- Non-significant increase in 10th decile of cumulative use, but notable ↓↓ in 9th decile
- No excess for use of phone on same side of head as tumor

*INTERPHONE Study Group. Cancer Epidemiol (2011)
Conclusions for glioma and meningioma:
> “overall no increase…”
> “for glioma…suggested increases at highest exposure levels, but biases and errors prevent causal interpretation”
> “for meningioma…little evidence to counter a global null hypothesis”
> “the possible effects of long-term heavy use of mobile phones require further investigation”
• Conclusions for acoustic neuroma:
  > no overall association
  > non-significant increase in 10\(^{th}\) decile of cumulative use could be due to chance
Case-Control Studies of Cell Phone Use and Malignant Brain Tumor Risk in Sweden*

• Population:
  > incident cases adults ages 20-80
  > 1,251 cases (85% participation) vs. 2,438 matched (age, sex, region, & vital status) population controls (84% participation)

• Exposure assessment:
  > self-administered questionnaires to subjects or next of kin

• Results:
  > ↑ risk with increasing latency & cumulative hours of use
  > highest risks for glioma with >10 yrs latency (OR=2.7, 1.9-3.7) and with first use before age 20 *OR=4.9, 2.2-11)

Hardell L et al. *Int J Oncology* (2011)
International Agency for Research on Cancer

- IARC: Vol 102, 2013
- Classified cell phone use/RF exposure 2B
- Basis of assessment:
  > INTERPHONE results
  > Swedish pooled case-control studies
# Epidemiologic Studies Post IARC Report

## Cohort design: Million women prospective study*

- 791,710 women followed up an average of 7 years
- 571 gliomas, 251 meningiomas, 96 acoustic neuromas
- gliomas & meningiomas: no associations for ever or for 10+ years use
- acoustic neuroma: increased risk for long-term use & dose-response trend

## Case-control design: CERENAT§

- 253 gliomas, 194 meningiomas, 892 controls
- participation: gliomas (66%), meningiomas (75%), controls (45%)
- ↑ gliomas & meningiomas with cumulative hours of use
- ↑ gliomas with occupational use, urban use
- ↑ gliomas on same side as use but ↓ ↓ on opposite side

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* Benson VS et al. *Int J Epidemiol* (2013)

Inskip PI et al (2010); Glioma incidence downward or flat in U.S., 1992+


Projected* vs. Observed Glioma Incidence Rates

- Simulated vs observed Nordic glioma incidence rates†
  - Assumed risk of 1.2 – 2.0 and latencies of 5 – 15 years
  - Excess risks were incompatible with observed 1979-2008 rates

- Projected vs. observed U.S. glioma incidence rates§
  - Projected from Interphone consistent with observed 1997-2008
  - Projected from Swedish studies at least 40% higher than observed and thus Swedish risks not reflected in U.S. incidence trends

* INTERPHONE Study (2010) and Swedish studies by Hardell L et al (2011)
Reducing RF Exposures from Cell Phones*

• Cell phones for short, landlines for longer calls

• Hands-free devices except Bluetooth, which has higher exposures

• Use cell phones with lowest SARs

• Text rather than call (neither when driving)

• Phone on belt or bag


Occupational and Environmental Studies of RF Exposure and Cancer Risks
Workers Manufacturing Cell Phones*

- RF exposure: job exposure matrix
- No association between RF & brain cancer mortality

U.S. Navy Veterans of Korean War*

- 49,581 Navy veterans
- Potential exposure to high-intensity radar
- No ↑ brain cancer
- Increased non-lymphocytic leukemia in subgroup

Cell Phone Base Stations and Cancer Risk

- Major concern is pediatric cancer risk residing near base stations
- Few studies
- No increase in risk associated with individual level exposures*
- Need better exposure assessment in populations with high RF

Methodological Issues: Focus on INTERPHONE Study
Limitations

- Exposure assessment

Methodologic Investigations


<table>
<thead>
<tr>
<th>Limitations</th>
<th>Methodologic Investigations</th>
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</table>
How Methods Studies Informed Study Results

• INTERPHONE study interpretation:
  >“We have no certain explanation for the overall reduced risk of brain cancer among mobile phone users…”
  > ”Selection bias is almost certainly a contributor”
  >“Some evidence that very high users had excess glioma, but inconclusive due to possible bias.”
  >“Results are uninformative for longer lag periods since few subjects used cell phones more than 12 years.”

• Non-participation bias (non-participants had lower prevalence of cell phone use) could have caused reduction of OR of 5-15%
Challenges in Studying Cell Phone Use and Cancer risks
Challenges in Assessing Cancer Risks Associated with Technological Changes
Challenges in Assessing Cancer Risks Associated with Technological Changes
# Mechanisms and Biology Poorly Understood

## Limitations

- Relevant metric unknown

- Biologically relevant surrogate measure?
  - cumulative hours of use?
  - duration of use in years?
  - cumulative numbers of calls?

- Mechanism for occurrence of neoplasms unknown

- Tumor biology poorly understood

## National Toxicology Program

- large rodent RF studies

- mimic human exposure (up to 10 hrs/day)

- study 900 and 1900 MHz & 2 modulations in U.S

- specially designed labs

- final results in 2016
Ongoing Epidemiologic Studies
Rationale for Ongoing Studies

- Research driven by public concern about new communication technologies which have dramatically increased in a short time period.

- To date no clear risks observed but research needed to monitor risks of long term use and/or new applications:
  - Prospective studies among adults
  - Childhood studies
The Cosmos Project
International Cohort Study of Mobile Phone Use and Health

Denmark     Sweden       Finland    Netherlands   U.K.

Courtesy of R. Vermeulen
Cohort: 250,000+ Ages 30-59

The Cosmos Questionnaire

Every 4 Years

DATA

Health Registers (Country Dependent)

On demand

Mobile Phone Usage Data

Yearly

Courtesy of R. Vermeulen
### Main Health Endpoints

<table>
<thead>
<tr>
<th>Main health outcomes</th>
<th>Cancer</th>
<th>Neurological</th>
<th>Other diseases</th>
<th>Non-specific symptoms</th>
<th>General health (HRQoL)</th>
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<tbody>
<tr>
<td></td>
<td>Malignant brain tumors</td>
<td>Alzheimer’s</td>
<td>Cardio/cerebrovascular diseases</td>
<td>Memory problems (e.g., dementia)</td>
<td>General health (HRQoL)</td>
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<tr>
<td></td>
<td>Benign brain tumors (including acoustic neuromas)</td>
<td>Parkinson’s</td>
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<td>Parkinson-like symptoms</td>
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<td></td>
<td>Breast cancer</td>
<td>Amyotrophic Lateral Sclerosis</td>
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<td>Depressive symptoms</td>
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<td>Hematopoietic cancers</td>
<td>Multiple Sclerosis</td>
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<td>Sleep problems, fatigue, headache, tinnitus, etc</td>
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Courtesy of R. Vermeulen
# Cosmos: Advantages & Disadvantages

<table>
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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Improved exposure assessment</td>
<td>Large populations needed to study rare outcomes</td>
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<tr>
<td>Multiple endpoints</td>
<td>Attrition (loss of participation)</td>
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<td>Rapid assessment of new hypotheses</td>
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Courtesy of R. Vermeulen
Cell Phone Use & Childhood Cancer: Rationale

- Greater susceptibility of developing nervous systems
- Greater penetration of RF relative to head size
- Longer exposure than adults
- Only 1 epidemiologic study
- Ongoing childhood cohort studies (N=200,000)
Childhood Cell Phone Use & Brain Tumor Risk*

- **Population:**
  - incident tumors ages 7-19, Denmark, Norway, Sweden, Switzerland
  - 352 cases (83% participation) vs. 646 controls (71% participation)

- **Exposure assessment:**
  - questionnaires to children and parents & operator records

- **Results:**
  - no association with regular use, duration of use, cumulative use or side of head where phone held; ↑ risk with time since 1st use

- **Conclusion:** little evidence of a relationship

MOBI-Kids

Courtesy of R. Vermeulen

http://www.mbkds.com
Objectives

• Overall objective
  – To assess the potential tumorigenic effects of childhood and adolescent exposure to RF and RF from mobile telephones on tumours of the central nervous system

… build upon the methodological experience of INTERPHONE

Courtesy of R. Vermeulen
Study Design

• Case-control study
  – Cases (~2000)
    • benign and malignant brain tumours
    • ages 10-24
    • rapid ascertainment
  – Controls
    • 2 per case
    • hospital-based, to minimize selection bias related to non-participation
    • individually matched on age, sex, region
  – Estimated publication 2016

Courtesy of R. Vermeulen
Will Ongoing Epidemiologic Studies Clarify Whether Cell Phone Use Increases Cancer Risks?
