Mobile phone use and brain tumour risk: early warnings, early actions?

Authors: Lennart Hardell, Michael Carlberg and David Gee

Chapter 21 from Late lessons from early warnings: science, precaution, innovation- Report 2013

Exam protocol for
Terrestrial Ecozones and Ecosystems (MNF-eco 107)

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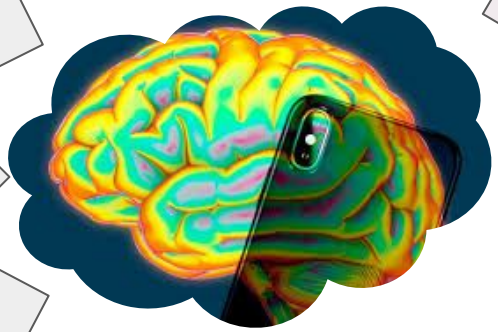
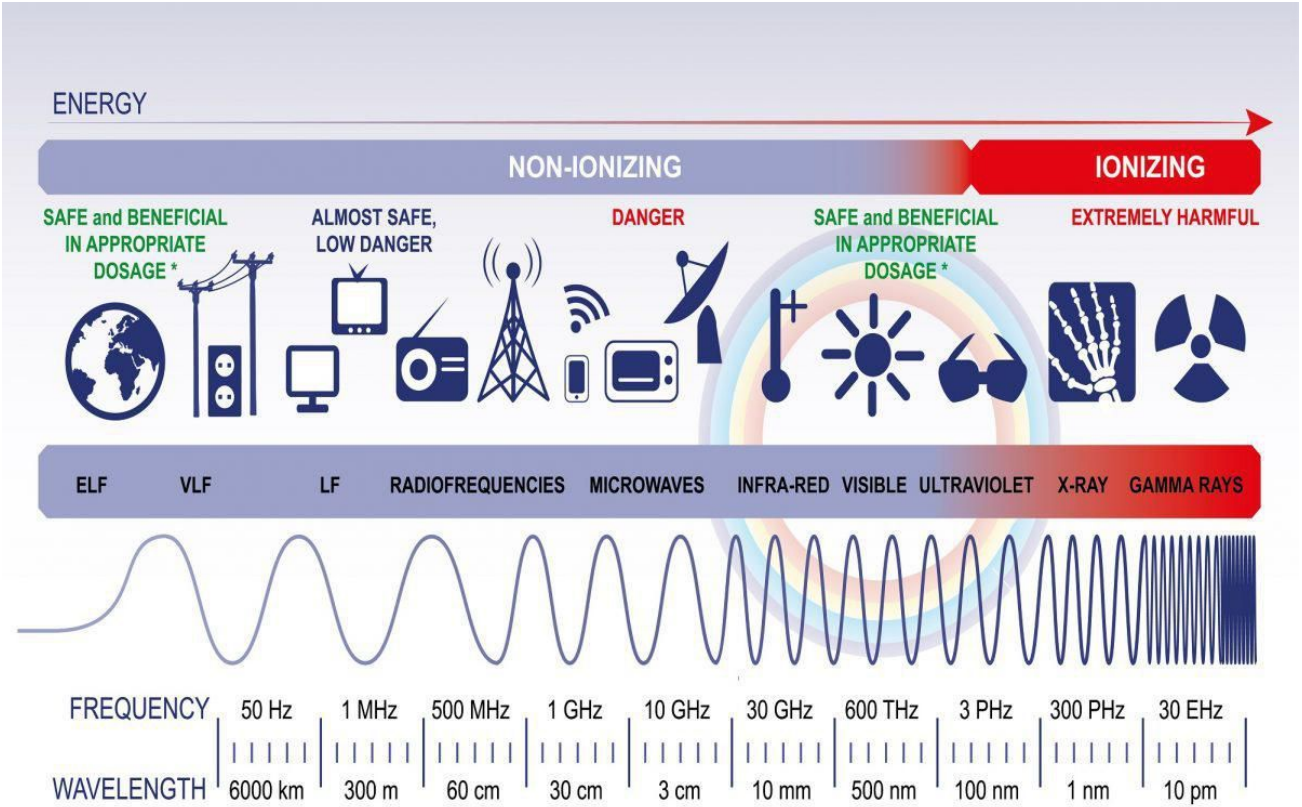
Outline

- Background Story
- Researchers' View
- Public Opinion
- Further Research
- Tools used
- Recommendations



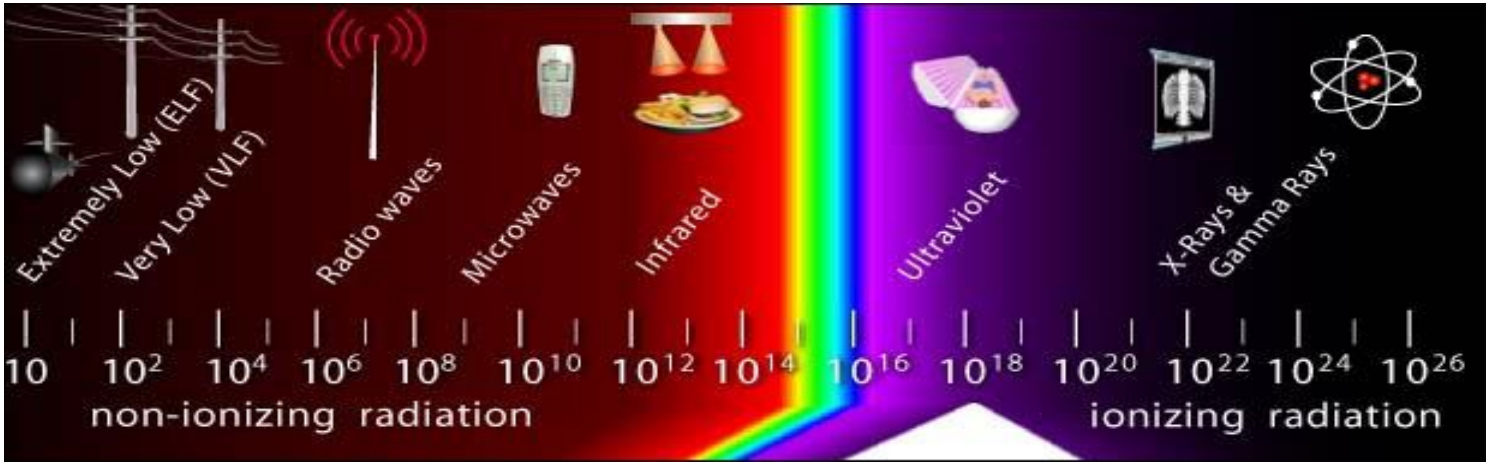
Electromagnetic Spectrum

Source: Forbes.com



What is Ionizing and Non- Ionizing radiation??

When the radiation has enough energy to ionize other atoms (can remove negatively-charged particles electors) in its path, it is referred to as "ionizing radiation



Source: United States Department of Labor, **Occupational Safety and Health Administration**

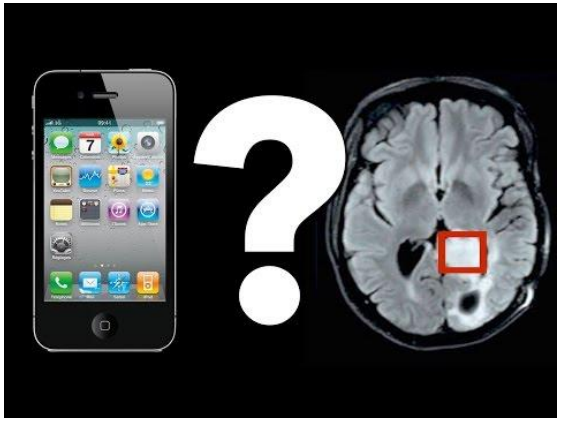
EMF frequencies used by the major mobile service providers in USA

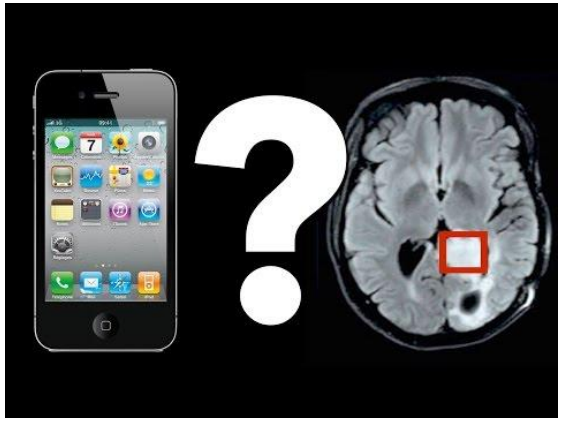
Provider	3G Frequency	4G Frequency	5G Frequency
AT&T	GSM/UMTS/HSPA+ 1900 MHz, 850 MHz	1900, 1700/2100, 850, 700 2300	850 MHz, 39 GHz
Sprint	CDMA 1900 MHz, 800 MHz	1900, 850, 2500	2.5 GHz
T-Mobile	GSM/UMTS/HSPA+ 1900 MHz, 1700/2100 MHz	1900, 1700/2100 700, 600	600 MHz, 28 GH, 39 GHz
Verizon	CDMA 850 MHz, 1900 MHz	1900, 1700/2100, 850, 700	28 GHz

https://www.allconnect.com/blog/cellular-frequency-bands

First video has approx. 1 M view on YouTube, and this number indicates that people are concerned about EMF (although the video is itself deceiving one).

In the second video the claim of first one is debunked





This video has more than 1.2 M views on YouTube, and mainly talking to the people how do they think about the consequences of EMF exposure

No conclusive evidence of correlation between wireless phone and brain tumor

Dr. Ross Walker, Preventive Health Expert and cardiologist at Sydney Heart Health Clinic

Brain simulation by wireless phone use shows no long term association

Tools Used

The total chapter is mainly summary of two study groups:

1. Hardel Group Studies (1,2,3,& 4), and
2. Interphone study by International Agency for Research on Cancer, IARC

Both group's approach were based on CASE-CONTROL study:

A brief overview on the statistical tools used in the studies are-

Odds Ratio, OR
Risk Ratio, RR
Standardized Incidence Ratio, SIR
Confidence Interval, CI
Statistical Significance, p-value

For recent study paper, they used-

Heterogeneity, I squared value to summarize the pooled result of meta analysis

OR: Odds ratio. The odds ratio is an estimate of the relative risk, showing how much more likely it is that someone who is exposed to a factor (e.g. cell phones) will develop an outcome (e.g. brain tumour) compared to someone who is not exposed. An OR of 1 indicates no risk, OR < 1 decreased risk and OR > 1 increased risk. For example, an OR of 1.5 indicates that those who are exposed have a 1.5 times higher risk of developing a disease compared to those who are not exposed.

SIR: Standardized incidence ratio. The SIR compares the observed number of cases in a specific population (e.g. cell phone subscribers) to the number of cases expected would the same rates apply as observed in a reference population (e.g. general population). A SIR of 1 indicates no risk, SIR < 1 decreased risk and SIR > 1 increased risk.

CI: Confidence interval. A confidence interval shows the uncertainty of the statistical estimate. In the case of OR and SIR, if the corresponding CI range does not cover 1.0, the result is considered **statistically significant**. Usually 95 % confidence intervals are reported indicating the range of the true OR/SIR with 95 % statistical confidence. The absence of 'statistical significance' can often be a weak guide to the strength of evidence for a risk compared to the power of a study to detect a risk ([5]).

Latency period. Time between first exposure and identification of the disease. For cancer, particularly the solid tumours like brain cancers in contrast to cancers of the blood, such as leukemia, the latency period can be from 15–45 years on average, depending on age at exposure, type and intensity of exposure ([6]) etc. This means that any study of cancer has to be at least as long as the average latent period for the tumour being studied before there will be any clear evidence of a cancer risk.

Tools Used

- Contingency Table
- Odds Ratio, OR
- Confidence level table
- Confidence Interval
- Is the result significant??

The aim of the analysis is to come to a conclusion whether the calculated difference is **Statistically** significant or not!

- Confidence Interval, CI
- Z- Score
- P-value
- Is the result significant??

Tools Used

- Contingency Table
- Odds Ratio, OR
- Confidence level table
- Confidence Interval

Control ⬇️ : Cases ➡	Tumor or symptom	No tumor or no symptom
Exposed to EMF	A	B
Not exposed	C	D

Odds Ratio, $OR = \frac{A*D}{B*C}$

An odds ratio (OR) is a measure of association between an exposure and an outcome.

source: US National Library of Medicine

Tools Used

- Contingency Table
- Odds Ratio, OR
- Confidence level table
- Confidence Interval

Common Values	
Confidence Level	Value of $Z_{\alpha/2}$
80%	1.28
90%	1.645
95%	1.96
98%	2.33
99%	2.58
99.8%	3.08
99.9%	3.27

$$95\ \%,\ CI - Upper:\ e^{[ln(OR) + 1.96\sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}}$$

$$95\ \%,\ CI - Lower:\ e^{[ln(OR) - 1.96\sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}}$$

Tools Used

Odds Ratio, $OR = \frac{A*D}{B*C}$

Risk Ratio, $RR = \frac{A(C+D)}{C(A+B)}$

Standardized incidence ratio,

$SIR = \frac{Observed\ cases}{Expected\ Cases}$

Control ⬇️ : Cases ➡	Tumor or symptom	No tumor or no symptom
Exposed to EMF	A	B
Not exposed	C	D

Ratio > 1 : Increased Risk
Ratio < 1 : Decreasing Risk
Ratio = 1 : No association between cases and controls

If the OR, lower, and upper both confidence levels are greater than 1, it is concluded that the difference is statistically significant.

Tools Used

- Confidence Interval, CI
- Z- Score
- P-value
- Is the result significant??

$$p - value = (1/\sqrt{2 * \pi}) * e^{-Z^2/2}$$

If p-value is less than 0.05, it is concluded that the result/difference is **statistically significant**

	Ipsilateral, > 10 year latency	> 10 year latency	Total, > 1 year latency
	OR, CI	OR, CI	OR, CI
Glioma (n = 1148)			
Wireless phone	-	**2.1 1.6–2.8**	**1.3 1.1–1.5**
Mobile phone	**2.9 1.8–4.7**	**2.5 1.8–3.3**	**1.3 1.1–1.6**
Cordless phone	**3.8 1.8–8.1**	**1.7 1.1–2.6**	**1.3 1.1–1.6**
Meningioma (n = 916)			
Wireless phone	-	1.4 0.97–2.0	1.0 0.9–1.2
Mobile phone	1.6 0.9–2.9	1.4 0.9–2.1	1.1 0.9–1.3
Cordless phone	**3.0 1.3–7.2**	1.6 0.9–2.8	1.1 0.9–1.4
Acoustic neuroma (n = 243)			
Wireless phone	-	**2.2 1.3–3.7**	**1.5 1.1–2.0**
Mobile phone	**3.0 1.4–6.2**	**2.6 1.5–4.6**	**1.7 1.2–2.3**
Cordless phone	2.3 0.6–8.8	1.0 0.3–2.9	**1.5 1.04–2.0**

Note: Bold = statistically significant. Number of controls = 2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls). Only living cases and controls included in analyses of ipsilateral use of mobile and cordless phones.

Adjustment was made for age, gender, socioeconomic-code and year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

Table 21.2 Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for age at first use of a mobile phone

	Glioma (n = 1148)	Meningioma (n = 916)	Acoustic neuroma (n = 243)
	OR, (CI)	OR, (CI)	OR, (CI)
Mobile phone	**1.3**	1.1	**1.7**
	(1.1–1.6)	(0.9–1.3)	**(1.2–2.3)**
< 20 years old	**3.1**	1.9	**5.0**
	1.4–6.7	0.6–5.6	**1.5–16**
20–49 years old	**1.4**	1.3	**2.0**
	1.1–1.7	0.99–1.6	**1.3–2.9**
≥ 50 years old	**1.3**	1.0	1.4
	1.01–1.6	0.8–1.3	0.9–2.2

Note: Bold = statistically significant. Number of controls=2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls).

Adjustment was made for age, gender, socioeconomic-code, year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

Reasons for inconsistent results:

1. This task is itself complicated as it's not possible to evaluate the qualitative data 100 percent, there always be some randomness and uncertainty
2. Difference in questionnaire leading to heterogeneity in study outcomes
3. Sponsored research from industry itself to get the results biased towards them(for example tobacco industry research in the 1990s to subdue the IARC research. The IARC study cost USD 2 million over ten years; Philip Morris planned to spend USD 2 million in one year alone and up to USD 4 million on research (Ong and Glanz, 2000).
4. It is more difficult to evaluate the exact latency periods, as we usually forget what we had in our breakfast two weeks ago, for example.

Limitations:

1. All results were based on low numbers of Cases and Controls
2. Different histopathological types of brain tumours so no firm conclusions could be drawn.
3. Different groups have interpreted the authoritative IARC evaluation very differently.
4. Changes in exposure to other risk factors for brain tumours that are unknown in descriptive studies
5. The EEA has noted the increasing evidence of 'funding bias' in scientific research whereby results outcomes are strongly linked to source of funding.
6. Interphone study different research group reported different results, 5.5 m were funded by the industry, and other fundings in the different countries. There were provisions for the entry of industry consultants
7. public could assume that 'not causal' meant 'no link'
8. Mobile phone subscription holders not using the phone were classified as 'exposed'; non-subscribers using the mobile phone were classified as 'unexposed'; corporate subscribers of mobile phones (2,00,507 people), which are likely to have been heavy users, were classified as 'unexposed';

Recent Studies:

We have two more latest studies to summarize (not included in our Chapter 21).

1. Conducted by Martin Röösli and his colleagues in 2019, all the researchers are affiliated in European research groups(including International Agency for Research on Cancer(IARC))

2. Conducted by Dr. Ken Karipidis and his colleagues from Australia.
   a. Solely done in Australia
   b. Types of study: *Ecological Study*

What is an Ecological Study??

In simple words: disease incidences are compared over time/or space

Study No. 1

Brain and Salivary Gland Tumors and Mobile Phone Use: Evaluating the Evidence from Various Epidemiological Study Designs (**Martin Röösli et al, 2019**)

We just need to know one more term(!!) to understand this study is "*statistical heterogeneity*"

It is very useful statistic for quantifying inconsistency,

ChiSq, Q & df → *get data of expected and observed values*

$$Q = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

$$Degrees\ of\ freedom\ of\ a\ data\ matrix,\ df\ =\ (row\ -\ 1)(column\ -\ n1)$$

I^2 = Amount of Heterogeneity, Q = Chi-Squared Value, df = Degrees of Freedom, O = Observed value, E = Expected Value

interpretation

$$I\ Squared,\ I^2 = \frac{Q-df}{Q} * 100\ \%$$

Thresholds of I^2 can be misleading, A rough interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;

source : Identifying and measuring heterogeneity

Brain and Salivary Gland Tumors and Mobile Phone Use: Evaluating the Evidence from Various Epidemiological Study Designs (**Martin Röösli et al, 2019**)

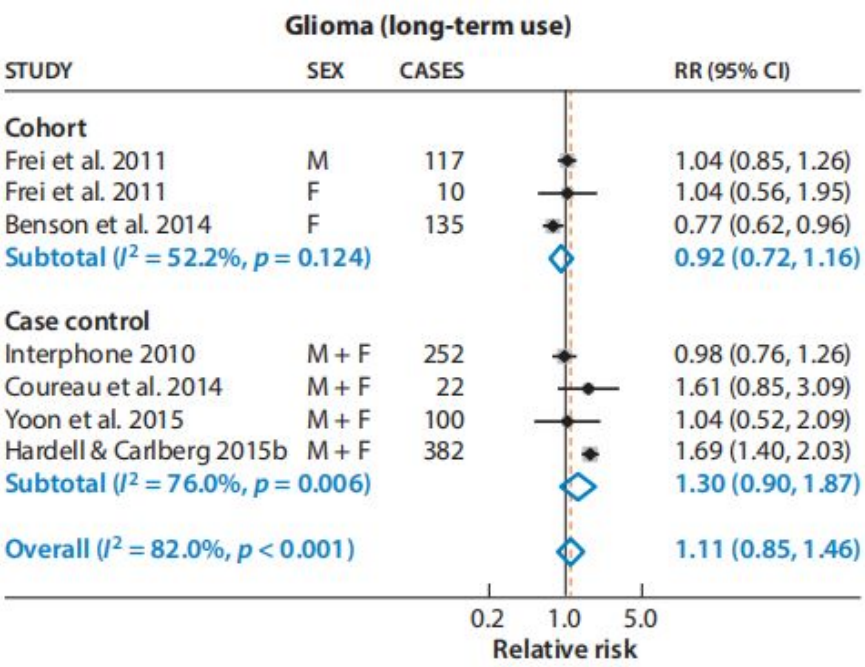
At a Glance:

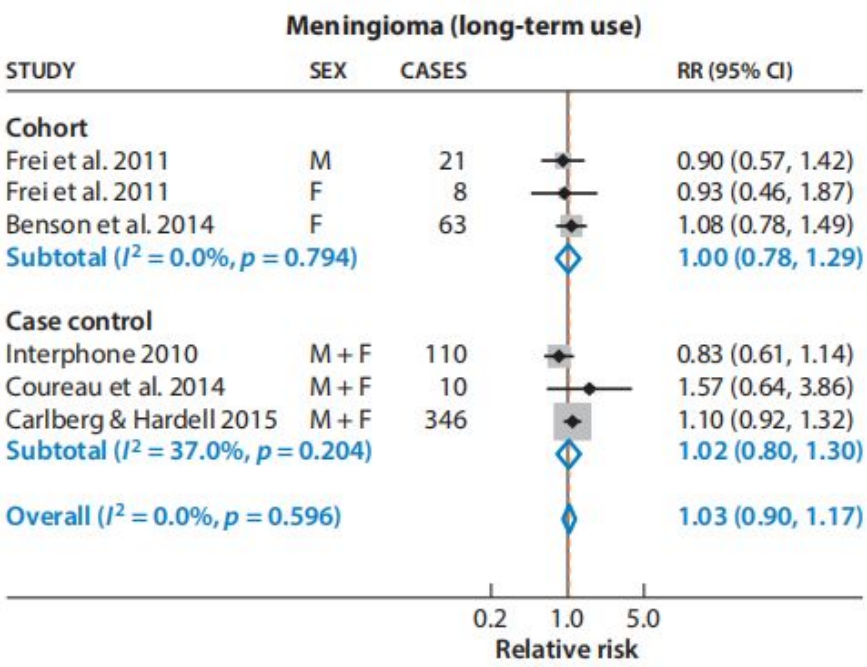
Method of study: Meta-analysis (including Hardell group & Interphone studies)
Types of studies analysed: Case-Control, **Cohort Studies, Ecological Studies, Case-Case Studies**
Data considered: early 90s - 2018

Result:

1. epidemiological studies **do not suggest increased** brain or salivary gland tumor risk with MP use

2. However some uncertainty remains regarding l**ong latency** periods (>15 years), rare brain **tumor subtypes,** and MP usage during **childhood**.


Glioma (long-term use)
STUDY SEX CASES RR (95% CI)
Cohort
Frei et al. 2011 M 117 1.04 (0.85, 1.26)
Frei et al. 2011 F 10 1.04 (0.56, 1.95)
Benson et al. 2014 F 135 0.77 (0.62, 0.96)
Subtotal ($I^2 = 52.2\%$, $p = 0.124$) 0.92 (0.72, 1.16)
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 ($I^2 = 76.0\%$, $p = 0.006$) 1.30 (0.90, 1.87)
Overall ($I^2 = 82.0\%$, $p < 0.001$) 1.11 (0.85, 1.46)
0.2 1.0 5.0
Relative risk


Meningioma (long-term use)
STUDY SEX CASES RR (95% CI)
Cohort
Frei et al. 2011 M 21 0.90 (0.57, 1.42)
Frei et al. 2011 F 8 0.93 (0.46, 1.87)
Benson et al. 2014 F 63 1.08 (0.78, 1.49)
Subtotal ($I^2 = 0.0\%$, $p = 0.794$) 1.00 (0.78, 1.29)
Case control
Interphone 2010 M + F 110 0.83 (0.61, 1.14)
Coureau et al. 2014 M + F 10 1.57 (0.64, 3.86)
Carlberg & Hardell 2015 M + F 346 1.10 (0.92, 1.32)
Subtotal ($I^2 = 37.0\%$, $p = 0.204$) 1.02 (0.80, 1.30)
Overall ($I^2 = 0.0\%$, $p = 0.596$) 1.03 (0.90, 1.17)
0.2 1.0 5.0
Relative risk

Study No. 2

Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: a population based ecological study (Ken Karipidis et al, 2018)

Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: a population based ecological study (Ken Karipidis et al, 2018)

At a glance:

1. Data considered between 1982 and 2013, and conducted in Australia
2. **Population:** 16 825 eligible brain cancer cases aged 20–59 from all of Australia (10 083 males and 6742 females).
3. **Funding:** This work was supported by National Health and Medical Research Council grant APP1042464 (No fund from the industry).
4. **Disclaimer** The funder had no role in the study design, data collection or analysis, decision to publish or preparation of the manuscript.

Result summary:

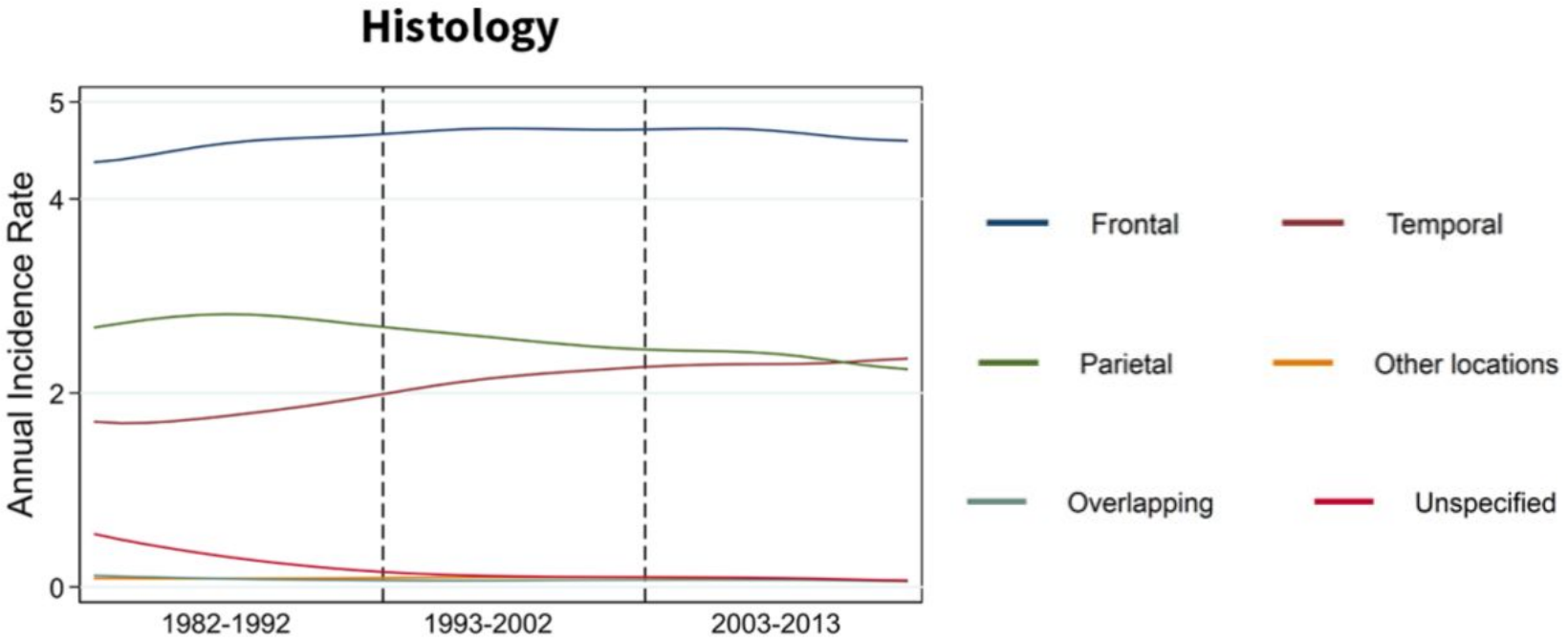
1. In Australia, there has been no increase in any brain tumour histological type or glioma location that can be attributed to mobile phones.

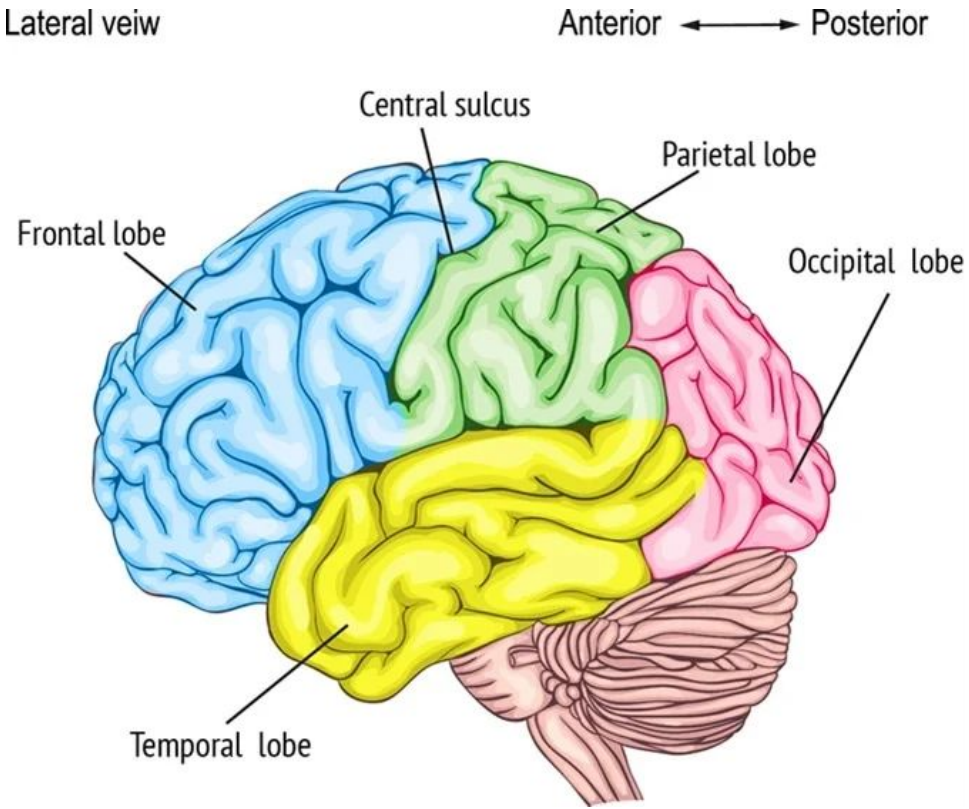
Table 3 Observed age-standardised brain tumour incidence trends in adults (both genders, 20–59 years old) after redistribution of unclassified tumours

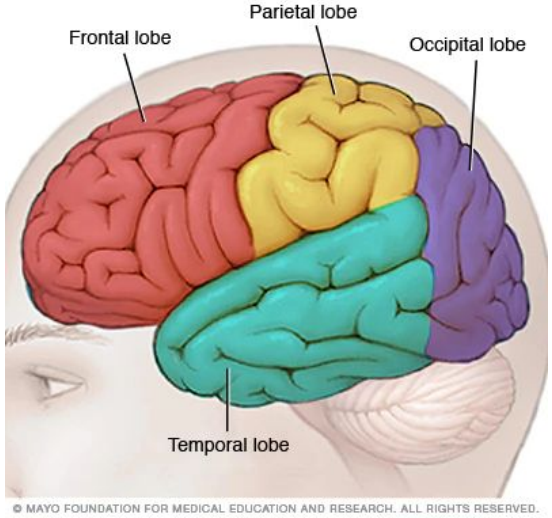
	1982–1992			1993–2002			2003–2013		
	N	APC	95% CI	N	APC	95% CI	N	APC	95% CI
All	4793	0.1	(–0.8 to 1)	5270	0.5	(–0.5 to 1.5)	6762	–0.8	(–1.6 to 0)
Histology									
Glioma	4623	0.2	(–0.7 to 1.2)	5094	0.5	(–0.5 to 1.5)	6547	–0.7	(–1.5 to 0.1)
Glioblastoma	1746	0.4	(–1.1 to 1.9)	2445	2.4	(0.9 to 3.8)	3353	0.7	(–0.5 to 1.9)
Other glioma	2886	0.1	(–1 to 1.2)	2649	–1.1	(–2.5 to 0.2)	3195	–1.9	(–3 to 0.8)
Meningioma	84	–1.6	(–7.9 to 5.2)	110	2.4	(–4.2 to 9.4)	120	–4.4	(–10.1 to 1.7)
Other	82	–8.6	(–14.7 to 2)	66	–1.5	(–9.5 to 7.2)	94	–5.3	(–11.3 to 1)
Glioma grade									
Low	2107	–0.2	(–1.5 to 1.2)	1548	–3.6	(–5.3 to 1.9)	1659	–2.8	(–4.3 to 1.3)
High	2240	2.4	(1.1 to 3.7)	3442	2.3	(1.1 to 3.5)	4762	0.2	(–0.7 to 1.2)
Glioma topography									
Frontal	1447	1.8	(0.2 to 3.5)	1719	2.3	(0.6 to 4)	2580	1.6	(0.3 to 2.9)
Temporal	929	1.8	(–0.2 to 3.9)	1252	1.5	(–0.5 to 3.5)	1656	–1.2	(–2.8 to 0.4)
Parietal	803	3.4	(1.2 to 5.7)	894	–2	(–4.2 to 0.3)	880	–1.1	(–3.3 to 1.1)
Other locations	948	–0.5	(–2.5 to 1.5)	996	–0.8	(–3 to 1.4)	1198	–3.3	(–5.1 to 1.4)

k. Karipidis et al, 2018

Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: a population-based ecological study (K. Karipidis et al, 2018).




Lateral veiw
Anterior ⟷ Posterior
Central sulcus
Parietal lobe
Frontal lobe
Occipital lobe
Temporal lobe


Parietal lobe
Frontal lobe
Occipital lobe
Temporal lobe
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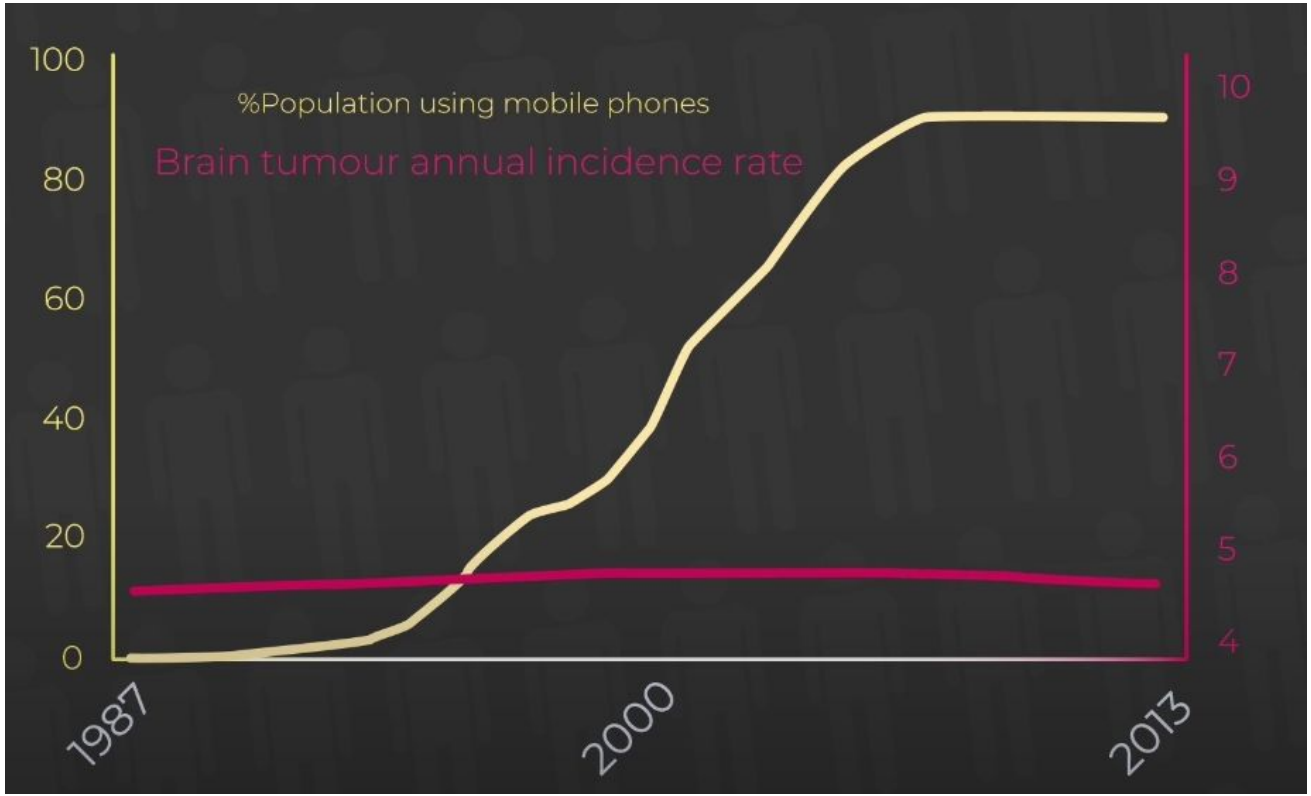

K. Karipidis et al, 2018

Recommendations:

1. Exposure reduction (texting, hands free devices and better phone design).
2. Adolescents seem to be at higher risk than adults, so they should have less exposure
3. Researches should be funded by public funds to avoid research biases
4. More robust study design to avoid heterogeneity, and robust meta-analysis, possibly a more homogeneous ones.

This is a public talk by Prof. Devra Davis

She is one of the leading experts in Public Health. People who are interested to learn more about EMF, we would recommend this video

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