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TOPIC REVIEW

Cell phones and glioma risk: a review of the evidence

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Introduction

Recently cell phones have become the target of much controversy because they are increasingly being viewed as potential carcinogenic agents with a causal role in brain tumor development. The overall incidence of malignant brain tumors in the United States from 1992 to 2007 declined slightly from 6.8 to 6.2 per 100,000, while the incidence in children has risen slightly over the past three decades [1, 2]. According to the Central Brain Tumor Registry (CBTRUS) [3] in 1995 the incidence of both benign and malignant brain tumors was 13.4 per 100,000 and in 2004 it was 18.2 per 100,000. The cause of the clear increase in benign tumor incidence is unknown, but there is concern that cell phones can trigger biological effects and that several decades of cell phone use in an individual may significantly increase the risk of a malignant brain tumor. The potential public health problem is sizeable as the most common malignant brain tumors are highly lethal and cell phone use in the U.S. alone has escalated dramatically, with approximately 70 million new cell phone subscriptions between 2006 and 2010, and 250 million subscriptions overall in 2007 [4, 5].

The concern relating to cell phone use and brain cancer is underscored by the fact that teens and children are beginning to use cell phones at younger ages [6]. Moreover, greater than 4 of 5 children/teens 12 years and older sleep with a cell phone next to them, often under the pillow [7]. Children and young adults are more susceptible to the harmful effects of carcinogenic agents such as radiation [8]. Therefore, a shift in incidence of brain tumors in younger age groups may emerge as their exposure to cell phones reaches long-term status and attains the 10-year or greater mark. A recent study revealed that children exposed to 1,800 MHz cell phone electromagnetic fields (EMF) can experience significantly higher exposures to cortical regions, hippocampus, hypothalamus and the eye than adults, and that this difference can be greater than one order of magnitude [6].

The most feared brain tumors in adults and children are the gliomas, which include the astrocytomas and oligodendrogliomas. These tumors are graded on a progressive scale of malignancy~~and tumor burden~~, and astrocytomas that have progressed to the Grade IV World Health Organization (WHO) classification level are also known as glioblastomas [9]. Glioblastomas are common brain tumors and most frequently arise de novo as primary cancers. The gliomas as a whole comprise approximately 33% of all brain tumors and 79% of malignant brain tumors [3]. Cure is not typical and the therapy of even low grade gliomas can be challenging. The glioblastomas are highly lethal and despite ~~heroic~~ treatment efforts patients are dead at a median of 14 months after diagnosis [10]. Five year survival is dismal, less than ~~5~~%. This review will focus specifically on glioma risk from cell phone use, and will begin with a brief overview of the state of the relevant cell phone—brain tumor risk literature.

The two significant, comprehensive databases concerning cell phone use and brain cancer risk are the often cited Hardell (Sweden) and the multicenter European Interphone studies [11, 12]. These two groups each include multiple studies, and they comprise the major focus of the current review. Glioma risk data derived from Hardell and Interphone, as well as from some smaller studies, is partitioned

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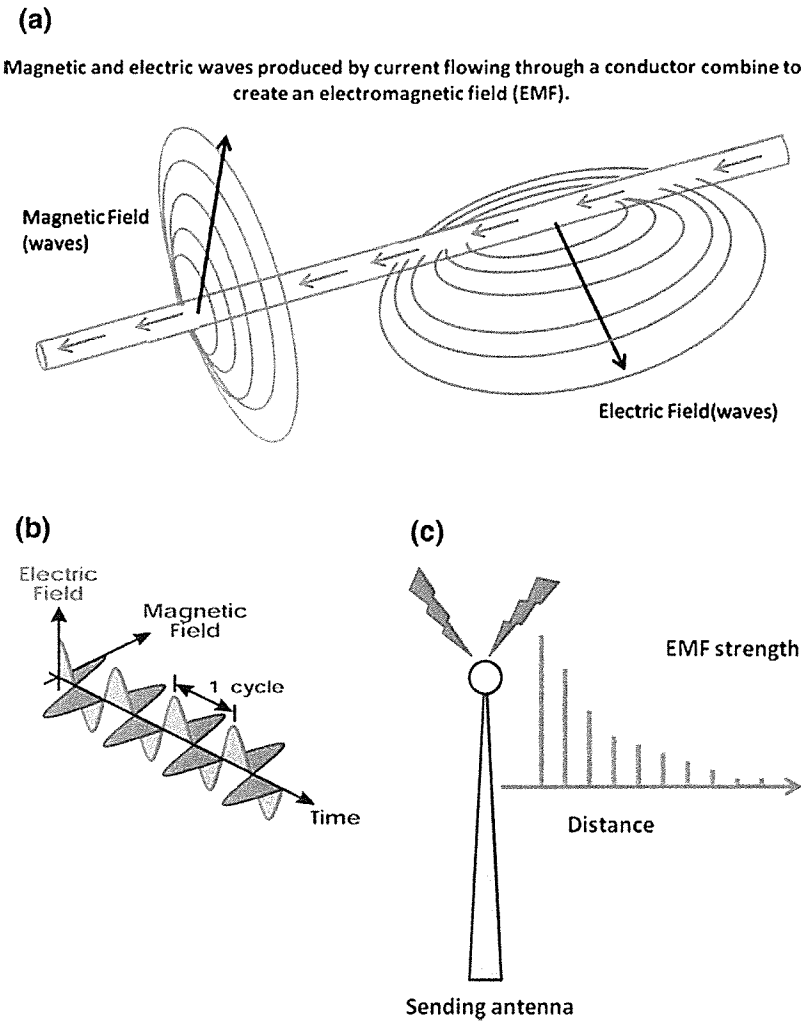

Fig. 1 **a** Electric current flowing in a conductor, either an antenna or a circuit inside the cell phone, generates both magnetic and electric fields. These fields consist of oscillating magnetic and electric waves which combine to form the EMF. **b** The magnetic and electric waves which make up the EMF oscillate perpendicular to each other and also perpendicular to the direction of propagation of the EMF. Each period of oscillation is 1 cycle, of which a certain number occur per unit time. This is known as the frequency. Cell phones emit electromagnetic waves that oscillate at a frequency of 800–2,200 MHz, or up to 2,200,000,000 times per second. **c** Cell phones emit EMF when they receive, process and amplify a signal, and also when they generate a signal from the built-in antenna. The EMF is strongest at the source and weakens exponentially according to the distance from the source. This is why it is best to keep the cell phone away from the body and the head

according to short term versus long term usage. The risk of generating gliomas in general, low grade gliomas alone, and high grade gliomas alone, is addressed according to the Hardell and the Interphone studies. Glioma risk is expressed in the context of the generally used exposure parameters associated with cell phone use, viz., duration of use in years (latency), total usage hours over the duration time period, and laterality (side of head involved).

Overview of current knowledge relating to cell phone use and gliomas

Cell phone emissions and recent physiological measurements in humans

Cell phones emit radiofrequency EMF (RF-EMF) (Fig. 1a, b) in the range of 800–2,200 MHz, and the exposure to the RF-EMF is highly localized to the temporal lobe when a person uses a cell phone, with the maximum dose deposition occurring in the outermost brain layers [13, 14]. A Swiss study found that 900 MHz EMF applied via cellular phones to the heads of human volunteers significantly increased cerebral blood flow in the ipsilateral (same) side of the brain, indicating that brain metabolism had been affected in that region [15]. Another more recent study which has received considerable attention revealed clear evidence of increased glucose metabolism on the ipsilateral side of the brain associated with 50 min of cell phone use [16]. This study which was well-controlled, is significant in that it shows a physiological effect caused by cell phone use; whether increased glucose consumption by brain tissue is a marker for long-term effects potentially leading to cancer or other deleterious effects remains to be determined.

A variety of human, rodent and cell culture experimental studies though inconclusive, do collectively suggest that mammalian brain tissue may be sensitive to cell phone levels of EMF and may exhibit measurable changes in

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function [16–20]. Whether these effects can trigger the development of cancer and whether they are pertinent to human cell phone use, is not known. Nonetheless, the available information, while still early and limited in nature, points to the possibility that cell phones have the potential to cause biological changes, and that these effects should be further characterized [21].

Overview of epidemiological studies

Myung et al. [22] performed a meta-analysis on 22 relevant case–control cell-phone risk studies to compare the results and derive an overall estimation of the risk of brain tumors from cell phone use. The authors determined that overall, there was a slight increase in the risk of brain tumors for regular cell phone users and this risk is most pronounced for an induction period of 10 years or greater [22]. When the results were analyzed in greater detail, the pooled data from eight studies showed a positive association between cell phones and brain tumors, seven of which were the Hardell group studies. These studies were considered by the Myung study [22] to have higher methodological quality because they used blinding as to whether the participant was a case or control. Fifteen other studies found an overall negative association between cell phone use and tumors, nine of these studies were Interphone related studies that were criticized for lack of subject versus control blinding [22]. Blinding in case–control studies, signifies that the interviewer does not know whether the subject being interviewed has the disease of interest (i.e.: brain cancer) or not. In this sense, they are less likely to be biased when directing questions to an interviewee. Therefore, blinding as to whether the subject is a case or control, is less likely to introduce bias into the study. For example, as Schulz and Grimes [50] state, the interviewer might ask more leading questions or look more in depth at a cases exposure status or background (i.e.: cell phone use and exposure) than he/she would for a control subject, which can in turn lead to skewed results.

Other observers have either determined that there is or is not a significant risk associated with cell phone use and the development of gliomas. Christensen et al. [23], Ahlbom et al. [24], Schoemaker et al. [25], Takebayashi et al. [45], Klaeboe et al. [46], and Johansen et al. [47] stated that the available evidence does not suggest an association. Kundi [26] however indicates that the Interphone studies are flawed and that the Hardell data reveals a definite association between cell phones and brain cancer. A review by Khurana and colleagues [5] states that the evidence supports an association between cell phone use and brain tumor risk, especially for those who have been exposed to cell phones for longer periods of time. Khurana's [5] paper represents a comprehensive effort at synthesizing data from different sources, as it incorporates the full weight of the evidence, including in vivo and in vitro studies, as well as evolving epidemiologic evidence. With the evidence pointing in both directions, it is clear that a comprehensive standardization of study design needs to be implemented before a clear determination can be made. Most authors agree that more evidence is needed, especially with regard to exposure in children, and that the effects of long latency periods and high intensity of cell phone use need to be systematically examined.

Glioma risk and duration of cell phone use (latency)

Short term exposure risk

There is considerable variation in the literature as to the definition of a short term versus a long term risk. For the purposes of this review, we will define short term use as less than 10 years of cell phone use and long term use as 10 years or greater. Table 1 summarizes the results of several papers addressing glioma risk for different latency periods, i.e., duration of use. Focusing on latency is an important factor of epidemiologic studies since the time from exposure to cancer development is often thought to be around 10 years [27]. Exposure time is also a relevant factor since some subjects might be using cell phones for longer call times, increasing their cumulative exposure times. The pertinent studies had different designs, and this should be borne in mind with the recognition that Table 1 is a summary of somewhat diverse information.

Overall short term risk assessment—Hardell and Interphone

The Hardell studies identified an association between short term cell phone use and an increased risk of glioma (Table 1) [28–31]. The 2006 study determined that astrocytoma patients with a 1–5 year latency period and a cumulative call time of greater than 64 h of digital cell phone use experienced a 2.0 (1.1–3.6) increased odds of astrocytoma than non-regular cell phone users. Similarly, patients with a 5–10 year latency period and cumulative call time of >64 h of digital cell phone use had a 2.7 (1.5–5.0) increased odds of cancer compared to non regular users. For less exposure time <64 h, there was no significant association between cell phone use and astrocytoma.

Pooled Interphone data reveal no association between cell phones and gliomas with use of less than 10 years, with the exception of >1,640 cumulative hours of cell phone use and a latency of 1–4 years (Table 1; odds ratio = 3.77 [1.25–11.4]) [12, 32, 33]. However some of the Interphone data point to significant study design flaws, as several of the Interphone related studies indicated a protective effect of cell

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Table 1 Summary of overall glioma risk in epidemiological studies to date

Paper	Histology	Cell phone type	Hours of exposure	Latency (years)	Number of cases/controls	OR	95% CI
Hardell (2006)	Astrocytoma	Digital	≤64	1–5	40/139	1.5	0.9–2.4
	Astrocytoma	Digital	>64	1–5	31/75	**2.0**	**1.1–3.6**
	Astrocytoma	Digital	≤64	5–10	19/44	2.0	1.03–3.8
	Astrocytoma	Digital	> 64	5–10	47/67	**2.7**	**1.5–5.0**
	Astrocytoma	Analog	≤80	5–10	8/24	1.3	0.5–3.4
	Astrocytoma	Analog	>80	5–10	9/12	2.7	0.97–7.7
	Astrocytoma	Digital	≤64	≥10	0/0	–	–
	Astrocytoma	Digital	>64	≥10	16/18	**3.6**	**1.6–7.8**
	Astrocytoma	Analog	≤80	≥10	6/13	2.2	0.8–6.5
	Astrocytoma	Analog	>80	≥10	34/27	**5.4**	**2.6–11**
Hardell (2009)	Astrocytoma	Both	–	>1	346/900	**1.4**	**1.1–1.7**
	Oligodendroglioma	Both	–	>1	51/900	1.5	0.9–2.4
	Other/mixed glioma	Both	–	>1	35/900	1.0	0.6–1.7
	Astrocytoma	Both	–	>10	78/99	**2.7**	**1.8–3.9**
	Oligodendroglioma	Both	–	>10	5/99	1.6	0.5–4.8
	Other/mixed glioma	Both	–	>10	5/99	1.8	0.6–5.3
Takebayashi [45]	Gliomas	Both	–	2.2–4.6	11/25	0.92	0.37–2.28
	Gliomas	Both	–	4.7–6.5	17/25	1.85	0.78–4.40
	Gliomas	Both	–	>6.5	7/29	0.60	0.20–1.78
Shuz (2006)	Gliomas	Both	–	<5	80/191	0.92	0.66–1.27
	Gliomas	Both	≤34.5	≥5	18/48	0.84	0.47–1.50
	Gliomas	Both	>34.5	≥5	25/42	1.31	0.77–2.26
Lonn (2005)	Gliomas	Both	Regular use[a]	<5	120/219	0.9	0.6–1.2
	Gliomas	Both	Regular use	5–9	69/138	0.7	0.5–1.0
	Gliomas	Both	Regular use	≥10	22/33	0.9	0.5–1.6
	Gliomas	Digital	Regular use	<5	119/243	0.7	0.5–1.0
	Gliomas	Digital	Regular use	≥5	83/136	0.8	0.6–1.2
	Gliomas	Analog	Regular use	<5	9/12	1.0	0.4–2.6
	Gliomas	Analog	Regular use	5–9	25/44	0.7	0.4–1.2
	Gliomas	Analog	Regular use	≥10	25/38	0.8	0.5–1.5
Lakhola (2007)	Gliomas	Both	Regular use	<10	724/1633	**0.76**	**0.65–0.88**
	Gliomas	Both	≤75	≥10	52/111	0.70	0.48–1.01
	Gliomas	Both	>75	≥10	81/105	1.13	0.82–1.57
	Gliomas	Analog	Regular use	0.5–4	156/313	0.90	0.69–1.16
	Gliomas	Analog	Regular use	5–9	59/125	0.75	0.51–1.08
	Gliomas	Analog	Regular use	≥10	16/31	0.92	0.48–1.77
	Gliomas	Digital	Regular use	0.5–4	587/1372	0.72	**0.62–0.85**
	Gliomas	Digital	Regular use	5–9	198/374	0.83	0.67–1.04
	Gliomas	Digital	Regular use	≥10	0/0	–	–
Klaeboe [46]	Gliomas	Both	Regular use	<2	38/61	0.6	0.4–1.0
	Gliomas	Both	Regular use	2–5	68/105	0.6	0.4–0.9
	Gliomas	Both	Regular use	≥6	55/61	0.7	0.4–1.2
	Gliomas	Digital	Regular use	<2	26/46	0.6	0.3–1.0
	Gliomas	Digital	Regular use	2–5	60/98	**0.5**	**0.3–0.8**
	Gliomas	Digital	Regular use	≥6	24/26	0.7	0.4–1.3
	Gliomas	Analog	Regular use	<6	5/42	0.4	0.1–1.4
	Gliomas	Analog	Regular use	≥6	10/46	0.7	0.4–1.2

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Table 1 continued

Paper	Histology	Cell phone type	Hours of exposure	Latency (years)	Number of cases/controls	OR	95% CI
Schuz (2006)	Gliomas	Both	Regular use	1.5–4	–	**0.77**	**0.65–0.92**
	Gliomas	Both	Regular use	5–9	–	0.75	0.62–0.90
	Gliomas	Both	Regular use	≥10	–	0.95	0.74–1.23
Johansen [47]	Gliomas	Both	–	SIR	–	0.94	0.72–1.20
Inskip (~~Duration-RU~~-2010)	Gliomas	Both	Regular use	<0.5	24/56	0.6	0.3–1.1
	Gliomas	Both	Regular use	0.5 to <3.0	31/55	0.9	0.5–1.6
	Gliomas	Both	Regular use	≥3.0	30/60	0.9	0.5–1.5
	Gliomas	Both	Regular use	≥5	11/31	0.6	0.3–1.4
Hepworth (~~Cum-hours-RU~~-2006)	Gliomas	Both		<10	429/772	0.93	0.77–1.13
	Gliomas	Both	≤113	≥10	23/56	0.61	0.36–1.04
	Gliomas	Both	>113	≥10	39/54	1.11	0.70–1.75
	Gliomas	Digital	–		378/685	0.95	0.79–1.16
	Gliomas	Analog	–	<10	69/115	0.86	0.61–1.22
	Gliomas	Analog	≤126	≥10	23/47	0.70	0.41–1.21
	Gliomas	Analog	>126	≥10	31/47	0.98	0.59–1.62
Hartikka (2009)	Gliomas	–	2–539	–	–	3.31	0.84–12.98
	–	–	>540	–	–	1.33	0.29–6.03
Interphone (multiple studies)	Gliomas	Both	<5	1–4	127/182	0.68	0.50–0.93
	Gliomas	Both	5 h–114.9	1–4	449/533	0.82	0.67–0.99
	Gliomas	Both	115.8–359.9	1–4	121/154	0.74	0.52–1.03
	Gliomas	Both	360–1639.9	1–4	80/95	0.75	0.50–1.13
	Gliomas	Both	1640+	1–4	23/8	**3.77**	**1.25–11.4**
	Gliomas	Both	<5 h	5–9	10/13	0.86	0.32–2.28
	Gliomas	Both	5 h–114.9	5–9	180/208	0.86	0.66–1.12
	Gliomas	Both	1158–359.9	5–9	156/192	**0.71**	**0.53–0.95**
	Gliomas	Both	360–1639.9	5–9	174/204	**0.72**	**0.54–0.95**
	Gliomas	Both	1640+	5–9	94/73	1.28	0.84–1.95
	Gliomas	Both	<5 h	≥10	4/2	1.13	0.16–7.79
	Gliomas	Both	5 h–114.9	≥10	20/25	0.63	0.32–1.25
	Gliomas	Both	115.8–359.9	≥10	41/42	0.89	0.53–1.50
	Gliomas	Both	360–1639.9	≥10	94/90	0.91	0.63–1.31
	Gliomas	Both	1640+	≥10	93/73	1.34	0.90–2.01

[a] Regular use is defined as at least one incoming or outgoing call per week for at least 6 months

(–) Dash denotes value not indicated in original report

Numbers in *bold* are statistically significant

phone use with respect to glioma, i.e., those subjects that used cell phones were less likely to develop glioma [23]. An Interphone study by Lakhola and colleagues [33], which encompassed data from five Northern European countries, found that cell phone non-regular users were 24% more likely to have glioma than subjects who used cell phones for 1–10 years (OR = 0.76 [0.65–0.88]). When this association was further analyzed based on the cell phone type, a significant protective effect emerged for digital cell phones but not for analog cell phones [33]. Moreover a pooled analysis showed that other Interphone studies also uncovered a protective effect. This analysis suggested that subjects who used cell phones for 1–114.9 h, for a latency period (duration) of 1–4 years, were less likely to develop gliomas compared to subjects that did not regularly use cell phones. Moreover the pooled analysis also indicated that those subjects who used cell phones for 115–1639.9 h for a latency period of 5–9 years were less likely to develop gliomas compared to subjects who used cell phone on an inconsistent basis.

Additional studies—overall short term risk assessment

There were few other studies conducted that were not associated with either the Hardell group or the Interphone

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study. Two studies, one by Hepworth and colleagues [34] and the second by Inskip et al. [35], did not uncover a significant association between cell phone use and gliomas for a latency period of less than 10 years.

Short term cell phone use risk according to grade of glioma

Tumor grade is an index of malignancy and low grade gliomas are capable of transforming into the very lethal high-grade gliomas. When subjects were divided based on whether they were diagnosed with a low or high-grade glioma, significant differences were observed (Tables 2, 3). There was no increased risk for low grade gliomas and cell phone use at short or long latency periods or for short and long cumulative call times. Although only six studies looked at low grade gliomas specifically, the results are all consistent.

Low grade gliomas short term risk Hardell and Interphone

Two Hardell analyses from 2006 examined short term exposure to cell phones and the risk of low grade gliomas. Neither study found a significant association [28, 52].

Only two studies associated with the Interphone study group examined this association. Shuz and colleagues [36] looked at the association between short term exposure and low grade gliomas in 2006, but did not find a significant association. Lonn and colleagues [37] also found no association between cell phones and low grade gliomas for short term use. Another study associated with Interphone by Christensen and colleagues [23] found a protective effect of cell phone use and the risk of glioma for those who used cell phones for greater than 5 years compared to non regular users.

High grade gliomas short term risk Hardell and Interphone

Two Hardell analyses from 2006 did find a significant association between cell phone use and high-grade astrocytomas [28, 52]. Those who used cell phones for 1–5 years and for greater than 64 h were 2.1 (1.05–4.1) times more likely to have astrocytoma than non-regular cell phone users. Digital cell phone users who had a cumulative call time of less than 64 h and a 5–10 year latency were 2.4 (1.2–4.8) times more likely to have astrocytoma than non regular users, while those with a cumulative call time of greater than 64 h had 3.3 (1.7–6.4) times greater odds of having astrocytoma than non-regular users. For analog cell phone users, Hardell found that those with 5–10 years of cell phone use and a cumulative call time of greater than 80 h were 3.9 (1.2–12) times more likely to have astrocytoma than non-regular users.

Four Interphone studies examined the association between cell phones and high-grade gliomas. As can be seen in Table 2, only one of these studies, by Shuz and colleagues [36], found a positive association between cell phones and gliomas. This study looked specifically at the association for men and women separately and found that women who were regular cell phone users had a 1.96 (1.10–3.50) increased odds of glioma, compared to non-regular cell phone users. This was not observed for men.

Long term exposure risk

Overall long term risk assessment Hardell and Interphone

Hardell studies did find a significantly increased risk of high-grade glioma with exposure to cell phone, with a greater risk for longer latency periods and higher cumulative call times. Hardell and colleagues [38] did find an increased risk of astrocytoma of 5.4 (2.6–11) for a latency period of over 10 years and a cumulative call time of greater than 80 h, for analog phones. Similarly, digital cell phone users with a latency period of greater than or equal to 10 years and greater than 64 h of cell phone use were 3.6 (1.6–7.8) times more likely to have astrocytoma than non regular users. A similar finding was found for astrocytoma cases in another Hardell study from 2006 (Table 1).

Several Interphone studies looked at the association between cell phones and gliomas, although only a few looked at the association for greater than 10 years of latency. Of those that did, none found a significant association between cell phone use and gliomas, even at long term exposure.

Additional studies

One study by Hepworth and colleagues [34] looked at the association between cell phones and gliomas at greater than 10 years of latency, and did not find a significant association between cell phones and gliomas. An interesting Swedish study by Navas-Acien et al. [39], found that subjects with long-term exposure to solvents, lead, and pesticides/herbicides only exhibited increased glioma incidence when they were also exposed to moderate or high levels of low frequency magnetic fields.

Long term cell phone use risk according to grade of glioma

Low grade gliomas long term risk Hardell and Interphone

There are 5 studies that specifically examined long term exposure (latency) and low-grade glioma risk, including 2

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Table 2 Summary of high grade glioma risk in epidemiological studies to date

Variable	Histology	Cell phone type	Hours of exposure	Latency (years)	Number of cases/ controls	OR	95% CI
Hardell (2006)	Astrocytoma	Digital	≤64	1–5	34/139	1.7	0.96–2.9
	Astrocytoma	Digital	>64	1–5	22/75	**2.1**	**1.05–4.1**
	Astrocytoma	Digital	≤64	5–10	18/44	**2.4**	**1.2–4.8**
	Astrocytoma	Digital	>64	5–10	40/67	**3.3**	**1.7–6.4**
	Astrocytoma	Analog	≤80	5–10	6/24	1.4	0.5–4.0
	Astrocytoma	Analog	>80	5–10	8/12	**3.9**	**1.3–12**
	Astrocytoma	Digital	≤64	≥10	0/0	–	–
	Astrocytoma	Digital	>64	≥10	15/18	**4.5**	**2.0–10**
	Astrocytoma	Analog	≤80	≥10	6/13	**3.2**	**1.05–9.6**
	Astrocytoma	Analog	>80	≥10	32/27	**7.4**	**3.4–16**
Hardell (2006b)	Astrocytoma	Digital	≤64	1–5	90/349	1.4	1.01–1.9
	Astrocytoma	Digital	>64	1–5	53/235	1.2	0.8–1.7
	Astrocytoma	Analog	≤85	1–5	13/67	1.0	0.5–1.9
	Astrocytoma	Analog	>85	1–5	8/19	1.9	0.8–4.7
	Astrocytoma	Digital	≤64	5–10	22/70	1.6	0.9–2.8
	Astrocytoma	Digital	>64	5–10	64/107	**2.9**	**1.9–4.4**
	Astrocytoma	Analog	≤85	5–10	22/63	1.6	0.96–2.8
	Astrocytoma	Analog	>85	5–10	13/64	1.0	0.5–1.9
	Astrocytoma	Digital	≤64	≥10	0/0	–	–
	Astrocytoma	Digital	>64	≥10	15/18	**3.8**	**1.8–8.1**
	Astrocytoma	Analog	≤85	≥10	8/26	1.4	0.6–3.3
	Astrocytoma	Analog	>85	≥10	51/58	**3.7**	**2.3–5.9**
Shuz (2006)	Gliomas (males)	Both	Regular use	–	76/170	0.78	0.53–1.14
	Gliomas (females)	Both	Regular use	–	30/38	**1.96**	**1.10–3.50**
Lonn (2005)[a]	Glioma III–IV	Both	Regular use	<5	83/213	0.9	0.7–1.4
	Glioma III–IV	Both	Regular use	5–9	55/139	0.8	0.5–1.2
	Glioma III–IV	Both	Regular use	≥10	16/38	0.8	0.4–1.5
	Glioblastoma	Both	Regular use	<5	50/213	0.9	0.6–1.3
	Glioblastoma	Both	Regular use	5–9	35/139	0.8	0.5–1.2
	Glioblastoma	Both	Regular use	≥10	9/38	0.7	0.3–1.6
Lakhola (2007)	Glioblastoma	Both	Regular use	<10	304/1633	0.75	0.61–0.92
	Glioblastoma	Both	≤75	≥10	25/111	0.66	0.41–1.07
	Glioblastoma	Both	>75	≥10	32/105	0.93	0.34–1.01
Christensen (2005)	Gliomas	Both	–	1–4	24/66	0.59	0.43–1.75
	Gliomas	Both	–	≥5	34/88	**0.55**	**0.32–0.96**
	Gliomas	Both	–	5–9	26/66	0.57	0.32–1.02
	Gliomas	Both		≥10	8/22	0.48	0.19–1.26

[a] Regular use is defined as at least one incoming or outgoing call per week for at least 6 months

(–) Dash denotes value not indicated in original report

Numbers in *bold* are statistically significant

Hardell studies and 3 Interphone studies. None of them found an association. Aside from Hardell and Interphone, no other studies examined the risk of low-grade gliomas with long term cell phone use.

High grade gliomas long term risk—Hardell and Interphone

Both Hardell 2006 studies found significant associations between cell phones and high grade gliomas for long latency periods. Digital cell phone users with greater than 10 years of latency and greater than 64 h of exposure, were 4.5 (2.0–10) times more likely than non-regular users to have astrocytoma. Analog cell phone users with greater than 10 years of latency and with greater than 80 h of exposure were 7.4 (3.4–16) times more likely to have astrocytoma (Table 2).

Three Interphone studies examined the association between cell phones and high grade gliomas for long term exposure and none found a significant association between cell phones and brain tumors.

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Table 3 Summary of low grade glioma risk in epidemiological studies to date

Variable	Histology	Cell phone type	Hours of exposure	Latency (years)	Number of cases/ controls	OR	95% CI
Hardell (2006)	Astrocytoma	Digital	≤64	1–5	6/139	1.1	0.3–3.9
	Astrocytoma	Digital	>64	1–5	9/75	2.3	0.7–7.9
	Astrocytoma	Digital	≤64	5–10	1/44	0.4	0.04–4.6
	Astrocytoma	Digital	>64	5–10	7/67	1.1	0.3–4.6
	Astrocytoma	Analog	≤80	5–10	2/24	1.8	0.3–13
	Astrocytoma	Analog	>80	5–10	1/12	1.3	0.1–15
	Astrocytoma	Digital	≤64	≥10	0/0	–	–
	Astrocytoma	Digital	>64	≥10	1/18	1.5	0.1–15.0
	Astrocytoma	Analog	≤80	≥10	0/13	–	–
	Astrocytoma	Analog	>80	≥10	2/27	1.8	0.3–12
Hardell (2006b)	Astrocytoma	Digital	≤64	1–5	90/349	1.4	1.01–1.9
	Astrocytoma	Digital	>64	1–5	53/232	1.2	0.8–1.7
	Astrocytoma	Analog	≤85	1–5	13/67	1.0	0.5–1.9
	Astrocytoma	Analog	>85	1–5	8/19	1.9	0.8–4.7
	Astrocytoma	Digital	≤64	5–10	3/70	1.2	0.3–4.3
	Astrocytoma	Digital	>64	5–10	11/107	1.7	0.7–4.1
	Astrocytoma	Analog	≤85	5–10	4/63	1.4	0.4–4.2
	Astrocytoma	Analog	>85	5–10	3/64	0.8	0.2–2.8
	Astrocytoma	Digital	≤64	≥10	0/0	–	–
	Astrocytoma	Digital	>64	≥10	1/18	1.3	0.2–11
	Astrocytoma	Analog	≤85	≥10	0/26	–	–
	Astrocytoma	Analog	>85	≥10	6/58	2.2	0.8–5.9
Hardell (2009)	–	–	–	–	–	–	–
Shuz (2006)	Gliomas (males)	Both	Regular use	–	21/47	0.89	0.38–2.08
	Gliomas (females)	Both	Regular use	–	11/28	0.77	0.32–1.84
Lonn (2005)[a]	Glioma I–II	Both	Regular use	<5	22/213	0.6	0.3–1.1
	Glioma I–II	Both	Regular use	5–9	16/139	0.6	0.3–1.2
	Glioma I–II	Both	Regular use	≥10	6/38	1.0	0.4–2.8
Christensen (2005)	Gliomas	Both	–	1–4 Years	19/39	0.86	0.43–1.75
	Gliomas	Both	–	≥5	22/46	0.87	0.41–1.85
	Gliomas	Both	–	5–9	16/37	0.79	0.36–1.71
	Gliomas	Both	–	≥10	6/9	1.64	0.44–6.12

[a] Regular use is defined as at least one incoming or outgoing call per week for at least 6 months

(–) Dash denotes value not indicated in original report

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Study designs and potential pitfalls

Although the different group studies consistently find conflicting results, they all use a similar case–control approach. Case–control studies begin with individuals with disease, cases, and those without disease, controls. These two groups are then questioned about their exposure status, in this case cell phone use. In all of the cell phone studies, a questionnaire was used to determine the duration and frequency of phone calls, and ultimately the cumulative amount of cell phone exposure [22, 41]. One problem with this method is the high probability of recall bias, where both cases and controls might have a hard time remembering how often and for how long they used cell phones [22, 23]. A recently published paper took a different approach to studying this topic by looking at the correlation between cell phone subscriptions and brain tumors [40]. The authors found that there was a significant association between the number of cell phone subscriptions and brain tumors. Using multiple linear regression analysis, the effect of cell phone subscriptions was significant and independent of the effect of mean income, population and mean age [40].

One study from the Interphone group developed a case–control study of limited scope to determine how much bias

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there might be in cell phone recall studies [22, 23]. For 27 patients and 46 controls, they obtained cell phone records in order to compare them to self-reported call frequency and duration. The authors found that both cases and controls recalled the number of calls accurately, but recalled the duration of phone calls imprecisely [23]. This is always a potential pitfall with case control studies and is especially relevant in these studies since total amount of cell phone call time is being used to determine total exposure time. Inaccurate recall of total call time might cause an over or under estimation of true risk, depending on the magnitude of the error.

Laterality is another important issue in the cell phone brain cancer debate [14, 42]. Laterality refers to the location of the primary tumor and the side of the head that is routinely used for cell phone conversations. If a subject used their cell phone on the same side of the head as the tumor appeared, this is defined as ipsilateral exposure. Conversely, when the cell phone was routinely used on the opposite side of the head as the tumor appeared, this is defined as contralateral exposure. Laterality might be an important predictor of tumor risk, and a stronger association would be observed between glioma risk and ipsilateral versus contralateral use. But, the results in this context have been extremely variable (Table 4) [14, 42]. Some studies reported an increased risk for the ipsilateral scenario while others find a decreased risk. Moreover there are reports of decreased risk for the contralateral scenario while others found an increased risk, and still others found no association with laterality [5, 9, 23, 33, 42]. This perplexing data may have an as of yet undetermined biological basis, or may in part stem from errors in self reporting cell phone use. For example, subjects might try to rationalize the cause of their tumor and report ipsilateral cell phone use.

Hardell study design

The Hardell group has performed several epidemiologic studies examining the role of cell phone use in brain tumor development [11, 28–31, 38, 52]. Study participants were chosen from a cancer registry in Sweden and controls were chosen from the national Swedish population registry. The study population ranged from 20 to 80 years old and was given a self-administered questionnaire. If the questionnaire was incomplete or additional clarification was needed subjects were later interviewed over the telephone. Participation rates range from 85 to 91% for cases and controls in all published studies by the Hardell group. The Hardell group has consistently reported a significant association between brain tumors and cell phone and cordless phone use. They have found an association when analyzing all ages combined, for latency periods from 1 to 10 years and greater than 10 years with ipsilateral cell phone use. Many Hardell studies include participant overlap, as several of the published papers are extensions of previous studies or include adjusted age categories to match other studies. Also noteworthy is the fact that the highest risk values are obtained in Hardell studies where exposures began when the subjects were teenagers.

Interphone study design

The Interphone study is a large case control study involving 13 countries. It is coordinated by the Union for International Cancer Control (UICC) and is coordinated by an international Interphone study group that consists of 21 scientists who are in charge of the progress of the study, analyses and interpretation of the study results [41]. Funding for the Interphone study comes from the Mobile Manufacturers' Forum, the GSM Association which represents the world wide interests of the mobile communications industry and from other mobile phone operators and manufacturers. Approximately 6 million out of a total of 20 million Euros came from private funding. The bulk of Interphone funding came from public sources such as the European Commission. The U.S. did not participate in the Interphone study. Overall scientific coordination of Interphone was provided by the International Agency for Research on Cancer (IARC), rather than by UICC—which provided sole funding, but no technical oversight.

In the description of the Interphone study funding details, the UICC did state that there was a firewall mechanism provided by the UICC for some of the funding to guarantee the independence of the scientists [12, 32, 41]. Controls for the study were frequency or individually matched by age, sex and region of residence to control for these factors in analysis. A common core protocol and questionnaire were used for all study sites involved in the Interphone study. Study participants ranged from 30 to 59 years old and participation rates for the multiple Interphone study groups were 64% for gliomas and for 53% for controls.

Overall, most of the results in the multiple Interphone studies found no significant association between cell phone use and brain cancer, except at exposure times greater than 1,640 h of total cell phone use. In a recent publication on pooled Interphone study results, the only significant association the authors found between cell phones and brain tumors was for gliomas and meningiomas and ipsilateral cell phone use at greater than 1,640 h of cumulative call time [32]. In many instances, the Interphone study results showed a protective effect of cell phones, meaning that those who use cell phones are less likely to have brain cancer. This suggests that a significant study design flaw corrupted the statistical analysis, and may have also prevented the detection of an association between brain cancer

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Table 4 Summary of laterality and glioma risk in epidemiological studies to date

Variable	Histology	Cell phone type/latency	Cases/ controls	Ipsilateral	Cases/ controls	Contralateral
Paper						
Hardell 2006	Low grade astrocytoma	Analog	10/98	1.8 (0.8–4.1)	4/100	0.5 (0.2–1.6)
	Low grade astrocytoma	Digital	27/240	**1.9 (1.02–3.5)**	16/266	1.1 (0.5–2.1)
	High grade astrocytoma	Analog	62/98	**2.4 (1.6–3.6)**	37/100	1.6 (0.98–2.5)
	High grade astrocytoma	Digital	127/240	**2.3 (1.7–3.1)**	69/266	1.1 (0.8–1.5)
Hardell (2006)	Low grade astrocytoma	Analog	3/25	2.3 (0.4–1.4)	1/28	0.3 (0.03–3.7)
	Low grade astrocytoma	Digital	12/108	(1.7 (0.5–5.4)	6/124	0.7 (0.2–2.6)
	High grade astrocytoma	Analog	22/25	**4.2 (1.9–9.4)**	20/28	**5.4 (2.2–13)**
	High grade astrocytoma	Digital	65/108	**3.2 (1.9–5.6)**	38/124	1.6 (0.9–2.9)
Hardell (2009)	Astrocytoma Grade I–IV	Both (<1 year latency)	229/374	2.0 (1.5–2.5)	98/308	1.0 (0.7–1.4)
	Astrocytoma Grade I–IV	Both (<10 years latency)	50/45	**3.3 (2.0–5.4)**	26/29	**2.8 (1.5–5.1)**
Takebayashi [45]	Glioma	Both	31/50	1.24 (0.67–2.29)	25/49	1.08 (0.57–2.03)
Lonn (2005)	Glioma	Both (<5 years)	68/129	1.2 (0.8–1.7)	38/108	0.6 (0.4–1.0)
	Glioma	Both (5–9 years)	34/76	0.9 (0.6–1.4)	39/79	0.9 (0.6–1.3)
	Glioma	Both (>10 years)	14/15	1.8 (0.8–3.9)	9/23	0.6 (0.3–1.4)
Lakhola (2007)	Glioma	Both (<5 years)	275/639	1.07 (0.90–1.28)	199/625	0.70 (0.58–0.85)
	Glioma	Both (5–9 years)	144/282	1.18 (0.93–1.49)	109/280	0.79 (0.61–1.01)
	Glioma	Both (>10 years)	43/74	1.14 (0.76–1.72)	41/71	1.01 (0.67–1.53)
Klaeboe (2007)	Glioma	Both (<2 years)	22/35	0.9 (0.5–1.7)	19/32	0.8 (0.4–1.5)
	Glioma	Both (2–5 years)	39/57	0.9 (0.6–1.4)	28/54	0.6 (0.4–1.0)
	Glioma	Both (≥6 years)	30/30	1.2 (0.7–2.1)	27/34	0.9 (0.5–1.5)
Shuz (2006)	Glioma	Both (<5 years)	–	1.08 (0.88–1.31)	–	**0.70 (0.57–0.87)**
	Glioma	Both (5–9 years)	–	1.10 (0.89–1.35)	–	**0.74 (0.59–0.92)**
	Glioma	Both (>10 years)	–	**1.39 (1.01–1.92)**	–	0.98 (0.71–1.37)
Inskip (2010)	Any glioma	Both	–	RR 0.9 ($P = 0.77$)	–	–
	Astrocytic glioma	Both	–	RR 0.9 ($P = 1.0$)	–	–
Hepworth (2006)	Glioma	Both	278/486	**1.24 (1.02–1.52)**	199/491	**0.75 (0.61–0.93)**
Hartikka (2009)	Glioma	Both	–	1.45 (0.34–6.18)	–	**4.50 (1.07–18.86)**

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Numbers in *bold* are statistically significant

and cell phones. The authors of various Interphone studies generally admit that a protective effect is not plausible and do mention that participation rates differed between cases and controls. They also point to sampling bias, prodromal symptoms, confounding variables (a third variable related to both cell phone use and brain cancer can affect the association between the two variables), and ill-timed interviews, as potential reasons why this effect occurred. The Interphone studies did involve some personal interviews with patients while they were in the hospital [29, 41, 51]. Hence blinding as to whether the subject was a case or control did not occur, and might have led to interviewer bias and skewed the results [22].

Another limitation of the Interphone study was the fact that use of cordless phones was not systematically taken into account. This represents a potential source of bias as exposure to RF radiation from cordless phones may not have been uniformly shared between cases and controls. If cordless phone use was not universally shared between cases and controls, then this failure further hampered the ability to find important associations.

Future studies

Generating decisive evidence of an association between cell phones and brain cancer is challenging because cell phone technology, energy levels, and usage are evolving, and brain cancers are relatively rare and may take decades to develop. The scenario is further complicated by the likelihood of differing genetic susceptibility of individual subjects to brain cancer [43]. Genetically predisposed individuals may have a higher brain tumor risk with cell phone use, while other members of the population may

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have much reduced risk. Hence the studies have a selection bias because susceptible individuals may be very rare in the entire population, yet participants in the large scale studies with brain tumors typically outnumber controls. Finally, it is hard to detect short term changes in brain physiology or structure that may result from a cell phone call and are associated with, or lead to, a long-term process resulting in the development of a tumor.

A key problem with the large scale population studies evaluating cell phone use and brain tumor risk is the variability of study design. Although the Interphone study groups all use a similar design, other groups such as the Hardell have used different designs. This makes it difficult to directly cross reference and pool data originating from different studies. For example design differences are evident in the wide variation in the specific time epochs defined within short and long term latency periods, so that latency data cannot be readily compared among the different studies (Tables 1, 2, 3).

Lack of standardization in study design reduces the effective sample size which is a disadvantage when attempting to define a rare effect. Moreover, a lack of coordination and cooperation between researchers has allowed potentially flawed designs, like the Interphone group studies, to be implemented. Consequently evidence is effectively limited and it is difficult to determine whether there is an actual association between cell phones and brain cancer. The potential for recall bias, interviewer bias, participation bias and other potential pit falls associated with case–control studies make it difficult to understand how much of the information from these studies is a true association or a true lack of association. The best way to remedy this, is to conduct prospective studies, to follow those exposed to and not exposed to cell phones and determine if there is a difference in the incidence rates of brain tumors comparing the two groups. This type of study minimizes the recall bias present in case–control studies and also allows for collection of relevant exposure and disease information, rather than relying on data collected in the past. A prospective study was launched in Europe in March 2005, called the COSMOS study which will follow 250,000 participants for 20–30 years.

Prospective studies like COSMOS are an important step in studying the association between cell phones and brain tumors, but it will also be a long time before there will be results from such studies. While in an ideal world a nested prospective study would be of great value, this is a luxury that society cannot afford at this time, given the very rapidly rising use of cell phones in persons of all age groups. The potential for damage to the population is too great so research pursued over a shorter time scale is needed and must be standardized. Case–control studies should follow a similar study design and be controlled for potential bias in every way possible. Moreover a recent report stemming from a nationwide Israeli study on the sharp increase in parotid gland tumors associated phone use indicates that potentially a broad spectrum of pathologies will need to be considered [48]. Standardization of studies will allow for valid comparisons between study groups and will enable more sensitive and valid statistical analyses of pooled data. Realizing this goal will most probably require a multidisciplinary international body comprised of leading contributors to define an array of standard criteria to which studies must conform. This would be analogous to how neoplastic diseases are currently staged and evaluated in clinical trials. Several guidelines may be discussed and adopted for study design standardization and these could include:

(1) Cell phone energy levels need to be tabulated and matched between studies.
(2) The study population needs to be subdivided in a predictable manner according to age, sex, ethnicity, general health status, etc.
(3) The range of pathologies, e.g., brain tumors, parotid tumors, oral cancers, needs to be defined.
(4) The questionnaire should be the same for all studies, with reasons given for deviations, and appropriate blinding needs to be uniformly applied.
(5) If at all possible actual cell phone usage records should be used in place of subject recall, as recommended by Han et al. [49]. This should be mandated ~~by law.~~
(6) The latency periods (duration of use) should be defined uniformly.
(7) The overall statistical approach should be optimized and well-defined for prospective researchers.

Moreover, how the intensity of use is defined can be expanded to include an additional dimension. Length of phone use is one measure of exposure, but another important measure is average length of call over time. Cumulative integrated dose under the curve incorporates both duration of time of use along with average intensity. Thus, persons who use a phone for several hours a day have much more intense exposure even over less than 10 years, than those who use a phone for a few hours a month. Consideration of this additional measure highlights the need for researchers to be able to access cell phone provider call history data.

Contemplating the in vitro and in vivo experimental data

Although a comprehensive analysis of the current body of in vitro and in vivo experimental studies is beyond the scope of the present review, the authors do recognize that some future experimental studies may be designed to

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complement epidemiological studies so that data from these two sources can be cross-referenced to reveal important associations. For example short term epidemiological data that includes intense exposures might be related to in vitro and in vivo experiments that screen for the cell and tissue effects of short term, intense exposures. Moreover, studies involving humans, head phantoms, cell cultures and animal models may be integrated to provide a mechanistic understanding of events associated with ipsilateral and contralateral exposures and risks, as this is currently poorly understood and problematic.

Published reports suggest that mammalian brain tissue may be sensitive to cell phone levels of EMF and exhibit measurable changes in structure and function [5, 17–21]. For example there is evidence which shows that certain enzymes and DNA can be directly damaged by low-intensity EMFs, although more confirmatory work needs to be done and the precise mechanism(s) of damage has to be elucidated [5, 17, 18, 21]. The work of Volkow et al. [16] with human subjects shows that cell phone use at lower than typical energy levels can cause ipsilateral increases in brain glucose metabolism. This acute physiological finding indicates that biological effects can be caused by exposure to cell phone EMF, and it is reasonable to conclude that further in vitro and in vivo studies to elucidate potential mechanisms of biological damage are warranted [21].

Conclusions

Despite the results pointing to an association in one direction or another, it is clear that there is no definite answer to the question of whether cell phone use is associated with increased brain cancer risk. Notwithstanding the inconsistencies in the epidemiological studies, a few of the human studies do suggest an association between cell phone use and brain tumors for a 10 year or greater induction period and/or a high number of cumulative call hours. However, given the inconclusive nature of even the long term data, the best course of action is to pursue further studies and to execute these according to a standardized design. Moreover, in view of the conflicting epidemiological data, some researchers including the present authors suggest that cell phone use certainly continue, but that users might wish to consider using headsets if feasible to reduce EMF exposure, and that heavy cell phone use in children and young teens be avoided if at all possible [44].

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