Epidemiologic Evidence on Mobile Phones and Tumor Risk

A Review

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Abstract: This review summarizes and interprets epidemiologic evidence bearing on a possible causal relation between radiofrequency field exposure from mobile phone use and tumor risk. In the last few years, epidemiologic evidence on mobile phone use and the risk of brain and other tumors of the head in adults has grown in volume, geographic diversity of study settings, and the amount of data on longer-term users. However, some key methodologic problems remain, particularly with regard to selective nonresponse and inaccuracy and bias in recall of phone use. Most studies of glioma show small increased or decreased risks among users, although a subset of studies show appreciably elevated risks. We considered methodologic features that might explain the deviant results, but found no clear explanation. Overall the studies published to date do not demonstrate an increased risk within approximately 10 years of use for any tumor of the brain or any other head tumor. Despite the methodologic shortcomings and the limited data on long latency and long-term use, the available data do not suggest a causal association between mobile phone use and fast-growing tumors such as malignant glioma in adults (at least for tumors with short induction periods). For slow-growing tumors such as meningioma and acoustic neuroma, as well as for glioma among long-term users, the absence of association reported thus far is less conclusive because the observation period has been too short.

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Mobile phone use has increased with extraordinary rapidity, and is now nearly universal in some countries, with over 2 billion subscribers worldwide. The rise in use has generated concerns about safety, particularly potential cancer risk. When we reviewed this subject several years ago, we concluded that the studies at that time gave no consistent or convincing evidence of a causal relation between radiofrequency (RF) exposure and any adverse health effect. However, we could not rule out an association because of deficiencies in the research.[1] Mobile phone studies at that time had been able to address only relatively short induction and latency periods, and included a relatively small number of heavy users. In the last 5 years, the volume of literature has more than doubled. We have, therefore, conducted a new review of the cumulated evidence on tumor risk in mobile phone users.

The emphasis of our review, and of the majority of recently published studies, is on tumors of the brain and other sites in the head that have the highest exposure from mobile phones held against the ear. These include the glial and meningeal tissue close to the surface of the head, the vestibular portion of the eighth cranial nerve where acoustic neuromas (vestibular Schwannomas) develop, and the parotid gland. For the rest of the human body the exposure is negligible except for the skin, hand, and other potential sites where hands-free devices are placed. We first discuss the key methodologic issues, then review in sequence the study methods, results, and interpretation of findings for each of the cancers for which there is a substantial literature: glioma, meningioma, acoustic neuroma, and salivary glands.

METHODOLOGIC CONSIDERATIONS

Exposure Characteristics

The first mobile phone systems were analog and operated at 450 and 900 MHz. Digital systems, operating at higher frequencies (1800–1900 MHz) and using different modulation techniques, became prevalent in the early 1990s. Around 2004, third-generation systems using the Universal Mobile Telecommunication System, which operates in the 1900–2200 MHz frequency range, were introduced.

The systems differ also in other parameters that can influence radiofrequency exposure, including maximum power output and patterns of handovers (the manner in which the phone's connection is handed over from one base station to another). Analog systems operated at higher power levels than digital systems and probably resulted in a higher exposure per unit of use. Adaptive power control (a technology to adapt the transmission power to what is required given actual conditions, such as distance between the phone and base station) may reduce the emitted power by as much as a 1000-fold. With adaptive power control, exposure is generally higher at greater distance from the base station (eg, in rural areas), when the user is moving (eg, in a car), and in places where there is intensive use with frequent handovers.[2,3] To compensate for the shielding effect of building materials, power levels of phones are, on average, higher when a phone is used indoors than outdoors.[2,3] The importance of the various usage circumstances may vary with geographic location and over time.[2,3] In addition to system characteristics, the radiofrequency exposure also depends on the characteristics of the phone itself, including the type and location of the antenna (eg, pull-out rod or built-in) and the tilt of the phone relative to the head. The spatial distribution of RF energy in the brain has been studied using measurements made on phantoms.[4] It appears that nearly all of the energy (97%–99%) is absorbed in the brain hemisphere on the side where the phone is used, mainly (50%–60%) in the temporal lobe. Hands-free devices substantially reduce exposure to the head.

Most studies of mobile phones and cancer have asked the participants (or their proxies) directly about their history of use, including frequency and duration of calls. Some studies have also asked for more details, including questions about types of phones. A few studies have instead used information on calls recorded by network operators for billing purposes. Each approach has advantages and disadvantages. More detailed data can be collected when information is obtained directly from the participants, but at the price of compromised accuracy and increased potential for recall and reporting bias. Validation studies have shown that healthy individuals have a tendency to overestimate the length of their calls and to underestimate the frequency.[5,6] This pattern was dependent on the amount of use; heavy users tended to overestimate, whereas light users underestimated their use. A validation study including both brain tumor cases and healthy controls[5] found a similar pattern among cases; however, the overestimation by cases increased with increasing time before interview, which was not seen among controls. The potential differential exposure misclassification in studies using self-reported phone use, especially for more distant time periods, may cause positive bias in estimates of disease risk. Network operator information is presumably more accurate and objective, but may be lacking in validity: some networks have information only about outgoing calls, and the information they have refers to subscribers rather than actual users. Neither self-report nor records provide all the relevant or completely accurate data. Thus, all studies based on phone use are affected by exposure misclassification, which (if nondifferential) could dilute risk estimates. This is in addition to the errors inherent in inferring radiofrequency radiation exposure even from accurate information on use, for the reasons noted above.

Tumor Location and Laterality of Tumor in Relation to Habitual Side of Phone Use

When a mobile phone is held to the ear, maximum RF energy absorption occurs within the lobes of the brain or other sites near the ear that are within a few centimeters of the phone antenna. Thus, tumors in these locations are more plausibly associated with RF exposure from mobile phones than tumors at other locations.

Some case–control studies have asked about the habitual side of mobile phone use when the phone is hand-held, and have sought to investigate the association with ipsilateral and contralateral brain tumors. However, there is no evidence of consistency over time in a person's preferred side of use. Retrospective self-report of preferred side of use may be subject to bias. If cases believe that mobile phone use may have caused their tumor, they might over-report mobile phone use on the same side as the tumor. In addition, analysis of data regarding laterality of phone use presents analytic problems. First, a method is needed for handling cases and controls who say they have no preferred side of use. Second, the analysis of control data regarding laterality of mobile phone is problematic because controls have no tumor to determine a reference side. Several techniques have been employed to deal with this issue.[7–9] One should keep in mind that the one employed by Inskip et al[7] results in a relative risk that cannot be compared with other relative risks. If a causal effect were operative, one would expect null findings for contralateral use and elevated risk for ipsilateral use, with an overall elevation in risk for all users. On the other hand, if individuals with cancer believed that phone use caused their tumor and over-report use on the affected side, this would result in an apparent excess risk of brain tumor on the side of reported phone use and a deficit in risk on the other side.

Induction and Latency Periods

Because mobile phones are a new technology, there is epidemiologic evidence on cancer risk only for relatively short periods since first exposure; data on exposures more than 10 years before cancer diagnosis are still limited. Most types of cancer occur many years, or even decades, after initial exposure to known carcinogens. A widely expressed view has been that it is therefore too soon to know whether mobile phones have an effect on cancer risk. However, the important issue is not how long it takes for maximum risk to

occur, but how long before detectable risk is present. Even for asbestos, a carcinogen that has a notoriously long induction period, detectable elevations in risk occur 10–14 years after first exposure.[10] Furthermore, it has been argued that RF fields cannot plausibly initiate cancer since they do not damage DNA, and that if RF acts at a later stage in carcinogenesis, the effects on tumor occurrence should be relatively rapid. However, epidemiologic studies are based on diagnosed tumors, whose identification depends not just on the induction period (period between exposure and initiation of disease) but also on their latency (ie, how long they are present before being detected). Latency is likely to be short for fast-growing maligancies, but could be decades for less-aggressive tumors such as acoustic neuromas and benign meningiomas. Hence for glioma (or at least the subset of gliomas that are fast-growing) information on risks 10 or 15 years after first exposure could provide meaningful information for determining whether mobile phone use has an etiologic effect, although this may not be true for slower-growing tumors.

Definition of Cases

The constitution of case groups has differed across studies, in some instances in clear and logically defined ways. For example, cases may be restricted to malignant or benign tumors or defined by histologic grade or anatomic location to create the subgroup of interest. Comparison of results across studies is challenging when the diagnostic groups are overlapping but not entirely consistent. Also, the varying ways of handling attrition from the target case group of interest—eg, losses due to death, inability to provide exposure or covariate information, and refusal—can be problematic methodologically.

Selection of Controls

The goal of identifying controls who are a representative sample from the population that gave rise to the cases is straightforward in principle, but it is not easily achieved in practice. For studies that identify cases comprehensively from a geographically-defined population, the desired composition of the control group is clear, although such controls are not necessarily easy to recruit and interview, as shown in 2 Nordic studies.[11,12] For hospital-based case–control studies, the health conditions of controls that resulted in their inclusion in the study need to be scrutinized for potential associations with mobile phone use, as seen for example in 2 US studies.[7,13]

Response Rates

Reported participation proportions have varied across studies, with inconsistent methods of calculation distorting comparisons (eTable 1, http://links.lww.com/A1450). While attrition from the intended study population is fully reported in some studies, incomplete reporting makes assessment of the potential effect of selection difficult in many studies.

The cohort studies and the registry-based case–control study did not require active subject participation, allowing essentially all of the subjects to be included. Other studies required personal contact and the completion of an interview, with lower participation rates. Participation has been highest in the Scandinavian countries, with reported rates above 70% for both cases and controls in Sweden, and generally worse in other countries.

In several studies, there were indications that nonparticipation was related to exposure status, with mobile phone users more willing to participate than nonusers.[14] To evaluate the potential magnitude of selection bias, most of the study centers of one study (Interphone; mentioned later) sought a short interview with nonparticipants.[14] They were able to elicit responses from 57% of control refusers and 41% of case refusers. In all centers, a lower rate of regular mobile phone use was found in controls who refused the full interview (56% overall) compared with controls who were full participants (69%), regardless of whether the study was presented as a "mobile phone" study or not. The same pattern was found for cases: 50% of case refusers were regular mobile phone users, compared with 66% among full participants. Selection bias introduced by nonparticipation was estimated to cause a downward bias of around 10% in odds ratios for regular mobile phone use.[14] It is not known if such a bias would be present differentially among various categories of users (eg, between regular versus infrequent users).

Precision of Risk Estimates

Precision is a concern in research on rare health outcomes, which applies to all the cancers of interest here. Nonetheless, large numbers of cases have been identified for study through population registries. The other determinant of precision is the prevalence of the exposure, ie, mobile phone use. The dramatic increase in mobile phone use over the past 20 years has implications for the power of epidemiologic studies to detect an association, with the optimal exposure prevalence for maximum power being 50%. For long-term exposure, which requires early usage given the secular trends, the numbers remain small and result in limited precision of effect estimates.

METHODS OF STUDIES

eTable 1 (http://links.lww.com/A1450) summarizes the methods of studies to date, conducted in 10 countries. Aside from a group of early studies conducted in the United States,[7,13,15–17] most of publications have come from Scandinavia. One set of studies within Scandinavia was conducted by Hardell et al: 3 on brain tumors[18–21] and one each on salivary gland tumors,[22] non-Hodgkin lymphoma,[23] and testicular cancer,[24] as well as pooled analyses of 2 of the brain tumor studies.[25,26] In addition, a large number of reanalyses of the brain tumor studies have been published. In this review we have considered the original publications; reanalyses were

considered only if they provided relevant information not available in the original publication.[27,28] A third set of studies was conducted within the Interphone collaboration. Interphone consisted of a series of 16 coordinated case–control studies conducted in 13 countries. While the overall results have not been published, results of several of the national analyses[8,9,12,29–38] and pooled studies from the Nordic countries and United Kingdom[39–41] have been published and are considered here. A group of independent studies—the 2 Nordic studies[11,42,43] using subscriber data for exposure assessment and one German study[44] on uveal melanoma—comprise the fourth group.

The tables in this manuscript are organized in the sequence of the preceding paragraph: Early US studies, Hardell studies, Interphone studies, and Subscriber list-based studies.

Only 2 studies have been cohort studies,[15,42,43] with the rest being case–control studies. All of the studies were limited to adults, although the age ranges varied somewhat. Most of the case–control studies were population-based, except for the US studies, which were hospital-based. Proxies were used to varying degrees for some of the deceased and ill cases (generally <10%).

The US studies and some of the Swedish studies were based on case ascertainment that started as early as 1994, while the Interphone studies ascertained cases from 2000 through 2004. Therefore, lifetime exposure prevalence among controls has varied substantially from <10%–65%. In addition, exposure definitions and methods of categorization (ever/never use of mobile phones; definition of regular, heavy, and long-term use; and the exposure cutpoints) were inconsistent across studies, making direct comparison difficult. Tables 1–5 present all the published original studies, plus published pooled analyses of the 2 sets of related studies (Hardell, Interphone). Pooled estimates across the overall literature are also presented. There are numerous further papers in the literature that at first sight appear to present different material but are in fact the same data analyzed in different ways or combinations. Figures 1–4 display the key results of the studies graphically. For details about the figures, refer to the footnotes in the corresponding tables. In the studies by Hardell, which provide results for both digital and analogue phones, we have chosen to present the analog results in the figures to avoid multiple representations and because analog phones give rise to higher exposure levels and were introduced earliest. For the Interphone group of studies we have chosen the results by Lahkola and Schoemaker instead of the original studies for tumor types (meningioma, acoustic neuroma) where they include data that are not presented in a separate publication.

GLIOMA: RESULTS AND INTERPRETATION

Among the 14 original studies addressing mobile phone use and risk of glioma (Table 1), most found risk estimates close to or below unity with ever-use of mobile phones,[7,12,13,20,21,29,31,32,34,35,38,43] while 2 did not.[11,19] These 2 studies found risk increases after short-term exposure; Auvinen et al[11] found odds ratios (ORs) ranging from 1.2 to 1.7 across indices of mobile phone exposure, with the maximum exposure category (more than 2 years of use) giving an OR of 1.7 (95% CI = 0.9–3.5). The most recent study by Hardell et al[16] found increased risks in all categories of time since first use, with an OR of 1.6 (1.1–2.4) within 5 years based on 100 exposed cases. Hours et al[38] found an OR of 2.0 (0.7–5.2) for 3.8 or more years since first use, which was the maximum exposure category analyzed in this French Interphone study. Takebayashi et al[35] also reported an elevated OR after intermediate term exposure duration, but found a reduced OR after longer term exposure (>6.5 years). Both the Hours et al and Takebayashi et al studies included few exposed cases. For at least 10 years since first exposure, Hardell et al[19] found a more than 3-fold risk increase (OR = 3.6 [1.7–7.5] for digital use) and Schuz et al[34] reported a 2-fold risk increase based on 12 exposed cases (2.2 [0.9–5.1]). Most studies, however, tended to find no evidence for an association based on duration of use or cumulative exposure.[7,12,13,20,27–29,31,32,43] The pooled analysis of Nordic and UK Interphone studies,[39] which to date includes the largest number of glioma cases, found an OR of 1.0 (0.7–1.2) based on 143 exposed cases, among persons who started to use a mobile phone 10 or more years before diagnosis. Pooling all original studies gave summary risk estimates close to unity in all exposure duration categories (OR = 1.1 [0.8–1.4] for long-term use), as well as for ever-use of mobile phones (1.0 [0.8–1.2]) (Table 1). A sensitivity analysis shows that if the third Hardell et al study[19] were excluded, the long-term pooled OR would be 0.9 (0.8–1.1) and the heterogeneity across studies would vanish ($P = 0.25$). This could not be achieved by, for example, excluding the Interphone studies.

Laterality of phone use in relation to laterality of tumor is a potentially important aspect of study results, but, as discussed above, there are methodologic problems with this approach. In particular, if the ipsilateral risk is raised without a raised overall risk, biased recall of side of use is implicated. Similarly, an increased ipsilateral risk together with a decreased contralateral risk also suggests that recall bias operates. This pattern is commonly found in the laterality results presented in Table 2.

Lobe-specific results did not differ substantially from the corresponding overall results.[7,11–13,19,20,43]

The overall pattern of results does not support the presence of an association between mobile telephone use and glioma. However, 2 issues call for clarification: (1) the basis for the discrepancy between the predominantly null findings and the few studies suggesting a positive association and (2) the tendency for studies not finding an association to report

TABLE 1. Results of Studies on Mobile Phone Use and Risk of Glioma[a]

Reference	Time Since First Use: Short-term Use — No. Exposed Cases (Exposure Period)	Short-term Use — OR (95% CI)	Intermediate-term Use — No. Exposed Cases (Exposure Period)	Intermediate-term Use — OR (95% CI)	Long-term Use — No. Exposed Cases (Exposure Period)	Long-term Use — OR (95% CI)	Ever/Never Use — No. Exposed Cases	Ever/Never Use — OR (95% CI)
US studies								
Muscat et al 2000[13] (malignant brain)	49 (1–3 years)	0.9 (0.6–1.4)[b]	17 (≥4 years)	0.7 (0.4–1.4)			66	0.7 (0.5–1.1)
Inskip et al 2001[7] (glioma)	31 (0.5–3 years)	0.9 (0.5–1.6)	11 (≥5 years)	0.5 (0.2–1.3)			201	1.0 (0.7–1.4)
Hardell studies								
Hardell et al 1999[21] (all brain)	78 (>1 year)	1.0 (0.7–1.4)	34 (>5 years)	0.8 (0.5–1.4)	16 (>10 years)	1.2 (0.6–2.6)	78	1.0 (0.7–1.4)
Hardell et al 2002[20,27] (all malignant)	36 (analog)	1.1 (0.7–1.8)			43 (analog)	1.2 (0.8–1.8)	79 analog	1.1 (0.8–1.6)
	100 (digital) (1–6 years)	1.1 (0.8–1.4)			12 (digital) (>6 years)	1.7 (0.7–4.3)	112 digital	1.1 (0.9–1.5)
Hardell et al 2006[19] (all malignant)	0 (analog)		20 (analog)	1.8 (0.9–3.5)	48 (analog)	3.5 (2.0–6.4)	68 analog	2.6 (1.5–4.3)
	100 (digital) (1–5 years)	1.6 (1.1–2.4)	79 (digital) (6–10 years)	2.2 (1.4–3.4)	19 (digital) (>10 years)	3.6 (1.7–7.5)	198 digital	1.9 (1.3–2.7)
Hardell pooled analysis								
Hardell et al 2006[25c] (all malignant)	39 (analog)	1.2 (0.8–1.8)	57 (analog)	1.1 (0.8–1.6)	82 (analog)	2.4 (1.6–3.4)	178 analog	1.5 (1.1–1.9)
	265 (digital) (1–5 years)	1.2 (1.0–1.5)	118 (digital) (6–10 years)	1.7 (1.2–2.2)	19 (digital) (>10 years)	2.8 (1.4–5.7)	402 digital	1.3 (1.1–1.6)
Interphone studies								
Christensen et al 2005[29] (glioma)[d]	43 (1–4 years)	0.7 (0.4–1.0)	42 (5–9 years)	0.6 (0.4–1.0)	14 (≥10 years)	0.7 (0.3–1.6)	106	0.7 (0.5–1.0)
Lonn et al 2005[12] (glioma)	112 (1–4 years)	0.8 (0.6–1.1)	75 (5–9 years)	0.7 (0.5–1.0)	25 (≥10 years)	0.9 (0.5–1.5)	214	0.8 (0.6–1.0)
Schuz et al 2006[34] (glioma)	82 (1–4 years)	0.9 (0.6–1.2)	39 (5–9 years)	1.0 (0.6–1.5)	12 (≥10 years)	2.2 (0.9–5.1)	138	1.0 (0.7–1.3)
Hepworth et al 2006[31] (glioma)	271 (1.5–4 years)	0.9 (0.7–1.1)	170 (5–9 years)	1.0 (0.8–1.3)	66 (≥10 years)	0.9 (0.6–1.3)	508	0.9 (0.8–1.1)
Klaeboe et al 2007[32] (glioma)	27 (<2 years)	0.6 (0.4–1.1)	64 (2–5 years)	0.5 (0.3–0.8)	70 (≥6 years)	0.8 (0.5–1.2)	161	0.6 (0.4–0.9)
Hours et al 2007[38] (glioma)	38 (<3.8 years)	0.9 (0.5–1.6)[e]	21 (≥3.8 years)	2.0 (0.7–5.2)			59	1.2 (0.7–2.1)
Takebayashi et al 2008[35] (glioma)	32 (<4.7 years)	1.3 (0.7–2.3)[f]	17 (4.7–6.5 years)	1.9 (0.8–4.4)	7 (>6.5 years)	0.6 (0.2–1.8)	56	1.2 (0.6–2.4)
Interphone pooled analysis								
Lahkola et al 2007[39g] (glioma)	384 (1–4 years)	0.8 (0.7–0.9)	342 (5–9 years)	0.8 (0.6–0.9)	143 (≥10 years)	1.0 (0.7–1.2)	867	0.8 (0.7–0.9)
Subscriber list studies								
Auvinen et al 2002[11] (glioma)	25 (≤2 years)	1.5 (0.9–2.4)[h]	11 (>2 years)	1.7 (0.9–3.5)			36	1.5 (1.0–2.4)
Schuz et al 2006[43] (nervous system)	266 (1–4 years)	1.0 (0.9–1.2)	235 (5–9 years)	1.0 (0.8–1.1)	28 (≥10 years)	0.7 (0.4–1.0)	580	1.0 (0.9–1.0)
Pooling all studies[i]		1.0 (0.9–1.1)		0.9 (0.8–1.1)		1.1 (0.8–1.4)		1.0 (0.8–1.2)
P for homogeneity		0.138		0.010		0.001		0.001

[a]All studies are case–control studies except Schuz et al 2006.[43]
[b]Pooled result for 1 year and 2–3 years.
[c]Data from Hardell et al 2002[27] and 2006.[19]
[d]Pooled results for low grade and high grade glioma.
[e]Pooled result for <1.3, 1.3–2.25, and 2.25–3.8 years.
[f]Pooled result for <2.2 and 2.2–4.7 years.
[g]Data from Christensen et al 2005,[29] Lonn et al 2005,[12] Klaebo et al 2007,[32] part of Hepworth et al 2006,[31] and data from Finland not previously published.
[h]Pooled result for <1 and 1–2 years.
[i]Pooling all studies except Hardell et al 2006[25] and Lahkola et al 2007,[39] using the random effects model. From Hardell et al 2002 and 2006, when results for both analogue and digital phone use were available, only the results for analogue phone use were included to avoid including duplicate data.

OR indicates odds ratio; CI, confidence interval.

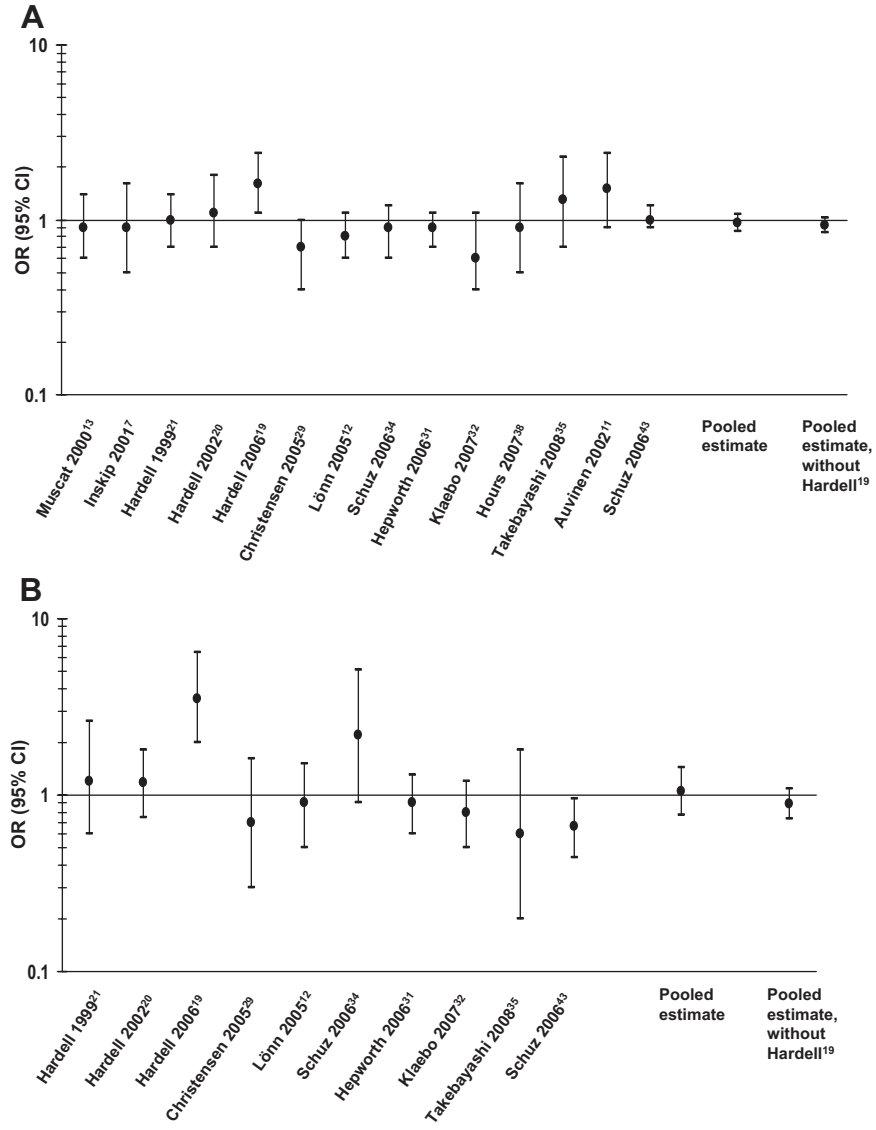

FIGURE 1. Mobile phone use and risk of glioma. A, short-term use (for pooled estimate, *P* for homogeneity = 0.138; without Hardell et al,[19] *P* = 0.443); B, long-term use (for pooled estimate, *P* for homogeneity = 0.001; without Hardell et al,[19] *P* = 0.251.

relative risks for ever-use slightly below the null value rather than dispersed symmetrically around it.

Nondifferential exposure misclassification could in principle produce these negative results even in the presence of a causal effect. Might the few positive studies have resulted from a markedly superior assessment of exposure compared with studies by other investigators? The studies by Hardell et al differed most notably in considering wireless phones in homes (DECT phones) in addition to mobile telephones.[19,24–27] However, the association between DECT phone use and glioma risk was investigated by the Swedish and German Interphone studies,[12,34,45] without finding an increased risk of glioma. The exposure assessment methods of Auvinen et al[11] are similar to the ones used in Schuz et al,[43] and the methods of Schuz et al[34] and Hours et al[38] are indistinguishable from those of other Interphone studies. Another potential reason for the discrepant results is selection bias through nonresponse among controls who did not use mobile phones, as discussed above. However, selection bias within the Interphone study was estimated to cause a downward bias in risk estimates of approximately 10%[14]; if this estimate is correct, this source of selection bias does not appear large enough to explain the differences in results.

If the series of negative studies is correct, it is appropriate to consider the potential reasons, including random error, for spurious positive findings in the studies generating positive results. The positive studies do not appear to have structural features with regard to case and control group constitution that would bias associations in a positive direction. The basic approach to exposure assessment does not appear to differ from that of other studies, with most studies based on self-report of use and various derived indices of

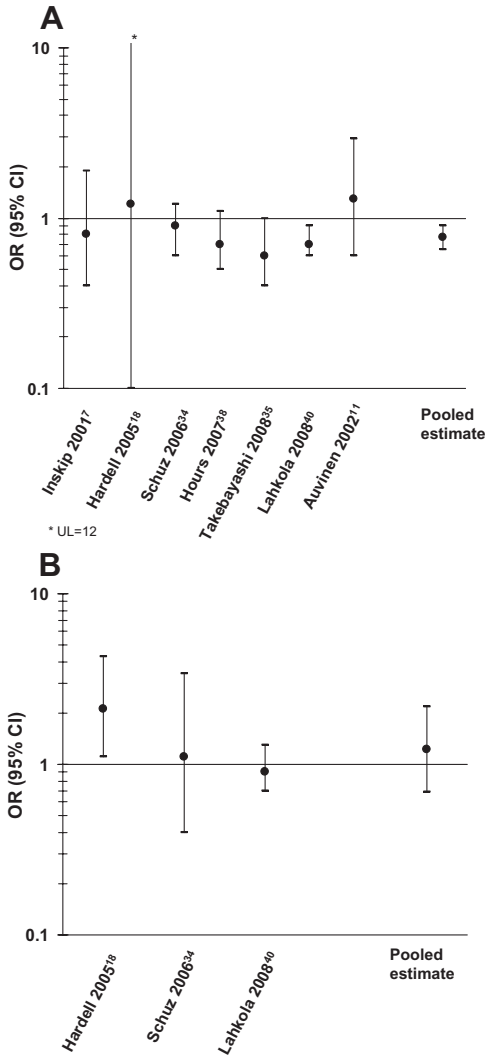

FIGURE 2. Mobile phone use and risk of meningioma. A, short-term use (for pooled estimate, *P* for homogeneity = 0.602); B, long-term use (for pooled estimate, *P* for homogeneity = 0.119). *Upper limit = 12.

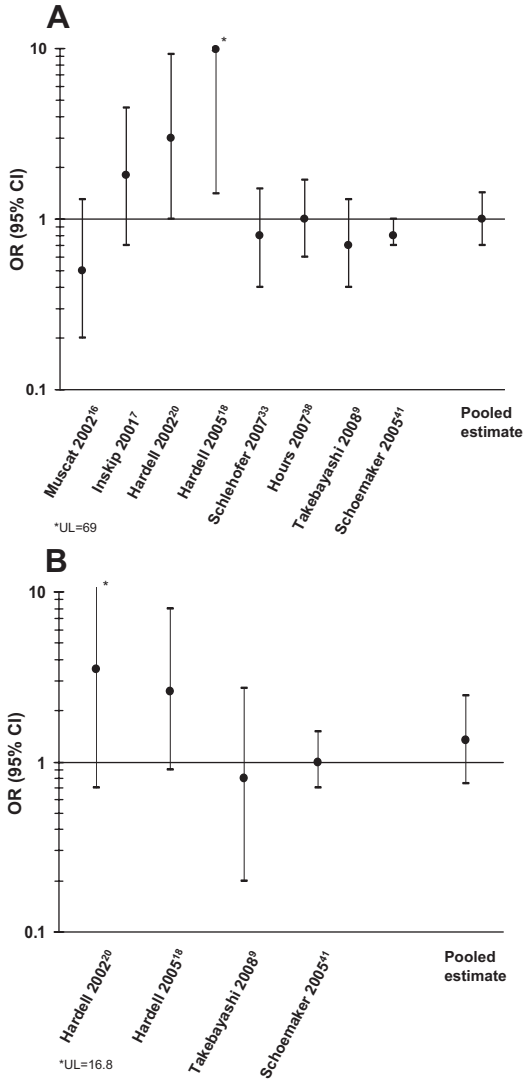

FIGURE 3. Mobile phone use and risk of acoustic neuroma. A, short-term use (for pooled estimate, *P* for homogeneity = 0.028); B, long-term use (for pooled estimate, *P* for homogeneity = 0.191). *Upper limit = 69; in B, Upper limit = 16.8.

exposure. While on the surface, the positive studies, including those by Hardell et al, are very much like the studies that obtained quite different results, subtle aspects of data collection and methods of analysis may be responsible for the apparent discrepancies. Investigators must make decisions regarding the exact constitution of the case groups, such as, whether to restrict by anatomic location, histology, stage, or malignancy. Exposure assignment requires even more complex decisions, including analog or digital phone use; how to define regular use; how to categorize hours of use or cumulative exposure; consideration of laterality of use and tumor location; and selection of reference dates of use for controls in relation to the timing of disease diagnosis. There is potential for differing recruitment methods to affect the magnitude and pattern of nonresponse, for interviewer training and monitoring to affect reporting tendencies of cases and controls, and even for the wording of questions to have subtle effects on the resulting data. Every team of investigators faces these decisions, and, presuming that there are compensating practices, the series of studies in the literature overall is expected to converge on a valid result. These decisions represent a major reason why replication of results by different research groups is needed before results can be considered as established.

The studies by Hardell et al are particularly problematic because of variation across their publications in the exact constitution of case groups, criteria for exclusion, exposure definitions, and the selection of results for presentation in the multiple overlapping publications. In our view, the series of

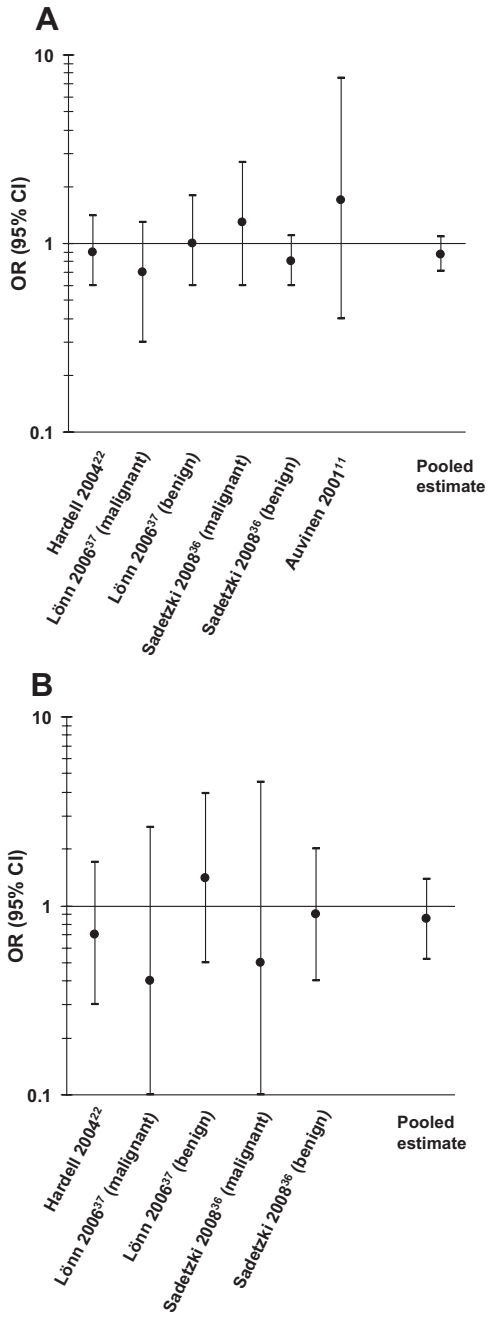

FIGURE 4. Mobile phone use and risk of salivary gland tumors. A, short-term use (for pooled estimate, *P* for homogeneity = 0.667); B, long-term use (for pooled estimate, *P* for homogeneity = 0.743).

decisions in methods, analysis, and presentation provide the most plausible explanation for the deviation of the findings of the Hardell studies from those of other investigators. This does not address the other positive reports, but they seem to fit more in the distribution of results expected given random error across studies.

In summary, the complete array of available data does not suggest a causal association of mobile phone use with risk of glioma. However, there remains some uncertainty due to inconsistencies across the studies, as well as the recognized problems of exposure misclassification and potential for bias due to selective participation. As discussed previously, nonparticipation in the Interphone studies has been estimated to result in a 10% downward bias of the odds ratios, which can not explain all of the observed risk reduction. In addition, the period between exposure to a causal agent and manifestation of glioma may range from 5 to 20 years or more, judging from the intervals observed between ionizing radiation exposure and tumor diagnosis. Symptoms depend on the site and nature of the tumor, with slowest onset for low-grade tumors and rapid onset for highly malignant and swiftly-growing tumors. The data for long-term phone use of more than 10 years are still sparse, and any increased risk of slow-growing tumors may not yet have become manifest.

MENINGIOMA: RESULTS AND INTERPRETATION

Eleven original case–control studies,[7,11,12,18,20,21,29,32,34,35,38] one cohort study,[42,43] and 2 pooled analyses[26,40] have investigated the association between mobile phone use and meningioma. With the exception of the most recent study by Hardell et al,[18] all studies found risk estimates close to or below unity, regardless of time since first mobile phone use (Table 3). The study by Hardell et al[18] found an increased risk with ever-use of an analog mobile phone (OR = 1.7 [1.0–3.0]), with the highest risk estimate for more than 10 years since first use (2.1 [1.1–4.3]). The largest study so far—the pooled analysis of the Nordic and UK Interphone studies—found an OR of 0.9 (0.7–1.3) for long-term use. Pooling all original studies gave risk estimates close to or below unity (Table 3). Thus, there is no consistent evidence of an increased risk of meningioma among mobile phone users.

Many of the methodologic concerns discussed above for glioma apply also to meningioma, since they were typically evaluated within the same epidemiologic studies. A particular consideration in the interpretation of studies of mengioma is the long latency for this disease. Unlike gliomas, meningiomas are typically very slow-growing tumors with probable latencies of up to 30 years or more.[46] Cases may have no symptoms for a long period before detection of their tumor because meningiomas compress rather than invade the brain. A proportion of patients diagnosed with meningiomas in the 1990s and included in early studies could well have had the tumor present prior to any substantive exposure to mobile phones. Thus, the negative results give weaker evidence regarding an absence of association than the corresponding negative results for glioma.

TABLE 2. Results of Laterality Analyses in Studies on Mobile Phone Use and Risk of Glioma

Reference	Ever/Never Use		≥10 Years Since First Use		Comment
	Ipsilateral RR (95% CI)	Contralateral RR (95% CI)	Ipsilateral RR (95% CI)	Contralateral RR (95% CI)	
Hardell et al 1999[21]/2001[28]	1.1 (0.6–1.8)	0.7 (0.4–1.2)			
Hardell et al 2002[20,27]	1.9 (1.2–3.0)	0.6 (0.4–1.1)	1.8 (1.0–3.4)[a]	0.7 (0.4–1.6)[a]	Analog
	1.6 (1.1–2.4)	0.9 (0.5–1.4)	2.3 (0.6–8.9)[a]	0.3 (0.0–2.9)[a]	Digital
Hardell et al 2006[19]	3.1 (1.6–6.2)	2.6 (1.3–5.4)			Analog
	2.6 (1.6–4.1)	1.3 (0.8–2.2)			Digital
Lonn et al 2005[12]	1.1 (0.8–1.5)	0.7 (0.5–1.0)	1.6 (0.8–3.4)	0.7 (0.3–1.5)	
Hepworth et al 2006[31]	1.2 (1.0–1.5)	0.8 (0.6–0.9)	1.6 (0.9–2.8)	0.8 (0.4–1.4)	
Klaeboe et al 2007[32]	1.0 (0.7–1.4)	0.7 (0.5–1.1)	1.3 (0.8–2.1)[b]	0.8 (0.5–1.4)	
Hours et al 2007[38]	1.2 (0.6–2.4)	1.2 (0.5–2.7)			
Takebayashi et al 2008[35]	1.2 (0.7–2.3)	1.1 (0.6–2.0)			
Lahkola et al 2007[39]	1.1 (1.0–1.3)	0.8 (0.6–0.9)	1.4 (1.0–1.9)	1.0 (0.7–1.4)	

[a]>6 years.
[b]≥6 years.

ACOUSTIC NEUROMA: RESULTS AND INTERPRETATION

The 13 original studies of acoustic neuroma[7–9,16–18,20,21,30,32,33,38,42,43] (Table 4) generally included small numbers of cases. The pooled analyses are larger,[26,41] especially the Nordic-UK pooled analysis.[41] Response rates for cases have been relatively high, reflecting the benign nature of this tumor, but control response rates have generally been lower. For ever-use of a mobile phone, all studies found risk estimates close to or below unity, except the 2 most recent studies by Hardell et al,[18,20] where up to 4-fold risk increases were reported. It is notable that Hardell et al[18,20,26] observed considerably increased risks also within a short time period since first use. Acoustic neuroma is a very slow-growing tumor,[47] and it seems likely that the majority of cases diagnosed within 5 years of their first mobile phone use would have had their tumor already present before they started to use the mobile phone. Two of the US studies[7,16] also reported somewhat elevated ORs relatively soon after first mobile phone use, but these were based on small numbers of exposed cases (Table 4).

For long durations of exposure (10 years or more), the Nordic-UK pooled analysis included the largest number of cases, and reported an OR of 1.0 (0.7–1.5). Most studies found risk estimates below one, sometimes with a considerable risk reduction (eg, Christensen et al,[30] with an OR of 0.2 [0.2–1.1], although the Swedish Interphone study[8] found an OR of 1.9 (0.9–4.1). The 2 recent Hardell et al studies[18,20] generated results that are discrepant from the other studies, with increased ORs of 3.5 (0.7–16.8) and 2.6 (0.9–8.0) for long-term analog phone use. Pooling all studies gave summary risk estimates of 1.2 (0.8–2.0) for long-term use, and 1.1 (0.8–1.4) for ever-use. Analyses in relation to cumulative hours of use or cumulative number of calls likewise indicated no clear associations except in one of the Hardell et al studies.[18]

The risk of acoustic neuroma after reported regular ipsilateral phone use was not increased in the Nordic-UK analysis (OR: 0.9 [0.7–1.1]). The same was true in the other datasets[7–9,16,32,38] except one by Hardell et al,[18] in which there were ORs of 5.1 (1.9–14) for analog use and 2.9 (1.4–6.1) for digital use. There was, however, a raised risk associated with first ipsilateral phone use at least 10 years prior to diagnosis in the study by Lonn (OR = 3.9 [1.6–9.5]). The corresponding result in the Nordic-UK pooled analysis was 1.3 (0.8–2.0), although a raised risk was associated with at least 10 years of use (OR = 1.8 [1.0–3.3]).[41] Handedness has not been associated with ipsilateral tumor risk.[41]

Acoustic neuroma can cause unilateral deafness, which could lead to cessation of phone use (and hence spuriously reduced risks). Alternatively, the deafness could lead to the diagnosis of an otherwise unrecognized tumor and hence lead to spuriously increased risks. Hearing loss associated with acoustic neuromas may influence the side of phone use as the tumor progresses, resulting in preferred contralateral phone use relative to the tumor. This is not predictable, however, since hearing can be preserved in the presence of large vestibular schwannomas and, conversely, hearing loss can frequently occur as the result of radiologically static, small tumors.[48] Potential effects on the side of mobile phone use or earlier detection of tumors should, however, affect all available studies similarly; this cannot explain the discrepancies in the results.

Unlike the situation for gliomas and meningiomas, laterality virtually defines the anatomic position of acoustic neuromas, and all ipsilateral acoustic neuromas arise close to the mobile phone handset position. Therefore, if reliable unbiased information on side of exposure could be obtained,

TABLE 3. Results of Studies on Mobile Phone Use and Risk of Meningioma[a]

	Time Since First Use							
	Short-term Use		Intermediate-term Use		Long-term Use		Ever/Never Use	
Reference	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases	OR (95% CI)
US studies								
Inskip et al 2001[7]	12 (0.5–3 years)	0.8 (0.4–1.9)	6 (≥5 years)	0.9 (0.3–2.7)			67	0.8 (0.5–1.2)
Hardell studies								
Hardell et al 1999[21]							16	1.1 (0.5–2.3)
Hardell et al 2002[20]							60 analog	1.1 (0.7–1.5)
							78 digital	0.8 (0.6–1.0)
Hardell et al 2005[18]	1 (analog)	1.2 (0.1–12)	14 (analog)	1.4 (0.7–2.8)	20 (analog)	2.1 (1.1–4.3)	35 analog	1.7 (1.0–3.0)
	96 (digital)	1.2 (0.8–1.8)	47 (digital)	1.4 (0.9–2.3)	8 (digital)	1.5 (0.6–3.9)	151 digital	1.3 (0.9–1.9)
	(1–5 years)		(6–10 years)		(>10 years)			
Hardell pooled analysis								
Hardell et al 2006[26b]	32 (analog)	1.2 (0.8–1.8)	47 (analog)	1.2 (0.8–1.8)	34 (analog)	1.6 (1.0–2.5)	113 analog	1.3 (1.0–1.7)
	220 (digital)	1.0 (0.8–1.3)	67 (digital)	1.1 (0.8–1.6)	8 (digital)	1.3 (0.5–3.2)	295 digital	1.1 (0.9–1.3)
	(1–5 years)		(6–10 years)		(>10 years)			
Interphone studies								
Christensen et al 2005[29]	35 (1–4 years)	0.8 (0.5–1.3)	21 (5–9 years)	0.7 (0.3–1.2)	6 (≥10 years)	1.0 (0.3–3.2)	67	0.8 (0.5–1.3)
Lonn et al 2005[12]	64 (1–4 years)	0.6 (0.4–0.9)	40 (5–9 years)	0.7 (0.5–1.1)	12 (≥10 years)	0.9 (0.4–1.9)	118	0.7 (0.5–0.9)
Schuz et al 2006[34]	73 (1–4 years)	0.9 (0.6–1.2)	18 (5–9 years)	0.8 (0.5–1.5)	5 (≥10 years)	1.1 (0.4–3.4)	104	0.8 (0.6–1.1)
Klaeboe et al 2007[32]	19 (<2 years)	0.6 (0.3–1.1)	41 (2–5 years)	0.7 (0.4–1.2)	36 (≥6 years)	1.0 (0.6–1.8)	96	0.8 (0.5–1.1)
Hours et al 2007[38]	56 (<3.8 years)	0.7 (0.5–1.1)[c]	15 (≥3.8 years)	0.7 (0.3–1.9)			71	0.7 (0.4–1.3)
Takebayashi et al 2008[35]	35 (<5.2 years)	0.6 (0.4–1.0)[d]	20 (>5.2 years)	1.1 (0.5–2.1)			55	0.7 (0.4–1.2)
Interphone pooled analysis								
Lahkola et al 2007[40e]	286 (1–4 years)	0.7 (0.6–0.9)	214 (5–9 years)	0.8 (0.6–1.0)	73 (≥10 years)	0.9 (0.7–1.3)	573	0.8 (0.7–0.9)
Subscriber list studies								
Auvinen et al 2002[11]	9 (≤2 years)	1.3 (0.6–2.9)[f]	2 (>2 years)	0.8 (0.2–3.5)			11	1.1 (0.5–2.4)
Schuz et al 2006[43]							68	0.9 (0.7–1.1)
Pooling all studies[g]		0.8 (0.7–0.9)		0.9 (0.7–1.0)		1.2 (0.7–2.2)		0.9 (0.8–1.0)
P for homogeneity		0.602		0.799		0.119		0.232

[a]All studies are case–control studies except Schuz et al 2006.[43]
[b]Data from Hardell et al 2002[20] and 2005.[18]
[c]Pooled result for <1.3, 1.3–2.25, and 2.25–3.8 years.
[d]Pooled result for <1.6 years, 1.6–3.2 years, and 3.2–5.2 years.
[e]Data from Christensen et al 2005,[29] Lonn et al 2005,[12] Klaebo et al 2007,[32] and data from the United Kingdom and Finland not previously published.
[f]Pooled result for <1 year and 1–2 years.
[g]Pooling all studies, except Hardell et al 2006,[26] Christensen et al 2005,[29] Lonn 2005,[12] and Klaebo et al 2007,[32] using random effects model. From Hardell 2005, only the results for analogue phone use were included.

TABLE 4. Results of Studies on Mobile Phone Use and Risk of Acoustic Neuroma[a]

	Time Since First Use							
	Short-term Use		Intermediate-term Use		Long-term Use		Ever/Never Use	
Reference	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases	OR (95% CI)
US studies								
Muscat et al 2002[16]	7 (1–2 years)	0.5 (0.2–1.3)	11 (3–6 years)	1.7 (0.5–5.1)			18	0.8 (0.4–1.7)[b]
Inskip et al 2001[7]	8 (0.5–3 years)	1.8 (0.7–4.5)	5 (≥5 years)	1.9 (0.6–5.9)			40	0.8 (0.5–1.4)
Warren et al 2003[17]							21	1.2 (0.6–2.2)
Hardell studies								
Hardell et al 1999[21]							5	0.8 (0.1–4.2)
Hardell et al 2002[20]	12 (analog)	3.0 (1.0–9.3)	19 (analog)	3.8 (1.4–10.2)	7 (analog)	3.5 (0.7–16.8)	38 analog	3.5 (1.8–6.8)
	21 (digital)	1.2 (0.6–2.2)	2 (digital)	2.0 (0.2–22.1)			23 digital	1.2 (0.7–2.2)
	(1–5 years)		(6–10 years)		(>10 years)			
Hardell et al 2005[18]	2 (analog)	9.9 (1.4–69)	11 (analog)	5.1 (1.9–14)	7 (analog)	2.6 (0.9–8.0)	20 analog	4.2 (1.8–10)
	29 (digital)	1.7 (0.9–3.5)	23 (digital)	2.7 (1.3–5.7)	1 (digital)	0.8 (0.1—-6.7)	53 digital	2.0 (1.1–3.8)
	(1–5 years)		(6–10 years)		(>10 years)			
Hardell pooled analysis								
Hardell et al 2006[26c]	16 (analog)	2.3 (1.2–4.1)	33 (analog)	3.4 (2.1–5.5)	19 (analog)	3.1 (1.7–5.7)	68 analog	2.9 (2.0–4.3)
	75 (digital)	1.4 (1.0–2.1)	29 (digital)	1.8 (1.1–3.0)	1 (digital)	0.6 (0.1–5.0)	105 digital	1.5 (1.1–2.1)
	(1–5 years)		(6–10 years)		(>10 years)			
Interphone studies								
Christensen et al 2005[30]	23 (1–4 years)	0.9 (0.5–1.6)	17 (5–9 years)	0.9 (0.4–1.9)	2 (≥10 years)	0.2 (0.0–1.1)	45	0.9 (0.5–1.6)
Lonn et al 2005[8]	44 (1–4 years)	0.8 (0.5–1.3)	30 (5–9 years)	1.1 (0.6–1.8)	14 (≥10 years)	1.9 (0.9–4.1)	89	1.0 (0.6–1.5)
Schlehofer et al 2007[33]	20 (1–4 years)	0.8 (0.4–1.5)	8 (5–9 years)	0.5 (0.2–1.3)	0 (≥10 years)		29	0.7 (0.4–1.2)
Klaeboe et al 2007[32]	4 (<2 years)	0.4 (0.1–1.4)	10 (2–5 years)	0.5 (0.2–1.2)	8 (≥6 years)	0.5 (0.2–1.4)	22	0.5 (0.2–1.0)
Hours et al 2007[38]	44 (<3.8 years)	1.0 (0.6–1.7)[d]	14 (≥3.8 years)	0.7 (0.3–1.6)			58	0.9 (0.5–1.6)
Takebayashi et al 2008[35]	26 (<4 years)	0.7 (0.4–1.3)	21 (4–7 years)	0.8 (0.4–1.5)	7 (≥8 years)	0.8 (0.2–2.7)	51	0.7 (0.4–1.2)
Interphone pooled analysis								
Schoemaker et al 2005[41e]	231 (1–4 years)	0.8 (0.7–1.0)	96 (5–9 years)	0.9 (0.7–1.2)	31 (≥10 years)	1.0 (0.7–1.5)	360	0.9 (0.7–1.1)
Subscriber list studies								
Schuz et al 2006[43f]							32	0.7 (0.5–1.0)
Pooling all studies[g]		1.0 (0.7–1.4)		1.3 (0.8–2.1)		1.4 (0.7–2.5)		1.0 (0.8–1.4)
P for homogeneity		0.028		0.002		0.191		0.000

[a]All studies are case–control studies except Schuz et al 2006.[43]
[b]Pooling of categorical analyses.
[c]Data from Hardell et al 2002[20] and 2006.[18]
[d]Pooled result for <1.3, 1.3–2.25, and 2.25–3.8 years.
[e]Data from Christensen et al 2005,[30] Lonn et al 2005,[8] Klaebo et al 2007,[32] and data from Finland, the United Kingdom-North and the United Kingdom-South not previously published.
[f]Nerve sheath tumors, cranial nerves.
[g]Pooling all studies except Hardell et al 2006,[26] Christensen et al 2005,[30] Lonn et al 2005,[8] Klaebo et al 2007,[32] using random effects model. From Hardell 2002 and 2005 only results for analogue phone use were included.

TABLE 5. Results of Studies on Mobile Phone Use and Risk of Salivary Gland Tumors

Reference	Time Since First Use						Ever/Never Use	
	Short-term Use		Intermediate-term Use		Long-term Use			
	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases (Exposure Period)	OR (95% CI)	No. Exposed Cases	OR (95% CI)
Hardell studies								
Hardell et al 2004[22]	31 (analog)	0.9 (0.6–1.4)	17 (analog)	0.8 (0.4–1.4)	6 (analog)	0.7 (0.3–1.7)	31 (analog)	0.9 (0.6–1.4)
	45 (digital)	1.0 (0.7–1.5)	8 (digital)	1.2 (0.5–2.8)	>10 years		45 (digital)	1.0 (0.7–1.5)
	>1 year		>5 years					
Interphone studies								
Lonn et al 2006[37]	14 (malignant)	0.7 (0.3–1.3)	8 (malignant)	0.7 (0.3–1.7)	2 (malignant)	0.4 (0.1–2.6)	25 (malignant)	0.7 (0.4–1.3)
	47 (benign)	1.0 (0.6–1.8)	23 (benign)	0.8 (0.4–1.5)	7 (benign)	1.4 (0.5–3.9)	77 (benign)	0.9 (0.5–1.5)
	(1–4 years)		(5–9 years)		(≥10 years)			
Sadetzki et al 2008[36]	21 (malignant)	1.3 (0.6–2.7)	11 (malignant)	0.9 (0.4–2.3)	1 (malignant)	0.5 (0.1–4.5)	33 (malignant)	1.1 (0.5–2.1)
	335 (benign)	0.8 (0.6–1.1)	246 (benign)	1.0 (0.7–1.3)	22 (benign)	0.9 (0.4–2.0)	252 (benign)	0.9 (0.6–1.1)
	(1–4 years)		(5–9 years)		(≥10 years)			
Subscriber list studies								
Auvinen et al 2002[11]	3 (1–2 years)	1.7 (0.4–7.5)	1 (>2 years)	2.3 (0.2–25.3)			4	1.3 (0.4–4.7)
Schuz et al 2006[43]							26	0.9 (0.6–1.3)
Pooling all studies[a]		0.9 (0.7–1.1)		0.9 (0.8–1.1)		0.9 (0.5–1.4)		0.9 (0.8–1.1)
P for homogeneity		0.667		0.884		0.743		0.957

[a]Using random effects model. From Hardell 2004, only results for analog phone use were included.

it would be possible to conduct a powerful unbiased analysis of the effect of mobile phone exposure on acoustic neuroma risk. This analysis, however, is hampered by inconsistency in side of phone use, reporting bias resulting from the tumor diagnosis, and the symptom-based changes in use noted above. The results indicating an increased risk associated with ipsilateral phone use but no overall raised risk again raise questions about the contribution of reporting bias. Thus, the elevated ipsilateral risk beyond 10 years in the large Nordic-UK analysis seems more likely to represent reporting bias than a causal effect, because the latter should lead to a raised risk (although diluted) for users overall beyond 10 years—a finding that was not seen in the overall Nordic-UK data.

As was the case for meningioma, acoustic neuromas are often present for years before diagnosis. Thus, the only data about phone use that are of any potential relevance to acoustic neuroma etiology may be the exposure occurring many years before diagnosis. The available data make it unlikely that there is any substantial raised risk of acoustic neuroma in relation to mobile phone use in the 10 years preceding the diagnosis of the tumor. The results leave uncertainty as to whether there are raised risks beyond 10 years from initial use.

SALIVARY GLAND TUMORS: RESULTS AND INTERPRETATION

There is no consistent evidence of an increased risk of salivary gland tumors among mobile phone users (Table 5, Fig 4) based on 4 case–control studies[11,22,36,37] and one cohort study.[43] One study[11] showed an increase in risk for ever-use compared with never-use and for greater cumulative years of exposure, but the results were based on few cases and had very wide confidence intervals. There was no indication of a raised risk in any of the other studies including that of Hardell. Pooling the results from all studies gave risk estimates slightly below unity in all exposure categories (Table 5). Both publications from the Interphone study reported higher risk estimates associated with ipsilateral phone use at least 10 years prior to diagnosis, with an OR of 2.6 (0.9–7.9) in the Lonn et al study,[37] and 1.6 (0.7–3.7) in the study by Sadetzki et al.[36] Corresponding ORs for contralateral use were, however, considerably reduced in both studies: 0.3 (0.0–2.3) and 0.6 (0.2–2.3), respectively. Thus, reporting bias seems likely to explain these findings.

Single studies of tumors at other sites (pituitary adenoma,[35] non-Hodgkin lymphoma,[23] testicular cancer,[24] uveal melanoma[44]) are not discussed here. The main results for these cancer sites are shown in eTable 2 (http://links.lww.com/A1450).

CONCLUSIONS

In the last few years, the epidemiologic evidence on mobile phone use and risk of brain and other tumors of the

head has grown considerably. In our opinion, overall the studies published to date do not demonstrate a raised risk within approximately 10 years of use for any tumor of the brain or any other head tumor. However, some key methodologic problems remain—for example, selective nonresponse and exposure misclassification. Despite these methodologic shortcomings and the still limited data on long latency and long-term use, the available data do not suggest a causal association between mobile phone use and fast-growing tumors such as malignant glioma in adults, at least those tumors with short induction periods. For slow-growing tumors such as meningioma and acoustic neuroma, as well as for glioma among long-term users, the absence of associations reported thus far is less conclusive because the current observation period is still too short. Currently data are completely lacking on the potential carcinogenic effect of exposures in childhood and adolescence.

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