Mobile Phone Radiation and Brain Cancer: An Epidemiologic Update

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Introduction

In May 2011, a Working Group of the International Agency for Research on Cancer (IARC) categorized RF radiation (RFR) as a Group 2B (possible) human carcinogen[1, 2], based on ***limited evidence in humans*** of an association of RFR with glioma and acoustic neuroma, from several studies of mobile and cordless phones arising from two different research groups, based on ***limited evidence from animal studies***, and ***weak mechanistic evidence*** for mutagenicity, cell-signaling and oxidative stress. Since then, the literature for evaluating the carcinogenicity of RFR has increased substantially, particularly the epidemiological evidence. There have been a number of new epidemiological studies on RFR risk that we feel can contribute to the overall evaluation of RFR and others that have serious flaws. In this poster we summarize some new epidemiologic studies on the association between RFR and glioma/acoustic neuroma and related studies on demographic trends in brain cancers. We do not include the growing number of experimental and mechanistic studies, many of which also find increased risks with RF exposures.

Cohort Studies

In a follow-up to an earlier report, Frei et al. [3] updated the results of a large, nationwide cohort study to cover mobile phone use from 1987 to 1995 with cancer follow-up through 2007. They found no relationship between RFR and glioma in mobile phone subscribers versus non-subscribers with a relative risk of approximately 1 for all evaluation groupings, including an exposure-response analysis using years of subscription. The biggest limitation of this study is the potential for exposure misclassification. Approximately half of the identified mobile phone subscribers were placed in the control group, primarily because they were corporate subscriptions and the individual using the phone could not be identified. This type of misclassification will reduce the relative risk of any exposure.

As part of the Million Women Study, Benson et al. [4] evaluated the relation between mobile phone use and incidence of intracranial central nervous system (CNS) tumours and other cancers in the UK. Their evaluation incorporated 791,710 middle-aged women. For long-term users (>10 years) compared to never users, there was no appreciable association for glioma (RR 0.78, 95% CI 0.55–1.10), however there was an increase for acoustic neuromas RR.2.46, 95% CI.1.07–5.64) with the risk increasing with duration of use (P.0.03).

Case Control Studies

A Swedish research group has published several different case-control studies and pooled analyses of new work with their earlier work. [5-8]. Their most recent study [5] is a pooled analysis of two case-control studies on malignant brain tumors with patients diagnosed during 1997-2003 and 2007-2009 that only included patients for which there was a histopathological verification of the tumor type leading to 1498 cases and 3530 controls. Any mobile phone use increased the risk of glioma (OR=1.3, 95% CI=1.1-1.6) and there was a strong exposure-response relationship with much higher risk (OR=3.0, 95% CI=1.7-5.2) for those with >25 years of exposure. Ipsilateral mobile phone use increased the OR in all exposure groups (e.g. OR=4.6, 95% CI=2.1-10 for <25 years of exposure). In a separate pooled analysis of studies of acoustic neuroma [7] with 316 cases and 3530 controls, the same group saw similar results. Mobile phone use for >1 year increased the risk of acoustic neuroma (OR=1.6, 95% CI=1.2-2.2) and there was a strong exposure-response relationship with much higher risk (OR=4.5, 95% CI=2.1-9.5) for those with >20 years of exposure.

In France, Coureau et al. [9] conducted a multicenter case-control study in four areas in France in 2004–2006. Data about mobile phone use were collected through a detailed questionnaire administered face-to-face by trained survey technicians. A marginal association was seen when comparing regular users to non-users (OR=1.24; 95% CI 0.86 to 1.77), but a statistically significant association was seen in the heaviest users (≥896 h, OR=2.89; 95% CI 1.41 to 5.93; ≥18 360 calls, OR=2.10, 95% CI 1.03 to 4.31). Their findings for ipsilateral tumors were not significant 2.11 (0.73 to 6.08), but this was done in a slightly different manner than in the Interphone and Hardell studies [10] and when the analysis was adjusted to be the same, they saw a stronger significant ipsilateral effect (OR=4.21, 95% CI 0.70 to 25.52) if they used the same method as Inskip et al. [11] (OR=2.40, 95% CI 1.002 to 5.73) [12].

A South Korean study by Moon et al. [13] compared 119 patients undergoing surgery for acoustic neuroma to 238 matched controls and found no significant difference in phone use, years of use, cumulative hours or long term use (>10 years) OR=0.96, 95%CI 0.91 to 1.01. A supplementary analysis of tumor size found regular users had a significantly larger tumor volume at diagnosis. This is an interesting finding, which the authors attribute to promoting effects of RFR.

A Nordic, multicenter, case-control study [14] of brain tumors in children and adolescents ages 7-19 years examined the association with mobile phone use (Table 3.). All case-control studies that use questionnaires to determine past exposures may suffer from recall bias, particularly for the highest exposures [9]. This study used personal interviews with children and/or their parents to obtain exposure estimates, but also, where possible, used mobile operator records, which avoid recall bias. Use of mobile phones at least 5 years prior to tumor onset and regular use both showed elevated, but not statistically significant risk estimates (OR 1.26, 95% CI 0.7-2.28 and OR 1.36, 95% CI 0.92-2.02, respectively). In study participants for whom mobile operator recorded data were available, time since first subscription was significantly associated brain tumor risk (>2.8 years OR 2.15, 95% CI 1.07-4.29) with a significant trend, but the trend for cumulative hours of use was not significant (p=.36). The study found a stronger association between tumors on the side opposite phone use than on the ipsilateral side. Although the authors interpreted this to indicate the absence of risk, they urged additional study and there was controversy regarding their interpretation [15, 16]. The study is noteworthy for excluding recall bias by using operator records, but the limited number of subjects with records reduced statistical power.

Table 1: Relative Risk Estimates for Glioma Associated with Ten or More Years of Mobile Phone Use [4, 5, 9]*

Study	Exposure in Years of Use	RR/OR estimate	95% CI	Design
Hardell et al. [5]	>10 - 15	1.4	1.1-1.9	Case-Control
	>25	3.0	1.7 – 5.2	
Coureau et al. [9]	≥10	1.61	0.85-3.09	Case-Control
Benson et al. [4]	>10	0.78	0.55-1.10	Cohort

Figure 1. Odds ratios (with 95% CI) for glioma associated with weighted cumulative hours of cell phone use from Coureau et al. [9].

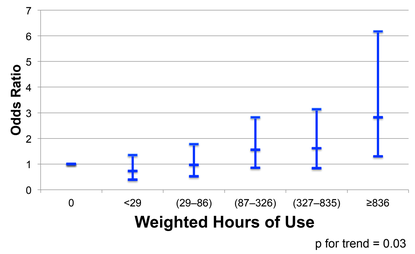


Table 2: Relative risk estimates for acoustic neuroma associated with ten or more years of mobile phone use [4,7,13]

Study	Exposure in Years of Use	RR/OR estimate	95% CI	Design
Hardell et al. [7]	>10 - 15	2.1	1.3-3.5	Case-Control
Moon et al. [13]	>10	0.96	0.91-1.01	Case-Control
Benson et al. [4]	>10	2.46	1.07-5.64	Cohort

Table 3. Case-control study of brain tumors in children and adolescents using operator records for exposure in Nordic countries from Aydin et al. [14].

Exposure	Cases	Controls	OR	95% CI
Cumulative duration of calls, h				
Never regular user	133	259	1	(referent)
≤11	14	26	1.24	(0.61 to 2.55)
12–27	11	13	1.95	(0.81 to 4.73)
>27	9	13	1.38	(0.53 to 3.61)
			p= 0.36	
Years since initial subscription				
Never regular user	134	259	1	
≤1.8	19	51	0.78	(0.43 to 1.40)
1.8–2.8	19	25	1.71	(0.85 to 3.44)
>2.8	24	25	2.15	(1.07 to 4.29)
			p=0.001	

Figure 2: Observed and predicted glioma rates in Nordic countries among 40-59 year-old men with regular mobile use for 10 years from Deltour et al. [19,20]

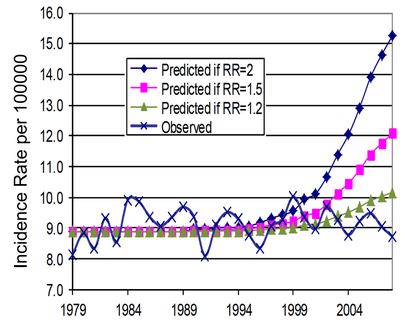
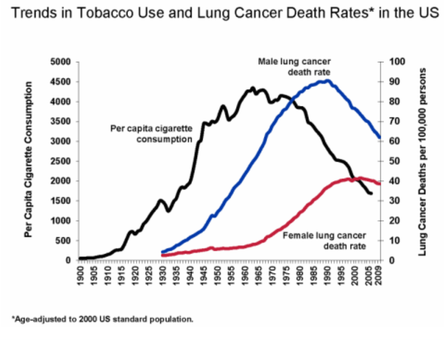


Figure 3. Observed time lag between rise in smoking rate



Ecological Studies

Four new studies compare time trends in use of mobile phones with incidence and/or mortality rates of glioma; one in England [17], one in the US [18], one in 4 Nordic countries [19] and one in Sweden [20]. De Vocht et al. [17] examined the trends in rates of newly diagnosed brain cancer cases in England between 1998 and 2007. They found trends in the location of brain tumors, but no trends in total brain tumors. Little et al. [18] used US population based data from 1992-2008 from 12 registries in the Surveillance, Epidemiology, and End Results (SEER) program to compare cell phone use with glioma incidence. They found no change in age-specific tumor incidence rates in this period. In a further analysis ,based on relative risks of glioma by tumour latency and cumulative hours of phone use in Hardell et al. [20], concluded that predicted rates should have been at least 40% higher than observed rates in 2008. Deltour et al. [19] analyzed annual age-standardized glioma incidence rates in Denmark, Finland, Norway and Sweden in men and women aged 20 to 79 years during 1979–2008. They found a small trend in incidence among both men and women (0.4% and 0.3% respectively) that differed by age group. Based on simulations of cancer incidence the authors concluded that trend data were incompatible with estimates of risk by Hardell. These studies were only presented for the 40-59 age group and not for the two age groups showing a change over time.

These ecological studies have three common flaws.

1) They aggregate diagnoses and may hide trends in more specific diagnoses. Hardell et al. [21] read data from the Swedish National Inpatient Register (SNIPR), Causes of Death Register and Cancer Register (SCR) for the period 1998-2013. Using data from the SCR, they found an increase in the incidence of tumors of the brain that were not classified as to type that appears to begin in 2009. Zada et al. [22] examined trends in tumors at specific locations, particularly the frontal and temporal lobe and found increases in glioblastoma multiforma that were not seen when looking at all gliomas combined.
2) Lags in reporting will attenuate trends by reducing apparent incidence in recent years [23].
3) They are all susceptible to the ecological fallacy: other factors that cause brain tumors may be dropping the rate while cell phones increase the rates. In other words, we have no way to exclude the possibility that there is an unrelated decline in glioma incidence and a genuine, cell phone-related rise in incidence, which would result in level trends.

Finally, and perhaps most importantly, the lag between exposure and incidence may be far longer than that so far observed and, as was the case with smoking and lung cancer shown in Figure 3 [24], the rise in incidence substantially lags the rise in exposure.

Conclusions

Since the IARC review of RFR, there have been three additional reviews of RFR [22, 23, 25]. The SSM [25] concluded that "No convincing evidence links mobile phone use to the occurrence of glioma or other tumours of the head region among adults". The use of the term "convincing" implies that some level of causality has not been met, but this level is not specified. Health Canada [23] states that "It must be stressed that Safety Code 6 is based upon established adverse health effects", again a level of causality with no clear definition but implying a fairly high burden of proof. SCENIHR [24] conclude that "Overall, the epidemiological studies on RF EMF exposure do not indicate an increased risk of brain tumours" stating that since the IARC review, "the evidence for glioma has become weaker" but fails to mention acoustic neuroma in their summary. They argue that the new cohort studies and the ecological studies are convincing. Thus, SCENIHR has concluded there is no association.

We disagree with these reviews. Three of the four case-control studies of glioma and acoustic neuroma post the IARC review were positive and while the Benson et al. [4] cohort study was negative for glioma, it was positive for acoustic neuroma. The undeniable and substantial exposure missclassification in the Frei et al. [3] study make it unusable. Thus, the evidence is certainly stronger for acoustic neuroma and debatably stronger for glioma.

In light of this evidence and the widespread exposure to this agent, IARC should consider convening a Working Group to re-evaluate the classification of RFR. Educational and public health institutions should be encouraged to reduce exposures, especially of young children, to RF devices. Finally, there is a strong need for additional independent research on the effects of RFR on humans, animals and cells.

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