Cell phones and brain tumors: A review including the long-term epidemiologic data

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ABSTRACT

BACKGROUND: The debate regarding the health effects of low-intensity electromagnetic radiation from sources such as power lines, base stations, and cell phones has recently been reignited. In the present review, the authors attempt to address the following question: is there epidemiologic evidence for an association between long-term cell phone usage and the risk of developing a brain tumor? Included with this meta-analysis of the long-term epidemiologic data are a brief overview of cell phone technology and discussion of laboratory data, biological mechanisms, and brain tumor incidence.

METHODS: In order to be included in the present meta-analysis, studies were required to have met all of the following criteria: (i) publication in a peer-reviewed journal; (ii) inclusion of participants using cell phones for ≥10 years (i.e., minimum 10-year "latency"); and (iii) incorporation of a "laterality" analysis of long-term users (i.e., analysis of the side of the brain tumor relative to the side of the head preferred for cell phone usage). This is a meta-analysis incorporating all 11 long-term epidemiologic studies in this field.

RESULTS: The results indicate that using a cell phone for ≥10 years approximately doubles the risk of being diagnosed with a brain tumor on the same ("ipsilateral") side of the head as that preferred for cell phone use. The data achieve statistical significance for glioma and acoustic neuroma but not for meningioma.

CONCLUSION: The authors conclude that there is adequate epidemiologic evidence to suggest a link between prolonged cell phone usage and the development of an ipsilateral brain tumor.

Keywords: Acoustic neuroma; Brain tumor; Cell phone; Electromagnetic radiation; Glioma, Incidence; Mechanism; Meningioma; Radiofrequency fields

Abbreviations:

CBTRUS:	Central Brain Tumor Registry of the United States
CDMA:	code division multiple access
CI:	confidence interval
CNS:	central nervous system
EMF:	electromagnetic field
EMR:	electromagnetic radiation
FCC:	Federal Communications Commission
GSM:	global system for mobile communication
IARC:	International Agency for Research on Cancer
MRI:	magnetic resonance imaging
NHL:	non-Hodgkin lymphoma
OR:	odds ratio
SAR:	specific absorption rate
TDMA:	time division multiple access
WHO:	World Health Organization

1. **BACKGROUND**

1.1 Cell phone technology

Cell phone technology incorporates base stations, namely transmission tower antennae, and cell phone hand-held units. Cell phone networks were first deployed in Sweden in 1981 via the Nordic Mobile Telephone (NMT) System (analogue; 450MHz; 1st Generation or 1G). The digital system (Global system for mobile communication; GSM) started in 1991, representing the second generation of cell phone systems, or "2G". Mass deployment was present in most countries from the mid 1990s (**Figure 1**). The latest system currently in mass deployment is based on adaptations of CDMA and TDMA (Code and time division multiple access, respectively; 800 and 1900MHz; "3G"). Radio waves emitted by modern GSM handsets have a peak power of 1-2W while other digital cellular technologies have power outputs of below 1W, levels generally regarded as being safe by international regulatory authorities. The 3G has less than 0.25W peak power. Through “adaptive power control” the power generated by a cell phone can vary during a conversation according to the amount of interference with the signal, e.g., due to the user being in a moving vehicle, or within a building or elevator. The output power of the phone is generally set to the highest level during "handovers" between networked base stations as a user moves from one geographic area to another, or when signal interference is greatest. The output power of the new 3G is measured for small cells to be on the average 0.25mW and in a larger cell about 12mW. It should be noted that cordless phones operate as transmitters and receivers like GSM cell phones despite shorter signal distances to the home desktop base station. Although such phones have lower peak power than cell phones, user call times tend to be longer. Further, due to adaptive power control of cell phones, the average power output of cordless phones is comparable to cell phones at least in urban areas.

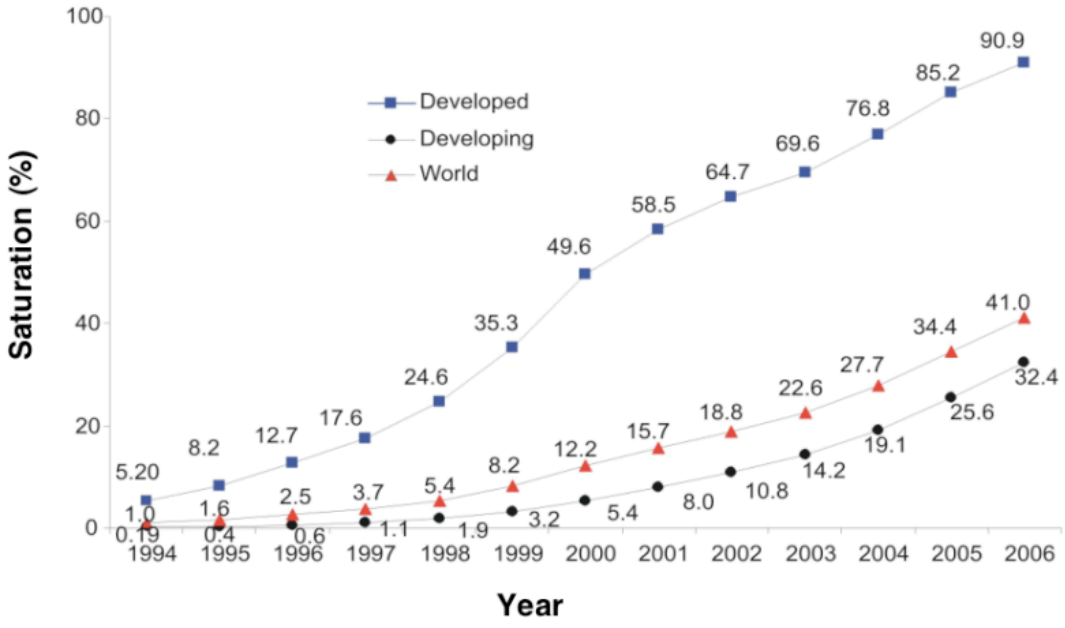

Fig. 1. Worldwide saturation: Cell phone subscribers per 100 inhabitants, 1994 - 1996 (data source: International Telecommunication Union, 2007).

Cell phone base stations or masts emit electromagnetic radiation (EMR) continuously and at far greater power than cell phones which emit EMR continuously only during calls. Between calls or "at rest" with the "screen asleep" but the power on, cell phones emit a regular pulse of EMR in order for base stations to continuously keep track of the geographic position of the phones in their "cellular network”. GSM antennae are associated with transmitter powers of 10-100W, although 3G antennae use less power, on average 3W in urban areas. In rural areas, base station power output is much higher because of the vast areas requiring coverage between sparsely distributed base stations, and cell phones rurally are more often at their maximum power output during use in order to maintain good

communication [13,37]. Overall, the number of towers has increased tremendously in the past decade and smaller but even more numerous “microcell” antennae throughout metropolitan environments now enable clear cell phone reception within previously reception-poor locations such as in elevators and building basements.

1.2 Electromagnetic field

An electromagnetic field (EMF) is comprised of an electric field generated by differences in voltage and a magnetic field generated by the flow of current. The field propagates at the speed of light in waves of a certain length that oscillate at a certain frequency. In the electromagnetic range, gamma rays given off by radioactive materials, cosmic rays, and X-rays are all dangerous to humans and other organisms because of the relatively high-energy "quanta" they carry via high-frequency or short-wavelength waves. Such rays lead to dangerous “ionizing” radiation with an ability to break intermolecular bonds. Cell phone systems also act via EMR but in the "microwave" or "radiofrequency" range close to that of a microwave oven (although cell phone power output is much less). These systems are supposedly safe because of the lower-energy quanta they carry via relatively low-frequency or long-wavelength waves, i.e., “non-ionizing” owing to insufficient energy to break intermolecular bonds. This notion, however, has been contested in the scientific literature [27,28,38] and, as detailed below, has led to concerns regarding non-thermal rather than thermal (direct tissue heating) effects of cell phone-related EMR on cells and tissue systems within the near-field of the antenna.

1.3 Exposure

The intensity of EMR (power density) varies with the distance from the source according to the inverse square law. The specific absorption rate (SAR) measures the rate at which radiation is absorbed by the human body and is therefore relevant to “exposure”. For the head, the Federal Communications Commission (FCC) has set an acceptable SAR of 1.6 W/kg. In cellular telephony, the SAR depends on several factors, including the antenna type and position, head morphology, the distance between the phone and the head, and the power output of the phone that can vary [3,13]. Exposure of the brain depends on the type of phone and position of the antenna [3], but tends to be highest in the temporal lobe and insular region, and overlying skull, scalp and parotid gland tissues. Irrespective of the type of phone, exposure is highest on the side of the head against which the cell phone is held [3] and appears to be even higher in children owing to thinner scalps and skulls, increased water content of their brain, and lower brain volume [26,65].

2. LONG-TERM EPIDEMIOLOGIC DATA

There are currently over 3 billion cell phone users globally, with developed nations already approaching saturation point (**Figure 2**). Users starting as young as three years of age are expected to be exposed to near-field cell phone EMR for their entire lifetimes. There has been much controversy regarding health risks associated with cell phones, with confusion partly arising from the relatively short length of participant follow-up in most of the published epidemiologic studies. In studies testing any association between long-term (i.e., ≥ 10-year) cell phone use and brain tumor development, the three groups of brain tumors assessed are glioma (specifically, astrocytoma), acoustic neuroma, and meningioma. In this section, the authors focus on all the currently published peer-reviewed epidemiologic studies that have attempted to address whether 10 or more years of cell phone use is associated with the development of intracranial tumors on the same side of the head (“ipsilateral”) as that preferred for cell phone usage (i.e., all long-term studies with a “laterality analysis”).

2.1 Meta-analysis methodology

In order to be included in the present meta-analysis, studies were required to have met all of the following criteria: (i) publication in a peer-reviewed journal; (ii) inclusion of participants using cell phones for 10 or more years (i.e., minimum 10-year latency); and (iii) incorporation of a laterality analysis of long-term (≥ 10-year) users. The PubMed database was comprehensively searched up to December 1 2008 using terms including mobile phone, cell phone, brain tumor, neoplasm, incidence, acoustic neuroma, meningioma, glioma, and astrocytoma. If a study had more than one publication on certain epidemiologic aspects, the latest publication giving the most relevant data was used. The present analyses are based on the adjusted odds ratios (OR) in the different studies. It should be reiterated that participant overlap (redundancy) has been avoided in the present meta-analysis by the appropriate handling of

pooled versus individual INTERPHONE publications where individual national data sets were available. Further, there is no overlap of participants in the two pooled studies of Hardell [14,18], as well as no overlap in participants between the Swedish studies of Hardell [14,18] and the Swedish arm of INTERPHONE [29,30,35,36] since persons from different parts of Sweden were included in those two groups of studies. The present statistical analysis was carried out using a fixed effects model based on the case-control design of all of the included studies (Stata/SE 10.1 for Windows; StataCorp., College Station, TX).

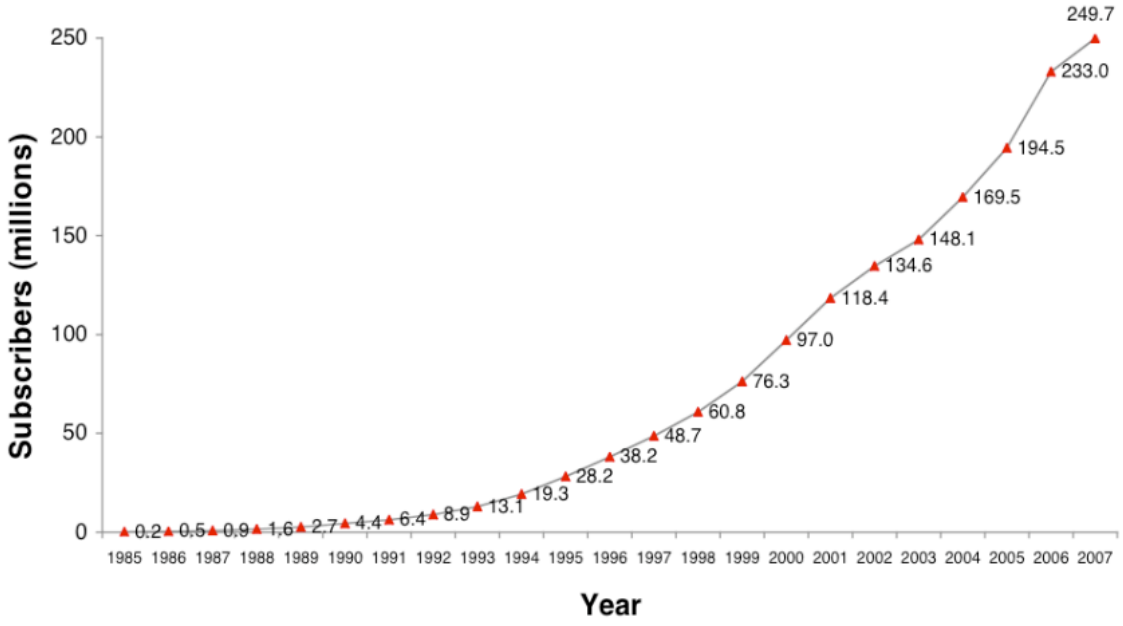

Fig. 2. Number of US cell phone subscribers by year
(data source: Cellular Telecommunications Industry Association, 2007).

2.2 Studies included in the meta-analysis fall into two data streams

To the authors' knowledge, there are only 11 published studies examining long-term cell phone use (i.e., use for 10 years or more) and the risk of developing a brain tumor [8,9,14,18,23,29,30,35,36,54,55] (**Table 1**). These 11 studies fall into two distinct streams of data. Namely: (i) the "Hardell group" studies [14,18] from Sweden that were the first case-control studies to report an association between the use of cellular and cordless phones and brain tumors [16]; and (ii) the "INTERPHONE group" studies [8,9,23,29,30,35,36,54,55], authored by researchers of the multinational INTERPHONE consortium (see below).

The Hardell studies are comprehensive case-control studies looking at data exclusively from Sweden acquired between 1997-2003, while the INTERPHONE study is a multinational collective of several comprehensive case-control studies looking at data acquired between 1999-2004. Detailed reviews of the methodological aspects of these two data streams, including their limitations pertaining to the extent of subject participation and selection and recall biases, are given elsewhere [4,15,63]. The studies incorporate thousands of cases and controls, although notably far fewer using cell phones for 10 or more years (**Table 1**) and are briefly summarized below.

Table 1. Meta-analysis of epidemiologic studies with results on long-term (> or ≥ 10 years) cell phone use.

Study [ref.]	Countries	Group	Overall			Ipsilateral			Contralateral		
			ca/co	OR	95% CI	ca/co	OR	95% CI	ca/co	OR	95% CI
GLIOMA											
Lonn (2005)[36]**	Sweden	Interphone	25/38	0.9	0.5-1.5	15/18	1.6	0.8-3.4	11/25	0.7	0.3-1.5
Christensen (2005)[9]**	Denmark	Interphone	14/31	0.8***	0.4-1.6	---------- No laterality analysis carried out ----------					
Hepworth (2006)[23]**	UK	Interphone	66/112	0.9	0.6-1.3	NA	1.6	0.9-2.8	NA	0.8	0.4-1.4
Schuz (2006)[55]	Germany	Interphone	12/11	2.2	0.9-5.1	---------- No laterality analysis carried out ----------					
Lahkola (2007)[29]	Denmark, UK, Norway, Finland, Sweden	Interphone	143/220	1.0	0.7-1.2	77/117	1.4	1.01-1.9	67/121	1.0	0.7-1.4
Hardell (2006)[18]	Sweden	Hardell	78/99	2.7	1.8-3.9	41/28	4.4	2.5-7.6	26/29	2.8	1.5-5.1
Overall Estimate*:		233/330	1.3	1.1-1.6	118/145	1.9	1.4-2.4	93/150	1.2	0.9-1.7	
ACOUSTIC NEUROMA											
Lonn (2004)[35]**	Sweden	Interphone	14/29	1.8	0.8-4.3	12/15	3.9	1.6-9.5	4/17	0.8	0.2-2.9
Christensen (2004)[8]**	Denmark	Interphone	2/15	0.2	0.04-1.1	---------- No laterality analysis carried out ----------					
Schoemaker (2005)[54]	Denmark, UK Finland, Scotland, Sweden, Norway	Interphone	47/212	1.0	0.7-1.5	31/124	1.3	0.8-2.0	20/105	1.0	0.6-1.7
Hardell (2006)[14]	Sweden	Hardell	20/99	2.9	1.6-5.5	10/28	3.5	1.5-7.8	6/29	2.4	0.9-6.3
Overall Estimate*:		67/311	1.3	0.97-1.9	41/152	1.6	1.1-2.4	26/134	1.2	0.8-1.9	
MENINGIOMA											
Lonn (2005)[36]**	Sweden	Interphone	12/36	0.9	0.4-1.9	5/18	1.3	0.5-3.9	3/23	0.5	0.1-1.7
Christensen (2005)[9]**	Denmark	Interphone	6/8	1.0	0.3-3.2	---------- No laterality analysis carried out ----------					
Schuz (2006)[55]	Germany	Interphone	5/9	1.1	0.4-3.4	---------- No laterality analysis carried out ----------					
Hardell (2006)[14]	Sweden	Hardell	38/99	1.5	0.98-2.4	15/28	2.0	0.98-3.9	12/29	1.6	0.7-3.3
Lahkola (2008)[30]	Denmark, UK, Norway, Finland, Sweden	Interphone	73/212	0.9	0.7-1.3	33/113	1.1	0.7-1.7	24/117	0.6	0.4-1.03
Overall Estimate*:		116/320	1.1	0.8-1.4	48/141	1.3	0.9-1.8	36/146	0.8	0.5-1.3	

NA = not available; ca/co = number of exposed cases/controls; OR = odds ratio; CI = confidence interval
* fixed effects model; ** not included in analysis because already part of pooled data; *** crude odds ratio, own calculations

2.3 The Hardell studies

Since the latter half of the 1990s, Lennart Hardell and his colleagues from Sweden have performed six case-control studies in the area of cellular and cordless phones and tumors [19]. Three of the studies concerned brain tumors, one salivary gland tumors, one non-Hodgkin lymphoma (NHL) and one testicular cancer. Exposure was assessed by detailed self-administered questionnaires. The Hardell brain tumor studies had approximately 90% case and control participation rates, with cases (n=2158 participants) and controls (n=2162 participants) identified from Swedish cancer and population registries, respectively [14]. Pooled analyses of their results regarding brain tumors are incorporated in the present review. In brief, significantly elevated risks of developing an ipsilateral astrocytoma and acoustic neuroma were found in analogue and digital cell phone and cordless phone users. The odds ratios (OR) increased with latency period, particularly > 10 years, and with cumulative cell phone use > 2000 hours. Higher OR were calculated for World Health Organization (WHO) grade III and IV astrocytomas than for WHO grade I and II astrocytomas. No association was found with salivary gland tumors, NHL or testicular cancer, but fewer persons in those particular studies were long-term users of cell phones [19]. The aforementioned findings of Hardell [19] suggest specific or differential effects of cell phone radiation on tumor development.

2.4 The INTERPHONE study

Following the completion of multinational feasibility studies in the late 1990s, the International Agency for Research on Cancer (IARC), a subsidiary of the WHO, commenced the INTERPHONE study. The primary objective of this study, involving 13 nations, was to assess whether radiofrequency radiation exposure from cell phones is associated with tumor risk, specifically, risk of glioma, meningioma, acoustic neuroma and parotid gland tumors. This non-blinded, interview-based, substantially wireless industry-funded case-control study was designed to have enough statistical power to detect a 1.5 fold increase in risk 5-10 years from the commencement of cell phone use. The "core protocol" was followed by each of the participating centres [4]. Overall participation rates

were relatively low: On average, 53% for controls (n=7658 participants) in various centres (range 35-74%), and 75% (range 37-100%) for brain tumor cases (n=6311 participants) [4,15].

Enrolment in the INTERPHONE study was completed by 2004 although, now almost 5 years later, the publication of the collective INTERPHONE results is still being awaited. In the interim, researchers from the INTERPHONE consortium have published 9 studies incorporating statistically analysed long-term cell phone usage data pertaining to brain tumors [8,9,23,29,30,35,36,54,55]. All of these publications are listed in **Table 1**. Only 6 of these 9 INTERPHONE publications involved a laterality analysis [23,29,30,35,36,54]. It should be noted that the Japanese arm [59] of INTERPHONE has been excluded from the present analysis because it did not specifically assess long-term cell phone usage (only 6 meningioma or glioma "cases" and 10 "controls" used cell phones > 10 years). It failed to meet the inclusion criteria of the present meta-analysis because that study only reported a laterality analysis of its short-term users (< 10 years) [59]. Further, the widely quoted nationwide Danish study [56] involving an assessment of over 420,000 cell phone subscribers is not part of the present analysis because it: (i) was a cohort study comparing incidence in these subscribers with the overall population that, in the meantime, had increased penetration rate of cell phone use from 16% to 80%; (ii) excluded over 200,000 corporate users (i.e., those expected to be using cell phones most heavily); (iii) followed users for an average of only 8.5 years; and (iv) did not incorporate any laterality analysis due to using only cell phone subscription data. Finally, other widely referenced US cell phone-brain tumor studies, including those of Inskip [24], Muscat [45], and the Wireless Technology Research Program [5] were not included in the present analysis because they were short-term studies.

2.5 Results of the long-term data meta-analysis

Meta-analysis of all available long-term epidemiologic studies reporting an analysis of laterality ("Hardell group" [14,18] and "INTERPHONE group" [23,29,30,35,36,54] but excluding those that were already part of pooled analyses that were used instead) gives the following odds ratios [OR (95% confidence intervals; CI)] for ipsilateral cell phone use > 10 years (**Table 1**): glioma OR=1.9 (CI=1.4-2.4); acoustic neuroma OR=1.6 (CI 1.1-2.4); and meningioma OR=1.3 (CI 0.9-1.8). These findings are similar to those in the publication by the Hardell group [16], although a random effects model was used in that publication, and indicate a statistically significant elevated odds of developing a glioma or acoustic neuroma on the same side of the head preferred for cell phone use over a duration of exposure ≥ 10 years. The authors note that Kan [25], in a meta-analysis of short- and long-term studies in this field, independently found an increased risk of developing a brain tumor with long-term cell phone use [OR=1.25 (95% CI 1.01–1.54)]. However, Kan's meta-analysis is limited by incorporating only 5 long-term epidemiology studies and excluding all of the epidemiologic data from the seminal studies of Hardell [14,18]. To the authors' knowledge, ours is among the first meta-analyses to include all 11 long-term publications, the most recent being the INTERPHONE group's multinational report on meningioma [30].

The authors acknowledge that while there is statistical variance between the different long-term studies for each tumor type, importantly, when all the available long-term data are considered together, there is no decreased risk for contralateral use of cell phones. In short, the meta-analysis shows that long-term cell phone usage can approximately double the risk of developing a glioma or acoustic neuroma in the more-exposed (ipsilateral) brain hemisphere, and does not protect the less-exposed (contralateral) brain hemisphere against developing a tumor. If the ipsilateral increased odds were caused by recall bias (e.g., cases mistakenly reporting more frequently that they used the phone on the same side as the tumor developed) then a decreased risk for contralateral use should be expected, but was not found in this meta-analysis. Further, the four publications with the largest numbers of cases and controls that showed elevated OR for ipsilateral glioma and acoustic neuroma did not find an OR<1.0 on the contralateral side [14,18,29,54]. The authors agree with Sadetzki [52] from INTERPHONE Israel that the side of the head to which an individual prefers to hold a cell phone tends to be related to an individual's handedness but the concordance is about 60%. The authors reiterate that the risks for the three tumor types analysed in this work are not the same, that is, the findings of the meta-analysis and its included studies are not "non-specific". Each of the three tumor types studied is associated with different odds ratios and confidence intervals, and elevated risks of only two of the three types, namely glioma and acoustic neuroma, reached statistical significance. These findings may be explained by the different depths and topography of such tumors, and differences in cell types, growth rates, and tumorigenic molecular pathways. As noted in papers from both data streams, there appears to be a statistically significant effect of cell phone usage in terms of tumor type and laterality, latency, and cumulative use of the phone in hours [14,18,29,54].

2.6 Limitations of the meta-analysis

The present work attempts to address an important and timely public health concern, namely, does long-term cell phone usage elevate the user's risk of developing a brain tumor? The authors have statistically analysed all of the published long-term cell phone epidemiologic data to the best of their abilities, however, also recognise the following limitations of the present meta-analysis. First, in the absence of all of the results of the INTERPHONE study, it is not possible at this time for the authors to assess the homogeneity of long-term associations across each of INTERPHONE's 13 participating nations. The delay in the INTERPHONE study, whose enrolment was completed in 2004, appears to be due to internal difficulties regarding interpretation of the data. Second, the design of each of the studies incorporated into the meta-analysis relies on participants recalling the amount of their use of cell phones through questionnaires and/or telephone interviews, rather than potentially more accurate data acquirable through cell phone company records for study participants. Reliance on recall by a participant regarding time spent using a cell phone (akin to "exposure") introduces the potential for recall bias, which can contribute to exposure overestimation or underestimation. Until individual account records are made available to researchers involved in epidemiologic studies comparing tumor incidence among cohorts of heavy versus minimal cell phone users, the results of studies relying on participant memory will continue to be subject to some degree of recall bias [63].

2.7 Exposure overestimation versus underestimation

Recall bias has been proposed by authors of the INTERPHONE study to lead to EMR-exposure overestimation (not underestimation) [63]. However, any overestimation due to recall bias may be countered by exposure underestimation secondary to four key methodological limitations in the INTERPHONE study discussed in detail elsewhere [15,17,40,41,42] and summarized as follows: In individual INTERPHONE studies, first, the reference group was "never"/"non-regular" cell phone users, which is appropriate. However, because the published INTERPHONE studies thus far have not taken into consideration cordless phone use by participants (a risk factor for intracranial tumors [19]), the reference group cannot be described as unexposed to near-field EMR. Second, in the analysis of laterality, persons who developed tumors on the opposite side of the head to the preferred side for cell phone usage were classified as "unexposed" to cell phone EMR. Hence, the INTERPHONE reference ("unexposed") category contains subjects using cell phones regularly but reporting use on the other side of the head to the diagnosed tumor. Although exposure to microwaves from cell phone use is substantially lower on the contralateral side [3], the discrepancy is less pronounced for regions of the brain (ventricular and subventricular) where glioma may originate. Third, in the INTERPHONE study, which compared regularly exposed to unexposed individuals, the definition of a "regular" cell phone user is relatively minimalistic, namely, a person who uses a cell phone more than once a week for > 6 months [4,41,42]. Fourth, the INTERPHONE study's participation rates for cases and controls was low (on average 53% for controls and 75% for cases [4]) compared with the Hardell studies (about 90% each) [14]. In the context of the aforementioned methodological issues, any statistically significant elevated risk in INTERPHONE studies may be expected to be an underestimate of the true risk.

3. LABORATORY DATA

Science Magazine has recently acknowledged that there are several peer-reviewed papers from laboratories in at least seven countries including the USA showing that cell phone or similar low-intensity EMF can (contrary to expectations of non-ionizing sources) break DNA or modulate it structurally [27]. Although the literature is inconsistent in terms of experimental reproducibility [33,39,50,53,60,62,68], many independent laboratory investigations have suggested adverse biological effects of cell phone radiation [7,11,12,27,31,32,43,47,50,51,58,64] reviewed in detail elsewhere [28,38,44,62]. An excess of malignant tumors was found in animals exposed for 1-2 years to radiofrequency radiation at levels comparable to current standards [7,51], while increased levels of DNA damage via "strand-breakage" have been reported in rat brain cells [31,32] and in human fibroblasts and rat granulosa cells [11] after exposure to cell and cordless phone radiofrequency radiation. Decreases in cell growth rate and survival were found in hamster ovarian cells exposed to radiofrequency radiation over brief time periods but at high specific absorption rates [58], while increased DNA fragmentation and cell death and altered reproductive frequency were seen in fruit flies exposed to cell phone radiation [47,64]. In human and other species' cells, significant gene and protein changes induced by cell phone radiation have been reported, with altered expression, structure and/or function in molecular pathways subserving the heat-shock response [50,64], immune response [50],

cellular metabolism [50], and genomic stability [43]. Further, using transcranial magnetic stimulation technology in a double-blind study in humans, local brain hyperexcitability was found during exposure to a GSM cell phone operating for 45 minutes, although that data could not be directly extrapolated to human disease [12].

It should be noted that the induction of stable DNA alterations does not require a DNA-damaging or genotoxic agent. Agents that interfere with epigenetic activities, for example, the processing of these damages, cell cycle control, or apoptosis of the deviating cell, will increase the likelihood of malignant transformation [28]. In this context, expression of genes related to cell death or apoptotic pathways were recently found to be dysregulated in primary cultured neurons and astrocytes following 2-hour exposure to a working GSM cell phone rated at a frequency of 1900 Mhz [67]. Finally, the precise mechanism by which GSM cell phone (nonionizing) EMR can cause or promote neoplasia remains unidentified, however, it has been proposed that the mechanism is unlikely to be related to local heating (thermal effects; the basis of current public and occupational EMF exposure standards [2]) but rather a "nonthermal" interaction between incoming microwaves and exquisitely sensitive oscillatory electrical processes found in living tissues. This interaction that has been referred to as "oscillatory similitude" is akin to the reception of a clock radio being susceptible to interference from a nearby cell phone [22]. It is possible that the phenomenon of oscillatory similitude may lead to genetic or epigenetic damage through increased local production of reactive oxygen species or "free radicals" [2].

3.1 Why has the laboratory data been inconsistent?

One key problem with the design of all laboratory studies, both for and against a molecular link between cell phone EMR and brain tumor development, is that such studies fail for understandable reasons to be carried out in larger mammals over time frames consistent with brain tumor development, i.e., > 10 years. Another shortfall of experimental design is failure to take into account the cumulative effects of multiple, varying long-term exposure sources (cell phones, cordless phones and their base stations, high-voltage power lines, WiFi systems, and TV and radio antennae). Finally, naturally occurring genetic variations between individuals (gene polymorphisms) may account for differences in susceptibility to developing brain tumors in humans. Polymorphic genes implicated in brain tumor susceptibility include those subserving immune responses [57], cell-cycle control [49] and DNA repair [1,34]. In this context, Yang et al. [66] have recently shown that polymorphisms in DNA repair genes appear to enhance susceptibility to leukaemia from the low-frequency EMF of high-voltage power lines. Further, Nylund and Leszczynski [46] have shown that different human endothelial cell lines exposed to the same 1 hour of GSM 900 MHz EMR at a SAR of 2.8 W/kg showed varying degrees of gene and protein expression alterations. They therefore concluded that the cell response to cell phone radiation might be genome- and proteome-dependent, stating: "It is likely that different types of cells and from different species might respond differently to cell phone radiation or might have different sensitivity to this weak [GSM EMR] stimulus. Our findings might also explain, at least in part, the origin of discrepancies in replication studies between different laboratories" [46].

3.2 BioInitiative Report

In August 2007, an international working group of scientists, researchers and public health policy professionals (The BioInitiative Working Group) released its report on EMF and health [2]. It raises evidence-based concern about the safety of existing public limits that regulate how much EMF is allowable from power lines, cellular phones, base stations and many other sources of EMF exposure in daily life. The BioInitiative Report [2] provides detailed scientific information on health impacts when people are exposed to electromagnetic radiation hundreds or even thousands of times below limits currently established by the FCC and International Commission for Non-Ionizing Radiation Protection in Europe (ICNIRP). The authors reviewed more than 2000 scientific studies and reviews, and conclude that: (i) the existing public safety limits are inadequate to protect public health; and (ii) from a public health policy standpoint, new public safety limits, and limits on further deployment of risky technologies are warranted based on the total weight of evidence [20].

As reviewed in Sections 1, 15 and 17 of the BioInitiative Report [2], there are several hundred papers that support the existence of low-intensity non-thermal effects of cell phone radiation on biological systems. The consequence is mostly adverse: DNA single and double strand damage, changes in gene transcription, changes in protein folding, heat shock protein generation, production of free radicals, and effects on the immune system. However, that there are also therapeutic effects demonstrated (e.g., bone healing and wound healing) from other frequencies and

intensities of EMF also gives support for the fact that the human body senses, reacts to and can be differentially affected by low-intensity EMF. This divergent sensitivity is unlikely to be explained by thermal effects alone [20].

4. CLINICAL IMPLICATIONS

Taken together, the long-term epidemiologic data suggest an increased risk of being diagnosed with an ipsilateral brain tumor related to cell phone usage of 10 years or more. The data achieve statistical significance for glioma and acoustic neuroma, but not for meningioma. The authors wish to reiterate that the current long-term epidemiologic data are consistent in determining an increased risk of brain tumors associated with ipsilateral long-term cell phone usage. That is, findings of the laterality analysis of the Hardell group are consistent with those of the INTERPHONE group when the long-term data are specifically assessed [14,18,29,54]. The authors of the present review recognize that the results are subject to the effects of variations in subject participation rates and selection and recall biases, however, conclude that the currently available long-term epidemiologic evidence points to the aforementioned adverse health effects. Further, the findings pertaining to brain tumors are strengthened by the long-term data recently reported by Sadetzki [52], head of INTERPHONE Israel. Sadetzki et al. [52] have found significantly elevated odds for the development of ipsilateral parotid gland tumors among heavy cell phone users, effects observed to be dose-dependent. Findings from the unrelated publications of Hardell [14,18] on brain tumors and Sadetzki [52] on parotid tumors, two groups that comprehensively assessed cell phone users in a "dose-dependent" manner, suggest an effect of tumor type and laterality, latency (time to tumor development), and exposure (or "EMR dose", i.e., cumulative cell phone use in hours).

4.1 Tumor Incidence data from CBTRUS

The Central Brain Tumor Registry of the United States (CBTRUS) maintains a comprehensive and unique record of age-adjusted incidence of primary central nervous system (CNS) tumors. In its recently published 2007-2008 Statistical Report [6], which collected data from 2000-2004 from 15-19 state registries in the US, an age-adjusted incidence of 18.2/100,000 population was noted in 2004. According to its 2002-2003 Statistical Report, which collected data from 1995-1999 from 12 state registries, the incidence was 13.4/100,000 population in 1995. The change in incidence rates (**Table 2**) since 1995 is shown in **Figure 3**.

Table 2. Age adjusted incidence of primary CNS tumors in the sequential reports of CBTRUS*

		CBTRUS	REPORT	
	2002-2003	2004-2005	2005-2006	2007-2008
DIAGNOSIS YEAR				
1995	**13.4****	NA***	NA	NA
1996	**14**	NA	NA	NA
1997	14.2	**13.5**	NA	NA
1998	14.5	13.9	**14.2**	NA
1999	14	14.1	**14.5**	NA
2000	NA	14.2	14.8	**15.2**
2001	NA	14.7	15.3	**15.9**
2002	NA	NA	15.2	**16.2**
2003	NA	NA	NA	**17**
2004	NA	NA	NA	**18.2**

* Incidence is cases per 100,000 population age-adjusted to the US population 2000 standard.
** Latest published incidence for each year of diagnosis is highlighted in bold. Changes in incidence within and between years have been attributed by CBTRUS mainly to better surveillance and delayed reporting (*late ascertainment*; see text for details)[6].
*** NA = not available

Given that CBTRUS reports CNS tumor incidence age-adjusted to the 2000 US Standard population and that the time period of these reports is well embedded within the MRI era of the US, the observed increase in incidence of approximately 36% in less than a decade is not explained by an ageing population (since these figures were age-

adjusted to the same standard population) or by "better detection". However, the change may in part be due to the effect of delay in data accrual or reporting referred to as "late ascertainment" [10] (Personal Communication, Lloyd Morgan, Director of CBTRUS; 4/23/08). Alternatively, as stated in the CBTRUS 2007-2008 Report [6], it may also be due in part to the influence of increased surveillance of non-malignant tumors resulting from US Public Law 107-260 which was passed in 2002 and instituted beginning in 2004. For these latter reasons, it follows that the 2004 incidence may be an underestimation of the current true incidence in 2008, as observed in changes in yearly incidence between the consecutive Statistical Reports of CBTRUS (**Table 2** and **Figure 3**) [6]. Although the authors recognize that the current CBTRUS data suggest that malignant brain tumor age-adjusted incidence overall has not increased [6,21], the most recent data are already at least four years outdated. On the other hand, a statistically significant increase in benign brain tumor incidence is reported in the most recent publications of CBTRUS [6,48]. Specifically, pilocytic astrocytoma, nerve sheath tumors and pituitary tumors in people 0-19 years old; and nerve sheath tumors, meningioma and pituitary tumors in people 20-64 years old. While no firm conclusions can be drawn regarding the reasons for such changes, following and identifying reasons for any future changes in brain tumor incidence is imperative from a public health perspective, given the high morbidity and mortality associated with these lesions [61].

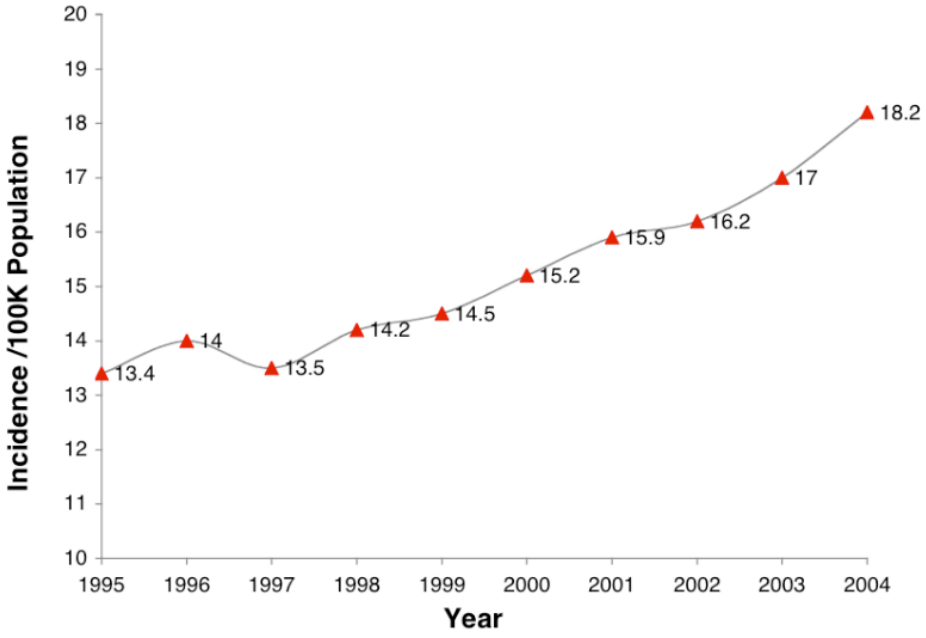

Fig. 3. Age-adjusted incidence of primary CNS tumors by year; US population 2000 standard (data source: CBTRUS, 2008 [6]).

5. CONCLUSION

The authors believe that the aforementioned epidemiologic and laboratory findings underscore the need for reassessment by Governments worldwide of cell phone and also mast radiation exposure standards and the usage and deployment of this technology. If the epidemiologic data continue to be confirmed, then in the absence of appropriate and timely intervention and given the increasing global dependence on cell phone technology especially among the young generation, it is likely that neurosurgeons will see increasing numbers of primary brain tumors, both benign and malignant. The earliest observation of this phenomenon may be commencing as noted in the latest Statistical Report of the Central Brain Tumor Registry of the United States (CBTRUS) [6].

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(see *Surgical Neurology* Section Editor's **Commentary** on next page)

COMMENTARY

The authors have provided the most comprehensive study and analysis to date of this topic, which, until the last year or so, has remained controversial - most studies denying a relation between cell phone use and a risk of brain tumor development. The sentinel work of Hardell et al (noted well in this article) has now alerted the medical community, and the warning in lay publication by Khurana [1] has brought attention of the problem to the lay as well as the medical community. As the authors suggest, further detailed analysis of what wattages and electromagnetic fields are dangerous and need adjustment to the regulation of acceptable wattages will undoubtedly necessitate access to data from the records of cell phone companies. In the United States, such access will undoubtedly require some form of legislative action on the part of the federal and perhaps state legislatures. In order to facilitate further research on this most important issue, a concerted effort on the part of our scholarly societies - the AANS and the CNS - to petition legislators for appropriate action is necessary. Dennis Kucinich, U.S. Congressman of Ohio, has held hearings on this topic, but thus far, no action has taken place as a consequence. It is time for action by the neurosurgical community.

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