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CLINICAL STUDY - PATIENT STUDIES

Cellular phone use and brain tumor: a meta-analysis

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Abstract
Background The dramatic increase in the use of cellular phones has generated concerns about potential adverse effects, especially the development of brain tumors. We conducted a meta-analysis to examine the effect of cellular phone use on the risk of brain tumor development.
Methods We searched the literature using MEDLINE to locate case-control studies on cellular phone use and brain tumors. Odds ratios (ORs) for overall effect and stratified ORs associated with specific brain tumors, long-term use, and analog/digital phones were calculated for each study using its original data. A pooled estimator of each OR was then calculated using a random-effects model.
Results Nine case-control studies containing 5,259 cases of primary brain tumors and 12,074 controls were included. All studies reported ORs according to brain tumor subtypes, and five provided ORs on patients with ≥10 years of follow up. Pooled analysis showed an overall OR of 0.90 (95% confidence interval [CI] 0.81–0.99) for cellular phone use and brain tumor development. The pooled OR for long-term users of ≥10 years (5 studies) was 1.25 (95% CI 1.01–1.54). No increased risk was observed in analog or digital cellular phone users.
Conclusions We found no overall increased risk of brain tumors among cellular phone users. The potential elevated risk of brain tumors after long-term cellular phone use awaits confirmation by future studies.

Keywords Brain tumors · Cellular phones · Radiation

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Introduction

With the widespread use of cellular phones in the past decade, human exposure to low-energy radiation in the 800- to 2,000-MHz range (microwave) has increased dramatically. With more than a billion current cellular phone users worldwide [1], this exposure could pose a serious public health problem even if the radiation emitted has only a small oncogenic effect. The risk of developing intracranial tumors from cellular phone use is of particular interest because of the proximity of exposure. Although it is agreed that any carcinogenic effect would have to be through a nonthermal, nonionizing mechanism, the nature or the existence of this mechanism remains unclear [2–5]. To date, most epidemiological studies published on cellular phone use and brain tumors have not demonstrated an increased risk with overall use [6–13], but positive associations have been reported in a few small subgroup analyses, such as with long-term users (increased risk of acoustic neuroma), analog phones, and ipsilateral use [14, 15]. The purpose of the study was to provide a pooled estimate on cellular phone use and the risk of brain tumor development using a meta-analysis. In addition, by pooling available studies together, we hope to explore further how potentially important clinical variables (e.g., duration of use and phone type) can affect the risk of brain tumor development in cellular phone users.

Methods

Literature review

A MEDLINE search was performed of literature dating from 1966 through April 2006 using the key words "cellular phones," "brain tumors," "cancer," "radiation," and "microwave" to identify all relevant articles on cellular phone use and brain tumors. For each selected article, the bibliography was searched to locate additional eligible publications.

Study selection and data abstraction

To be included in our review a study had to meet all of the following criteria: 1) it was published in English (no case-control studies were identified outside of the English literature); 2) it was case control in design (in the absence of randomized-controlled trials and prospective cohort studies for rare diseases like primary brain tumor, case-control studies provide the next highest level of evidence); 3) it presented sufficient data so that the crude odds ratios (ORs) for cellular phone use and brain tumors could be derived; and 4) the exposure to cellular phones was clearly defined and evaluated to minimize misclassification. Published case reports and studies with exposure other than cellular phones (e.g., cordless phones) were excluded from the study.

In addition to the original data, other data abstracted from the studies included the time period of study, country of origin, study setting (population versus hospital), information source for exposure measurement, adjusted estimates of effect, and potential confounding factors adjusted for in their estimates.

Statistical analysis

For each study, summary results were tabulated for analysis. Crude ORs for the risk of brain cancer associated with exposure to cellular phones and their standard errors were calculated based on the abstracted data. When possible, separate crude ORs were calculated for high-grade gliomas, low-grade gliomas, meningioma, and acoustic neuroma. In addition, when data were available, the results were stratified by length of exposure (≥10 years or <10 years), and by type of cellular phone (analog or digital). Pooled estimates of the crude ORs for all analyses were obtained by weighting each study with the standard error of the natural log of the OR. For our meta-analysis, the random-effects method of DerSimonian and Laird was used, with the estimate of heterogeneity taken from the Mantel–Haenszel model. Statistical heterogeneity was assessed using the chi-squared test; $P < 0.10$ was used as the criterion to represent statistical heterogeneity. The random-effects model incorporated both within- and between-study variability. Because heterogeneity was present in some of the comparisons (composite, high-grade glioma, analog versus unexposed, and digital versus unexposed, Table 1), it was more appropriate to use random-effects than fixed-effects meta-analysis. In addition, the random-effects method was selected because the results would be more conservative.

Begg's adjusted rank correlation test and Egger's regression asymmetry test were used to assess publication bias. A P value of 0.05 or less was considered significant.

All analyses were performed using Stata 8.0 (release 8, Stata Corporation, College Station, TX).

Results

We reviewed 48 articles and abstracts from our MEDLINE search and identified 10 case-control studies published between 2000 and 2006 that evaluated the association between cellular phone use and brain tumors (Table 2). One study was excluded from the meta-analysis because there were insufficient data to calculate the crude OR [14]. Other articles excluded from the original search included review articles, case reports, animal studies, or articles that were not relevant to the research question (e.g., studies that considered other forms of electromagnetic exposure or studies that had tumors other than primary brain tumors as their event of interest). In a further effort to be inclusive, we also searched the bibliographies of the articles identified and found no additional studies.

The 9 studies included in the meta-analysis contained a total of 5,259 cases of primary brain tumors and 12,074 controls. All studies reported ORs according to brain tumor subtypes, and five provided ORs on patients with 10 years or more of follow up. Five studies reported ORs according to the type of phone used (analog versus digital). All studies were performed in North America and Europe, and 6 of them [7, 8, 10, 12, 13, 15] were part of the Interphone

Table 1 Tests for heterogeneity between studies

	Chi-squared test—P value
Composite	0.052*
High-grade glioma	0.023*
Low-grade glioma	0.178
Meningoma	0.840
Acoustic neuroma	0.813
Composite–10 years exposure	0.833
Analog versus unexposed	0.001*
Digital versus unexposed	0.000*
Analog versus digital	0.452

* Statistically significant heterogeneity present

Table 2 Description of studies included in meta-analysis[a]

Study	Study description	# cases, # controls	Definition of exposure	Pooled OR (95% CI)	Adjusted OR from manuscript (95% CI)	Adjustments
Auvinen et al. 2002 [6]	Cases of brain tumors and salivary gland cancers diagnosed in Finland in 1996 from the population-based Finnish Cancer Registry. Five randomly sampled, population-based controls for each tumor case matched on age and sex were selected	796 cases, 3,972 controls	Regular cellular telephone use (defined as having a subscription to a cellular telephone service)	1.27 (0.94–1.72)	1.3 (0.9–1.8)	Adjusted for age and sex. Occupations, socioeconomic status, and places of residence were similar for controls and cases
Christensen et al. 2005 [7][b]	Cases of glioma and meningioma diagnosed in Denmark between September 1, 2000 and August 31, 2002. Randomly sampled, population-based controls matched on age and sex	427 cases, 822 controls	Regular cellular telephone use (defined as at least once a week for 6 months or more) compared with no regular use	0.73 (0.59–0.90)	Not reported	Adjusted for sex, age, educational level, use of hands-free devices in cars, marital status, and region of Denmark
Hepworth et al. 2006 [8][b]	Cases of glioma (age 18–69) identified between 2000 and 2004 from hospital records and cancer registries in 5 areas of the United Kingdom. Controls were randomly selected from practitioner's lists and frequency matched by age, sex, and region	966 cases, 1,761 controls	Regular cellular telephone use (defined as use for >6 months for at least 1 year prior to diagnosis)	1.01 (0.87–1.19)	0.94 (0.78–1.13)	Adjusted for age, sex, region, Townsend deprivation category, and interview reference date category
Inskip et al. 2001 [9]	Cases of glioma, meningioma, and acoustic neuroma diagnosed in hospitals in 3 regions of the United States. Hospital-based controls with nonmalignant conditions frequency matched by hospital, age, sex, race/ethnicity, and proximity of residence to the hospital	782 cases, 799 controls	Regular cellular telephone use (defined as two or more calls per week) compared to no use	0.80 (0.66–0.98)	0.9 (0.7–1.1)	Adjusted for matching variables (age, sex, race/ethnicity, and distance from patient's residence) as well as education, income, and date of interview
Lonn et al. 2004 [15][b]	Cases of acoustic neuroma diagnosed in regions of Sweden between 1999 and 2002. Controls randomly selected from population, frequency matched on age, sex, and residential area	148 cases, 604 controls	Regular cellular telephone use (defined as at least once per week during 6 months or more)	1.05 (0.73–1.52)	1.0 (0.6–1.5)	Adjusted for age, sex, residential area, and education

Table 2 continued

Study	Study description	# cases, # controls	Definition of exposure	Pooled OR (95% CI)	Adjusted OR from manuscript (95% CI)	Adjustments
Lonn et al. 2005 [10][b]	Cases of glioma and meningioma diagnosed in Sweden during 2000–2002. Controls randomly selected from population, frequency matched on age, sex, and residential area	644 cases, 674 controls	Regular cellular telephone use (defined as at least once per week during 6 months or more)	0.83 (0.69–0.99)	Not reported	Adjusted for age, gender, geographic region, and education
Muscat et al. 2000 [11]	Cases with brain cancer selected from 5 US academic medical centers between 1994 and 1998. Hospital-based controls with benign conditions frequency matched by age, race, and month of admission	469 cases, 422 controls	Regular cellular telephone use (defined as having/having had a subscription to a cellular telephone service)	0.75 (0.52–1.07)	0.8 (0.6–1.2)	Adjusted for age, education, sex, race, study center, proxy subject, month of interview, and year of interview
Schoemaker et al. 2005 [12][b]	Cases of acoustic neuroma were identified by medical centers in 4 Nordic countries and the United Kingdom between September 1, 2000 and August 31, 2002. Controls were randomly selected from the population register and matched on age and residence	678 cases, 3,553 controls	Regular cellular telephone use (defined as use for >6 months for at least 1 year prior to diagnosis)	0.95 (0.81–1.12)	0.9 (0.7–1.1)	Adjusted for center, region, age, sex, education, interview year, and interview lag time
Schuz et al. 2006 [13][b]	Cases were diagnosed with glioma or meningioma during 2000–2003 in 3 regions of Germany. Controls were randomly drawn from population registries and were matched on age, gender, and region	747 cases, 1,494 controls	Regular cellular telephone use (defined as at least one incoming or outgoing call per week for 6 months or more)	0.91 (0.75–1.09)	Not reported	Adjusted for gender, study center, age, socioeconomic status, and living in a city

[a] All studies included in the meta-analysis are case-control studies

[b] Study is part of the Interphone Study

Study, an international collaborative case-control study of the relationship between mobile phone use and primary brain tumors. All six studies shared the same methods to avoid discrepancies between designs. Among the nine studies, seven were population based [6–8, 10, 12, 13, 15] and eight [7–13, 15] obtained exposure information from direct interview of patients or their proxies. There was no evidence of statistically significant publication bias (Table 3).

Composite outcome

Associations between cellular phone use and brain tumor development were evaluated in all 9 studies. Pooling of data from all these studies resulted in an OR of 0.90 (95% [confidence interval] CI 0.81 to 0.99) (Fig. 1; Table 4) using a random-effects model. On the basis of the pooled estimate, there was no increased risk of brain tumors (all subtypes considered) associated with cellular phone use.

Brain tumor subtype

All studies evaluated the association between cellular phone use and brain tumor subtypes. The pooled OR (and 95% CI) for high-grade glioma [7, 8, 10, 11, 13] was 0.86 (0.70 to 1.05), for low-grade glioma [7, 8, 10, 11, 13] was 1.14 (0.91 to 1.43), for meningioma [6, 7, 9, 10, 13] was 0.64 (0.56 to 0.74), and for acoustic neuroma [9, 12, 15] was 0.96 (0.83 to 1.10) (Fig. 2A–D; Table 4) using random-effects models. On the basis of the pooled estimates, there appears to be no increased risk of any brain tumor subtypes associated with cellular phone use.

Composite outcome with exposure stratified by length of cellular phone use

Five studies [7, 8, 10, 12, 15] reported the association between cellular phone use of 10 years or more and brain tumor development. The pooled OR was calculated to be 1.25 (95% CI 1.01 to 1.54) (Fig. 3; Table 4) using a random-effects model.

Table 3 Tests for publication bias

	Egger's test—*P* value	Begg's test—*P* value
Composite	0.914	0.602
High-grade glioma	0.413	0.806
Low-grade glioma	0.126	0.086
Meningoma	0.666	0.806
Acoustic neuroma	0.945	1.000
Composite—10 years exposure	0.662	0.806
Analog verus unexposed	0.546	0.462
Digital versus unexposed	0.546	0.462
Analog versus digital	0.223	0.462

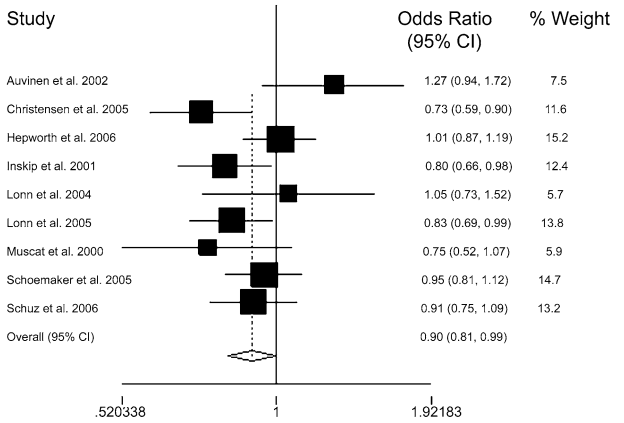

Fig. 1 Pooled odds ratio of brain tumor development associated with cellular phone use

Table 4 Summary of pooled estimates

Outcome	Pooled OR	95% CI
All brain tumors (with regular use as exposure)	0.90	0.81–0.99
Low-grade glioma (with regular use as exposure)	1.14	0.91–1.43
High-grade glioma (with regular use as exposure)	0.86	0.70–1.05
Meningoma (with regular use as exposure)	0.64	0.56–0.74
Acoustic neuroma (with regular use as exposure)	0.96	0.83–1.10
All brain tumors (with 10+ years use as exposure)	1.25	1.01–1.54
All brain tumors (with digital use as exposure)	0.86	0.68–1.09
All brain tumors (with analog use as exposure)	1.13	0.83–1.54
All brain tumors (comparing analog with digital)	1.22	1.06–1.41

Analog and digital cellular phones

Five studies [6, 8, 10, 12, 15] evaluated the association between the type of cellular phone used and brain tumor development. The pooled OR (and its 95% CI) for analog phone use compared with the unexposed group was 1.13 (0.83 to 1.54), whereas that for digital phone use compared with the unexposed group was 0.86 (0.68 to 1.09) (Fig. 4A, B; Table 4). When analog phone users were compared with digital phone users, the pooled OR was 1.22 (95% CI 1.06 to 1.41).

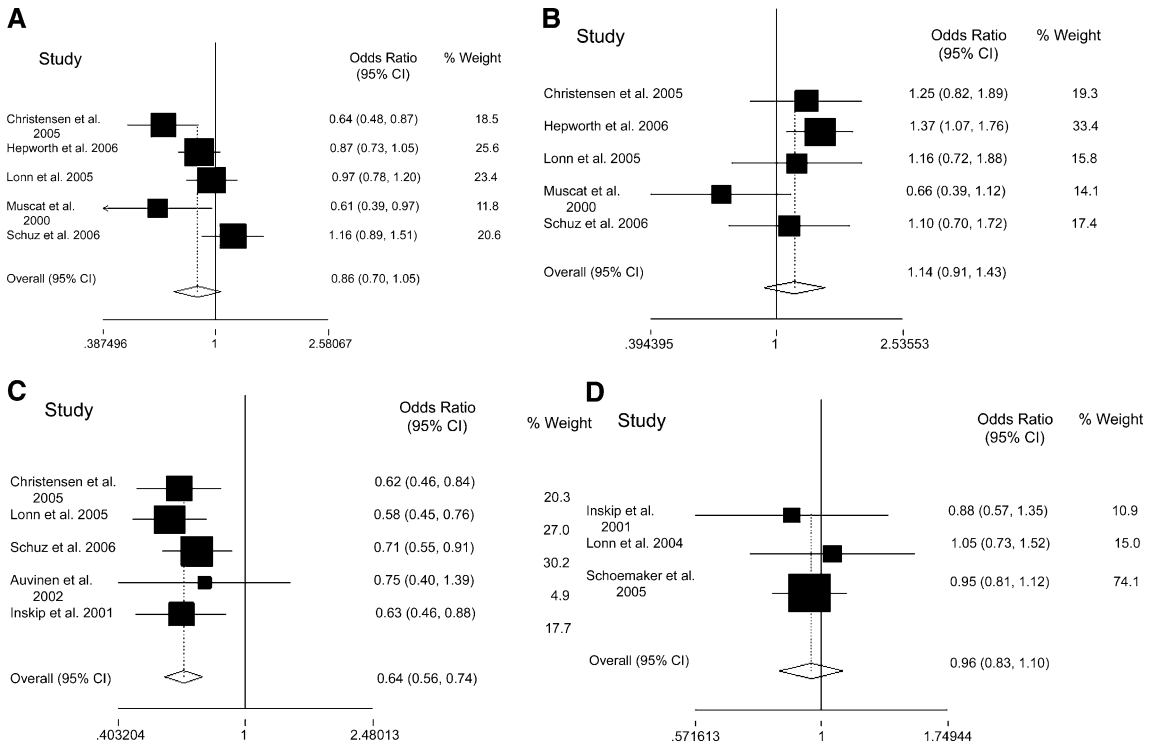

Fig. 2 Pooled odds ratio of high-grade glioma (**A**), low-grade glioma (**B**), meningioma (**C**), and acoustic neuroma (**D**) associated with cellular phone use

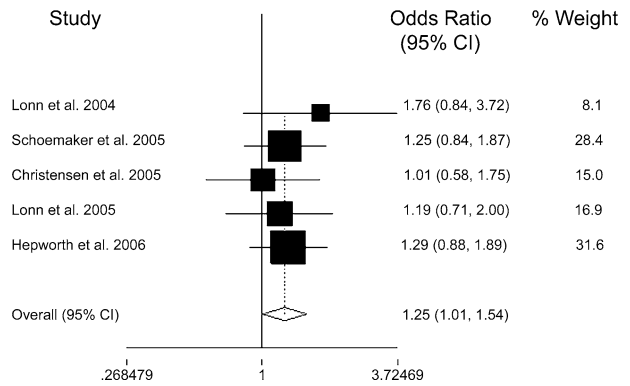

Fig. 3 Pooled odds ratio of brain tumor development associated with cellular phone use of 10 or more years

Discussion

We found no increased risk of brain tumors associated with cellular phone use when combining the findings from the 9 case-control studies. This finding is consistent with the literature; most of the studies included or reviewed did not report an overall OR that was significantly greater than unity.

When the risk of tumor development was stratified according to brain tumor subtype, we found no increased risk for any subtype of brain tumor among cellular phone users. Because exposure to low-energy radiation from cellular phones is highest at the surface meningeal tissue and the vestibulocochlear nerve closest to the handset, we would predict an increased risk for meningioma and/or acoustic neuroma (which was not observed in our meta-analysis) if an oncogenic effect were present.

When we combined studies that involved patients with 10 or more years of exposure, we found a slightly increased risk of tumor development among long-term users (OR 1.25, 95% CI 1.01 to 1.54). Ten years was chosen arbitrarily as the metric of exposure as some studies reported an increased risk after 10 years [10]. Of course, the true length of time for electromagnetic radiation to produce an oncogenic effect (latency) remains unclear as this analysis says nothing about latency but only about one particular metric of exposure (10 years).

In the association between brain tumors and long-term use of over 10 years, the type of phone used could be an important confounder because analog phone use is associated with both long-term use and an increased risk of tumor development when compared with digital phone use (OR 1.22; CI: 1.06–1.41). In fact, the similarity between the two ORs (1.25 and 1.22) suggests that a large proportion of the association observed between brain tumors and long-term users may be explained by the confounding relationship between duration of use and phone type (long-term users were also analog phone users). As a result, the

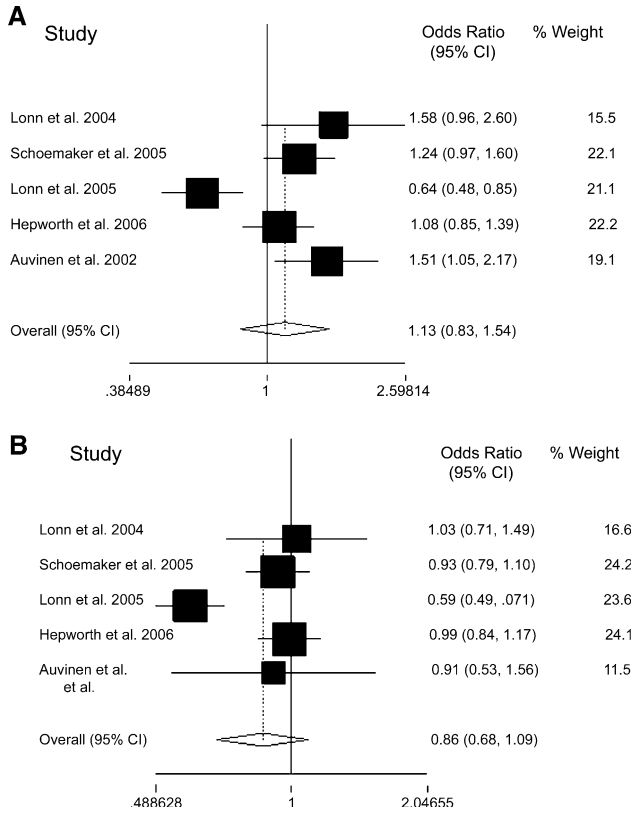

Fig. 4 (A) Pooled odds ratio of brain tumor development associated with analog phone use compared with individuals not exposed to analog phones; (**B**) pooled odds ratio of brain tumor development associated with digital phone use compared with individuals not exposed to digital phones

true risk of long-term cellular phone use remains inconclusive without the ability to control for confounding and would need to be validated by future studies.

In the past decade, there has been a substantial change in wireless technology. The earliest cell phones relied on analog technology. These have been replaced by phones using digital technology. Because analog cellular phones operate at a higher power, giving off more electromagnetic radiation, there has been concern that they may carry an increased risk of brain cancer. Based on our pooled estimates, although the risk of brain tumor development may be slightly higher with analog phone use than with digital phone use (OR 1.22, 95% CI 1.06 to 1.41), no increased risk of brain tumors was found in either analog or digital phone use when compared with the unexposed group. However, in any study, one must interpret results stratified by phone type with caution because almost all analog users have now switched to digital phones and therefore have been exposed to power settings of both designs.

Selection bias, information bias, and confounding interactions were potential limitations of our study. The method we used to identify the articles included in the study was comprehensive, which minimized selection bias for articles with either a positive or a negative result. Information bias, obtaining information from study subjects that will misclassify exposure in a nonrandom manner (often because of differential recall and intensity of surveillance between cases and controls), unfortunately cannot be controlled in a meta-analysis because it was inherent with each of the studies individually. Finally, without all of the original data, our study was also unable to control for confounding factors. However, as is evident from Table 2, the crude and adjusted OR for each study were very comparable, suggesting that confounding did not represent a significant threat to the validity of our results.

In summary, we found no overall increased risk of brain tumors among cellular phone users. The potential elevated risk of brain tumors after 10 years or more of cellular phone use should be confirmed by additional data from future studies.

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