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Review

Systematic Review of Wireless Phone Use and Brain Cancer and Other Head Tumors

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We conducted a systematic review of scientific studies to evaluate whether the use of wireless phones is linked to an increased incidence of the brain cancer glioma or other tumors of the head (meningioma, acoustic neuroma, and parotid gland), originating in the areas of the head that most

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absorb radiofrequency (RF) energy from wireless phones. Epidemiology and in vivo studies were evaluated according to an agreed protocol; quality criteria were used to evaluate the studies for narrative synthesis but not for meta-analyses or pooling of results. The epidemiology study results were heterogeneous, with sparse data on long-term use ($\geq$10 years). Meta-analyses of the epidemiology studies showed no statistically significant increase in risk (defined as $P < 0.05$) for adult brain cancer or other head tumors from wireless phone use. Analyses of the in vivo oncogenicity, tumor promotion, and genotoxicity studies also showed no statistically significant relationship between exposure to RF fields and genotoxic damage to brain cells, or the incidence of brain cancers or other tumors of the head. Assessment of the review results using the Hill criteria did not support a causal relationship between wireless phone use and the incidence of adult cancers in the areas of the head that most absorb RF energy from the use of wireless phones. There are insufficient data to make any determinations about longer-term use ($\geq$10 years). Bioelectromagnetics 33:187–206, 2012.

Key words: wireless phones; brain cancer; head tumors; radiofrequency fields; systematic review

INTRODUCTION

Cell phones are now in widespread use throughout much of the world [ITU, 2010] and it has been suggested that their use may be linked to an increased risk of brain cancer or head tumors. The recent Interphone Study of 10500 people in 13 countries focused on four tumors in the areas of the head that most absorb the radiofrequency (RF) energy emitted by cell phones [Interphone Study Group, 2010]. It used a common core protocol, was larger than all previous case–control studies combined, and included substantially more long-term and heavier users of cell phones than previous studies. We now have, along with previous studies, a substantial body of epidemiology and in vivo experimental laboratory data. Therefore, this is an appropriate time to review and assess scientific knowledge about the use of wireless phones (both cell and cordless).

Cell phones are low-powered RF transmitters and receivers operating at frequencies between 450 and 2700 MHz [ICNIRP, 2009a]. The international exposure guideline for exposure to RF fields from wireless phones is a local specific energy absorption rate (SAR) in the head of not more than 2.0 W/kg [ICNIRP, 1998, 2009b]. The maximum local SAR values from cell phones typically range between 0.2 and 1.5 W/kg [SCENIHR, 2009]. Digital enhanced cordless telecommunications (DECT) cordless phones operate at frequencies in the 1880–1900 MHz range [Valberg et al., 2007], with substantially lower local SAR values estimated to be in the range of 0.008–0.06 W/kg [HPA, 2008].

The objective of this review was to assess the overall state of scientific knowledge to evaluate whether a causal relationship has been established between the use of wireless phones and the incidence of four neoplasms originating in the areas of the head that absorb most of the RF energy from the use of wireless phones (the brain cancer glioma, and the three head tumors, meningioma, acoustic neuroma, and parotid gland tumors).

Recent efforts to improve the quality of evaluations of randomized clinical trials, such as the Cochrane Handbook for Systematic Reviews of Interventions [Higgins and Green, 2011], the PRISMA Statement [Moher et al., 2009] and the Centers for Reviews and Dissemination guidelines [CRD, 2008], highlight two important principles that can be used to improve the quality of reviews. These two principles are that reviews be systematic and transparent. To achieve that, a review must be based on an explicit methodology set forth in a protocol before the review begins, which was done for this review.

METHODS

The review was based on epidemiology research that has investigated whether there is an association between the use of wireless phones and brain cancer or other head tumors, and in vivo laboratory research that has investigated whether there is an increase in tumors of the head resulting from exposure to RF fields comparable to or greater than those from wireless phones. In vitro studies were considered in addressing possible mechanisms of action and the biological plausibility of a causal relationship in the overall assessment.

Before the review began, all authors agreed to and followed an explicit methodology for conducting the review that was set out in our protocol. The protocol is available in the online appendix. The protocol excluded reviewer participation involving any study he or she authored or co-authored. It included criteria for the search of relevant studies, inclusion of studies (in all languages), and quality assessment criteria for epidemiology and in vivo studies. Figures 1 and 2 in the online appendix are the worksheets used by the reviewers for evaluating the quality of the

epidemiology and in vivo studies. The protocol also included methods for data extraction and a narrative synthesis of the results based on the weight accorded to the studies by applying the quality assessment criteria. The protocol also provided for a meta-analysis of the epidemiology data and a pooled analysis of the in vivo data (without using the weight accorded each study). It also included the factors for overall assessment, based on the Hill Criteria [Hill, 1965].

The weight accorded to study results for the narrative synthesis was determined by systematically evaluating each study against the quality assessment criteria. Whether a study satisfies a criterion, however, is often not a simple yes or no answer. Therefore, additional weight was accorded to study results based on the extent to which the study satisfied a criterion. Thus, full weight was accorded to studies that fully satisfied a criterion. However, in the judgment of the reviewer, if the study only partially satisfied a criterion, it was accorded only partial additional weight, otherwise, studies were not accorded any additional weight under that criterion. The evaluations of the studies highlighted their strengths, weaknesses, and relative quality.

Our review considered all original in vivo laboratory and epidemiology study publications that were identified using the search criteria (detailed in the online appendix), and published in peer-reviewed scientific journals up to our cut-off date of 13 November 2010.

For the outcomes of each case–control and cohort study, effect estimates were extracted for risk of each tumor type (glioma, meningioma, acoustic neuroma, and parotid gland tumors) among cases that had ever used a cell phone (i.e., if the subject had ever been a regular user of a cell phone, defined as making an average of $\geq$1 call/week for $\geq$6 months) compared to non-users of cell phones (or non-regular users, defined as those making less calls than regular users or never having been a regular user), and for risks of disease since start of use as categorized in the original paper. Effect estimates, expressed as odds ratios (ORs), for those who ever used a cell phone were obtained by comparing regular phone users with non-phone users plus non-regular phone users (defined as not regular phone users). For long-term phone use, the OR was obtained by comparing groups of people who started to use their phone $\geq$10 years ago with the ''not regular phone user'' group. If studies assessed long-term risks from phone use over a period shorter than 10 years, those data were extracted but the shorter time period of the study was stated. The definition of short-term use is typically based on the distribution among controls and so the categorizations of duration of use are not consistent across studies. Thus, we combined risk estimates covering categories with $<$5 years since start of cell phone use. Short-term risks of glioma or meningioma from the Interphone Study results were obtained by combining their two ''time since start of cell phone use'' categories (1–1.9 and 2–4 years) in order to make them more comparable to other studies. For in vivo studies, the results for RF-induced changes in tumor incidence were grouped according to exposure levels.

For the epidemiology case–control and cohort studies, ORs and confidence intervals (CIs) of studies published after 1 January 2009 were combined in a meta-analysis with the results of the studies by Ahlbom et al. [2009], ensuring that no double counting of results occurred (as described in the online appendix). Tests for heterogeneity of results were conducted. Combined ORs were calculated by weighting each study proportionally to the inverse of the variance of the effect estimates. We did not accord any additional weight to any study based on the study quality criteria in our meta-analyses. We performed standard tests of heterogeneity and calculated the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. As there was often substantial heterogeneity between the study results, random effects models were used for all analyses [Song et al., 2001; Higgins et al., 2002, 2003; Thompson and Higgins, 2002].

To synthesize the data for the in vivo studies, we conducted a pooled analysis of all data from the tumor and tumor promotion studies (not according any additional weight the results of any study based on our quality criteria). The data from each study were separated into three exposure groups using the International Commission on Non-Ionizing Radiation Protection (ICNIRP) RF exposure guideline of 2 W/kg for the head as a dividing point (SAR $<$ 2.0 W/kg, SAR $\geq$ 2.0 W/kg), and these were compared to the sham-exposed group. SAR values for the head or brain were used when provided. Each study had only one set of data for the sham-exposed group so they were used for comparison with the other two exposure groups.

RESULTS

Epidemiology Studies

Our search initially identified 96 papers, excluding duplicates. After screening for relevant original research, our review included two new case–control,

two case-only, and seven ecological studies either published since or not addressed by Ahlbom et al. [2009]. Ahlbom et al. included the Schüz et al. [2006a] case–control study but not its cordless phone data, so we considered them in our review. There is very little data for long-term use of cell phones and essentially no data on childrens' use.

Case-only. Our search identified two case-only studies. Sato et al. [2010] results were based only on answers to a questionnaire mailed to acoustic neuroma patients. The results were accorded little additional weight based on our study quality criteria. The authors reported an increased risk of acoustic neuroma for cell phone use $>$ 20 min/day on average, but concluded that the more plausible explanation for the result was recall bias. Hartikka et al. [2009] assessed an approach for evaluating glioma risk using the distance between glioma tumor midpoints and the presumed location of the cell phone when in use. These results were therefore accorded some additional weight based on our study quality criteria. They found no statistically significant associations except for use of the phone on the opposite side of the head to where the tumor was located (OR = 4.93, 95% CI = 1.13–21.5) and concluded that the overall results do not indicate an association between cell phone use and the risk of glioma in the area of the brain likely to receive most of the RF exposure.

Case–control and cohort studies. Since the study by Ahlbom et al. [2009], two new case–control studies (and no new cohort studies) have been published: Hardell et al. [2010] conducted a study of deceased cases of brain tumors, and the Interphone Study Group [2010] combined results for glioma and meningioma. Though selection and recall bias limited the amount of additional weight accorded to the Interphone Study results, the investigators provided careful analyses of their biases and validation studies [Vrijheid et al., 2006, 2009a] so that overall the results were accorded almost full additional weight based on our study quality criteria. The Interphone Study reported statistically significant decreased risks for both glioma and meningioma for regular users compared with those that have never been regular users, which complicated the interpretation of the findings. Possible selection and recall bias also limited the amount of additional weight accorded to the results of Hardell et al. They used exposure data reported by relatives of deceased individuals up to 11 years after death and did not conduct any validation studies. Based on our study quality criteria, the results of Hardell et al. were accorded substantially less additional weight than the Interphone Study results. Hardell et al. reported an increased risk of malignant brain tumors among heavy users of cell phones (OR = 2.4, CI = 1.4–4.1). The Interphone Study reported suggestions of an increased incidence of glioma in heavy and long-term users ($\geq$10 years) but the results were not statistically significant. The Interphone Study found a significantly increased risk of tumors in the temporal lobe for heavy use (OR = 1.87, CI = 1.09–3.22) and also for ipsilateral use, but recall bias could not be ruled out as the reason for those findings. The Interphone Study concluded that overall there was no increased risk of glioma or meningioma from cell phone use.

Glioma. Results of meta-analyses for gliomas are given in Table 1 and Figure 1. Short-term use (1–6 years) of cell phones was included in eight studies. The majority of these studies did not find an association between short-term cell phone use and risk of glioma. Hardell et al. [2006] found an increased risk for short-term digital phone use (OR = 1.6, CI = 1.1–2.4) but the Interphone Study Group [2010] found a decreased risk (OR = 0.77, CI = 0.66–0.90). The heterogeneity of the pooled studies was large ($P = 0.008$, $I^2 = 64\%$) but decreased when either the Interphone Study (OR = 1.19, CI = 0.95–1.27) (P for heterogeneity = 0.29) or the Hardell et al. [2006] study (OR = 0.97, CI = 0.82–1.14, $P = 0.053$) was removed from the meta-analysis. The combined results (no studies removed) showed no statistically significant increase in risk with short-term use (OR = 1.03, CI = 0.86–1.24; Table 1, Fig. 1a). Long-term use of cell phones was addressed in five studies and three did not find a significantly increased risk for glioma but two Hardell et al. studies did report a significantly increased risk: Hardell et al. [2006] (OR = 3.5, CI = 2.0–6.4) and Hardell et al. [2010] (OR = 2.4, CI = 1.4–4.1). Heterogeneity was substantial ($P < 0.001$, $I^2 = 87\%$); however, the high heterogeneity cannot be attributed to a specific study. If the Schüz et al. [2006] or Hardell et al. [2006] studies, which provided the lowest and the highest risk estimates, respectively, were removed, heterogeneity remained high ($P < 0.001$ and $P = 0.002$, respectively). For long-term use, the combined results gave no statistically significant increase in risk (OR = 1.40, CI = 0.84–2.31; Table 1, Fig. 1b). Results for those that had ever used cell phones were similar to the short-term results. Heterogeneity was substantial ($P < 0.001$, $I^2 = 76\%$). The combined results showed no statistically significant increase in risk of glioma associated with ever having used a cell phone (OR = 1.07, CI = 0.89–1.29; Table 1,

TABLE 1. Results of Studies on Time Since First Cell Phone Use and Risk of Glioma, and Variation in Effect Estimates Attributable to Heterogeneity

	Short-term use[a]		Long-term use[a]		Ever used[a]	
Study	Exposed cases (exposure period)[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)
Muscat et al. [2000] [c]	49 (1–3 years)	0.9 (0.6–1.4)	—	—	66	0.7 (0.5–1.1)
Inskip et al. [2001] [c]	31 (0.5–3 years)	0.9 (0.5–1.6)	—	—	201	1.0 (0.7–1.4)
Auvinen et al. [2002]	25 (≤2 years)	1.5 (0.9–2.4)	—	—	36	1.5 (1.0–2.4)
Hardell et al. [2002] [b,c]	36 (1–6 years) (analog)	1.1 (0.7–1.8)	43 (>6 years)	1.2 (0.8–1.8)	79	1.1 (0.8–1.6)
Hardell et al. [2006] [b,c]	100 (digital)	1.6 (1.1–2.4)	48 (analog)	3.5 (2.0–6.4)	68 (analog)	2.6 (1.5–4.3)
Schüz et al. [2006] [c]	266 (1–4 years)	1.03 (0.91–1.17)	28	0.66 (0.44–0.95)	580	0.97 (0.89–1.06)
Interphone Study Group [2010]	800 (1–4 years)	0.77 (0.66–0.90)	252	0.98 (0.76–1.26)	1666	0.81 (0.70–0.94)
Hardell et al. [2010]	33 (1–5 years)	1.0 (0.6–1.7)	38	2.4 (1.4–4.1)	106	1.3 (0.9–1.9)
Combined OR	—	1.03 (0.86–1.24)	—	1.40 (0.84–2.31)	—	1.07 (0.89–1.29)
I^2	—	63.6%	—	87.0%	—	75.5%
Heterogeneity P	—	0.008	—	<0.001	—	<0.001

[a]Short-term use is a regular phone user (defined as at least 1 call/week for ≥6 months) for 1–6 years (depending on study); exposure period given in parentheses refers to the considered exposure window prior to diagnosis; Long-term use is start of mobile phone use ≥10 years ago or occasionally ≥10 years of cumulative mobile phone use; Ever used is defined as ever having been a regular user.
[b,c]Only analog data used in Hardell et al. [2002, 2006] to avoid duplicate data except for short-term use in Hardell et al. [2006] as there were no analog phone users in this category.
[c]These studies collected brain tumor cases. Since most brain tumors are gliomas, they are included here.

Fig. 1c). We used only the ORs for analog phone use from the studies of Hardell et al. because of the problem of double counting, except for short-term use in the Hardell et al. [2006] study, where there was no analog data and therefore digital data were used. The Hardell et al. study data generally have ORs higher for analog use than for digital phone use, resulting in some overstating of the overall results. If we had included the Hardell et al. ORs for digital phone use, the pooled ORs would have been slightly lower but not enough to affect the outcome of our analyses.

Gousias et al. [2009] conducted a small descriptive epidemiology study on gliomas in Greece, with little information on cell phone use and it was thus accorded little additional weight based on our study evaluation criteria. While their case–control analysis found no statistically significant association between gliomas and cell phone use, the information provided was insufficient to be included in the meta-analyses.

Meningioma. The four studies that addressed short-term risk of meningioma did not find an association between cell phone use and meningiomas (Table 2, Fig. 2). The Interphone Study Group [2010] found a decreased risk (OR = 0.81, CI = 0.70–0.93) and there was little heterogeneity between the studies ($P = 0.70$, $I^2 = 0\%$). The combined results for short-term use showed a statistically significant lowered risk for meningiomas associated with cell phone use (OR = 0.82, CI = 0.72–0.94; Table 2, Fig. 2a). For long-term use of cell phones, Hardell et al. [2005] reported an increased risk (OR = 2.1, CI = 1.1–4.3) and the Interphone Study Group [2010] reported a risk estimate close to unity (OR = 0.83, CI = 0.61–1.14). Heterogeneity of the studies was substantial ($P = 0.015$, $I^2 = 83\%$), and because there were only two studies, it was not possible to further evaluate the source of the heterogeneity. The combined results for these two studies showed no statistically significant increase in risk (OR = 1.25, CI = 0.51–3.10; Table 2, Fig. 2b). For those ever having used a cell phone, most studies did not find an association with meningioma. Hardell et al. [2005] reported an increased risk (OR = 1.7, CI = 1.0–3.0) and the Interphone Study Group [2010] reported a decreased risk (OR = 0.79, CI = 0.68–0.91). Heterogeneity among studies was moderate ($P = 0.10$, $I^2 = 46\%$). The combined results for meningiomas showed a statistically non-significant lowered risk of meningiomas for those who had ever used a cell phone (OR = 0.93, CI = 0.77–1.12; Table 2, Fig. 2c).

Acoustic neuroma. For short-term use of cell phones, eight studies were included in the meta-analysis (Table 3, Fig. 3). The majority did not find an association between short-term cell phone use and the risk of acoustic neuromas. Hardell et al. [2002] (OR = 3.0, CI = 1.0–9.3) and Hardell et al. [2005]

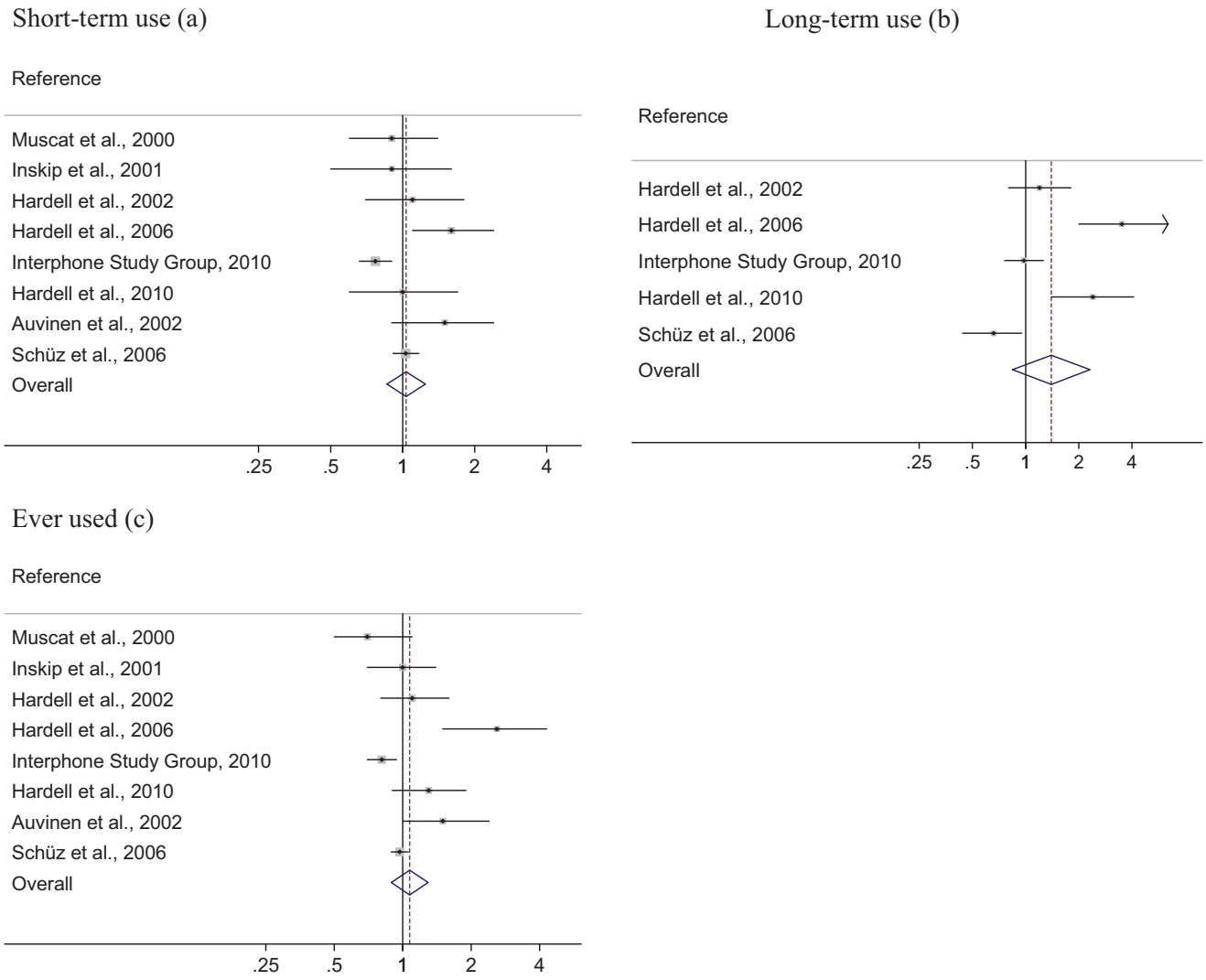

Fig. 1. Plots of the odds ratios (ORs, points) and their confidence intervals (CIs, bars) of glioma risk for short-term use (**a**), long-term use (**b**) and ever used (**c**) a cell phone. The diamond symbol gives the combined ORs and CIs, and the arrow indicates that the CI value extends past the limit of the OR axis.

(OR = 9.9, CI = 1.4–69.0) reported an increased risk for analog phone users, and Schoemaker et al. [2005] found a decreased risk (OR = 0.8, CI = 0.7–1.0). Heterogeneity was large ($P = 0.03$, $I^2 = 56\%$). The combined results showed no statistically significant increase in risk (OR = 0.99, CI = 0.70–1.41; Table 3, Fig. 3a). For long-term use of cell phones, addressed in four studies, heterogeneity was moderate ($P = 0.18$, $I^2 = 38\%$). The combined results for long-term use showed no statistically significant increase in risk (OR = 1.37, CI = 0.74–2.52; Table 3, Fig. 3b). Hardell et al. [2002] (OR = 3.5, CI = 1.8–6.8) and Hardell et al. [2005] (OR = 4.2, CI = 1.8–10.0) reported an increased risk for those ever having used analog cell phones while the other studies found risk estimates close to unity. Heterogeneity was substantial ($P < 0.001$, $I^2 = 72\%$). The combined results showed no statistically significant increase in the risk of acoustic neuromas associated with those who had ever used a cell phone (OR = 1.05, CI = 0.77–1.42; Fig. 3c).

Parotid (salivary) gland tumors. None of the five studies found an association between short-term use of cell phones and parotid gland tumors (Table 4, Fig. 4). The combined results for short-term use showed a non-statistically significant lowered risk of parotid gland tumors (OR = 0.88, CI = 0.72–1.08; Table 4, Fig. 4a). The combined results for long-term cell phone use (OR = 0.83, CI = 0.52–1.33;

TABLE 2. Results of Studies on Time Since First Cell Phone Use and Risk of Meningioma, and Variation in Effect Estimates Attributable to Heterogeneity

	Short-term use[a]		Long-term use[a]		Ever used[a]	
Study	Exposed cases (exposure period)[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)
Inskip et al. [2001]	12 (0.5–3 years)	0.8 (0.4–1.9)	—	—	67	0.8 (0.5–1.2)
Auvinen et al. [2002]	9 (≤2 years)	1.3 (0.6–2.9)	—	—	11	1.1 (0.5–2.4)
Hardell et al. [2002] [b]	—	—	—	—	60 (analog)	1.1 (0.7–1.5)
Hardell et al. [2005] [b]	1(1–5 years) (analog)	1.2 (0.1–12.0)	20	2.1 (1.1–4.3)	35	1.7 (1.0–3.0)
Schüz et al. [2006]	—	—	—	—	68	0.86 (0.67–1.09)
Interphone Study Group [2010]	735 (1–4 years)	0.81 (0.70–0.93)	110	0.83 (0.61–1.14)	1262	0.79 (0.68–0.91)
Combined OR	—	0.82 (0.72–0.94)	—	1.25 (0.51–3.10)	—	0.93 (0.77–1.12)
I^2	—	0.0%	—	83.0%	—	46.3%
Heterogeneity P	—	0.70	—	0.02	—	0.10

[a]Short-term use is a regular phone user (defined as at least 1 call/week for ≥6 months) for 1–6 years (depending on study); exposure period given in parentheses refers to the considered exposure window prior to diagnosis; Long-term use is start of mobile phone use ≥10 years ago or occasionally ≥10 years of cumulative mobile phone use; Ever used is defined as ever having been a regular user.
[b]Only analog data used in Hardell et al. studies.

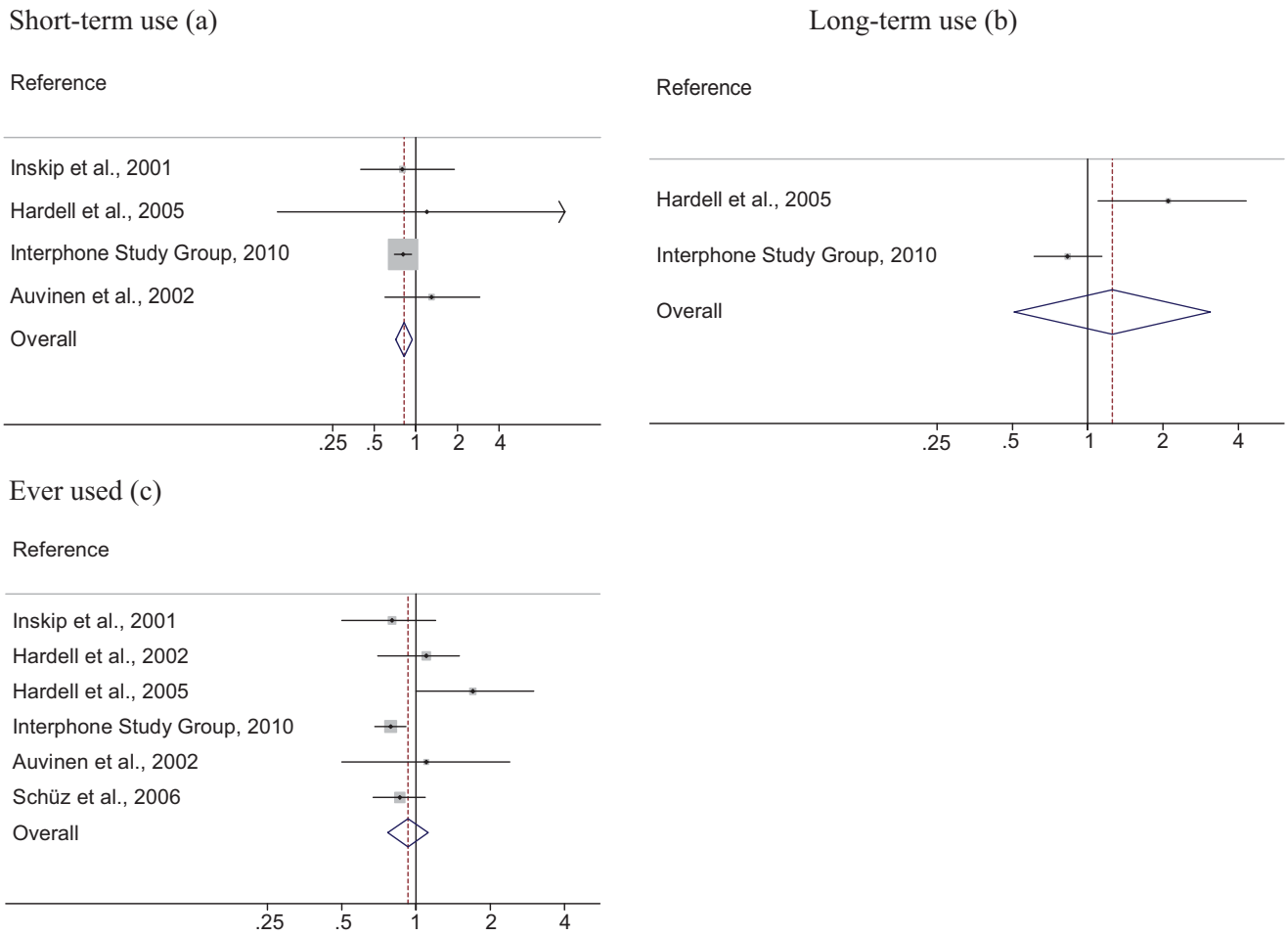

Fig. 2. Plots of the ORs (points) and their CIs (bars) of meningioma risk for short-term use (**a**), long-term use (**b**) and ever used (**c**) a cell phone. The diamond symbol gives the combined ORs and CIs, and the arrow indicates that the CI value extends past the limit of the OR axis.

TABLE 3. Results of Studies on Time Since First Cell Phone Use and Risk of Acoustic Neuroma, and Variation in Effect Estimates Attributable to Heterogeneity

	Short-term use[a]		Long-term use[a]		Ever used[a]	
Study	Exposed cases (exposure period)[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)
Inskip et al. [2001]	8 (0.5–3 years)	1.8 (0.7–4.5)	—	—	40	0.8 (0.5–1.4)
Muscat et al. [2002]	7 (1–2 years)	0.5 (0.2–1.3)	—	—	18	0.8 (0.4–1.7)
Hardell et al. [2002] [b]	12 (1–5 years) (analog)	3.0 (1.0–9.3)	7	3.5 (0.7–16.8)	38	3.5 (1.8–6.8)
Warren et al. [2003] [c]	—	—	—	—	21	1.2 (0.6–2.2)
Hardell et al. [2005] [b]	2 (1–5 years) (analog)	9.9 (1.4–69.0)	7	2.6 (0.9–8.0)	20	4.2 (1.8–10.0)
Schoemaker et al. [2005]	231 (1–4 years)	0.8 (0.7–1.0)	31	1.0 (0.7–1.5)	360	0.9 (0.7–1.1)
Schüz et al. [2006]	—	—	—	—	32	0.73 (0.50–1.03)
Schlehofer et al. [2007]	20 (1–4 years)	0.8 (0.4–1.5)	—	—	29	0.7 (0.4–1.2)
Hours et al. [2007]	44 (<3.8 years)	1.0 (0.6–1.7)	—	—	58	0.9 (0.5–1.6)
Takebayashi et al. [2008]	26 (<4 years)	0.7 (0.4–1.3)	7 (≥8 years)	0.8 (0.2–2.7)	51	0.7 (0.4–1.2)
Combined OR	—	0.99 (0.70–1.41)	—	1.37 (0.74–2.52)	—	1.05 (0.77–1.42)
I^2	—	56.3%	—	38.0%	—	72.0%
Heterogeneity P	—	0.03	—	0.18	—	<0.001

[a]Short-term use is a regular phone user (defined as at least 1 call/week for ≥6 months) for 1–6 years (depending on study); exposure period given in parentheses refers to the considered exposure window prior to diagnosis; Long-term use is start of mobile phone use ≥10 years ago or occasionally ≥10 years of cumulative mobile phone use; Ever used is defined as ever having been a regular user.
[b]Only analog data used in Hardell et al. studies.
[c]Facial nerve neuroma.

Table 4, Fig. 4b) or for those ever having used a cell phone (OR = 0.87, CI = 0.73–1.04; Fig. 4c) showed no statistically significant risk of parotid gland tumors with cell phone use. Heterogeneity was absent in all cases (short-term use: $P = 0.73$, $I^2 = 0.0\%$; long-term use: $P = 0.69$, $I^2 = 0.0\%$; ever use: $P = 0.97$, $I^2 = 0.0\%$).

Ecological Studies

These studies are based on population level data rather than individual level data. They can provide useful insights when comparing time trends of a disease with potential risk factors, provided unwarranted inferences about individual risk are not made. Because effect measures and groupings of these studies are generally incompatible, their results were not pooled.

The results of the following studies were accorded almost full additional weight because they satisfied most of our quality criteria. Lönn et al. [2004] studied the incidence trends of adult primary intracerebral brain tumors (combined) in Denmark, Norway, Sweden, and Finland over the period 1969–1998. They found a modest increase in the late 1970s and early 1980s that corresponded to the period of introduction of improved diagnostics (computed tomography and magnetic resonance imaging), but no increase in the incidence trends of adult brain tumors during the period of increasing cell phone use. Röösli et al. [2007] examined cell phone use and time trends in brain tumor mortality in two periods before and after analog cell phones were introduced in Switzerland. They found that brain tumor mortality remained stable in all age groups and there was no evidence of an increase in brain tumor mortality after the introduction of cell phones. Deltour et al. [2009] examined time trends in the incidence rates of glioma and meningioma from 1974 to 2003 for the entire adult populations of Denmark, Finland, Norway, and Sweden, which all have high quality cancer registries. They pointed out that cell phone use in those Nordic countries did not become widespread until the early 1990s and increased sharply in the mid-1990s. They reported that they ''did not detect any clear change in the long-term time trends in the incidence of brain tumors from 1998 to 2003 in any subgroup.'' They found that the brain tumor incidence rates were either stable, decreased, or showed a continued, gradual increase that started before the introduction of cell phones and was ''consistent with mobile phone use having no observable effect on brain tumor incidence during that period.'' Nelson et al. [2006] examined acoustic neuroma trends in England and Wales for 1979–2001 and found no trends associated with cell phone use.

Lehrer et al. [2011] was the only study to report a statistically significant correlation between brain cancer incidence in 19 states in the USA during 2000–2004, and cell phone subscriptions in 2007. Their study failed to take into account the population size when making comparisons of absolute numbers between states and thus was flawed and

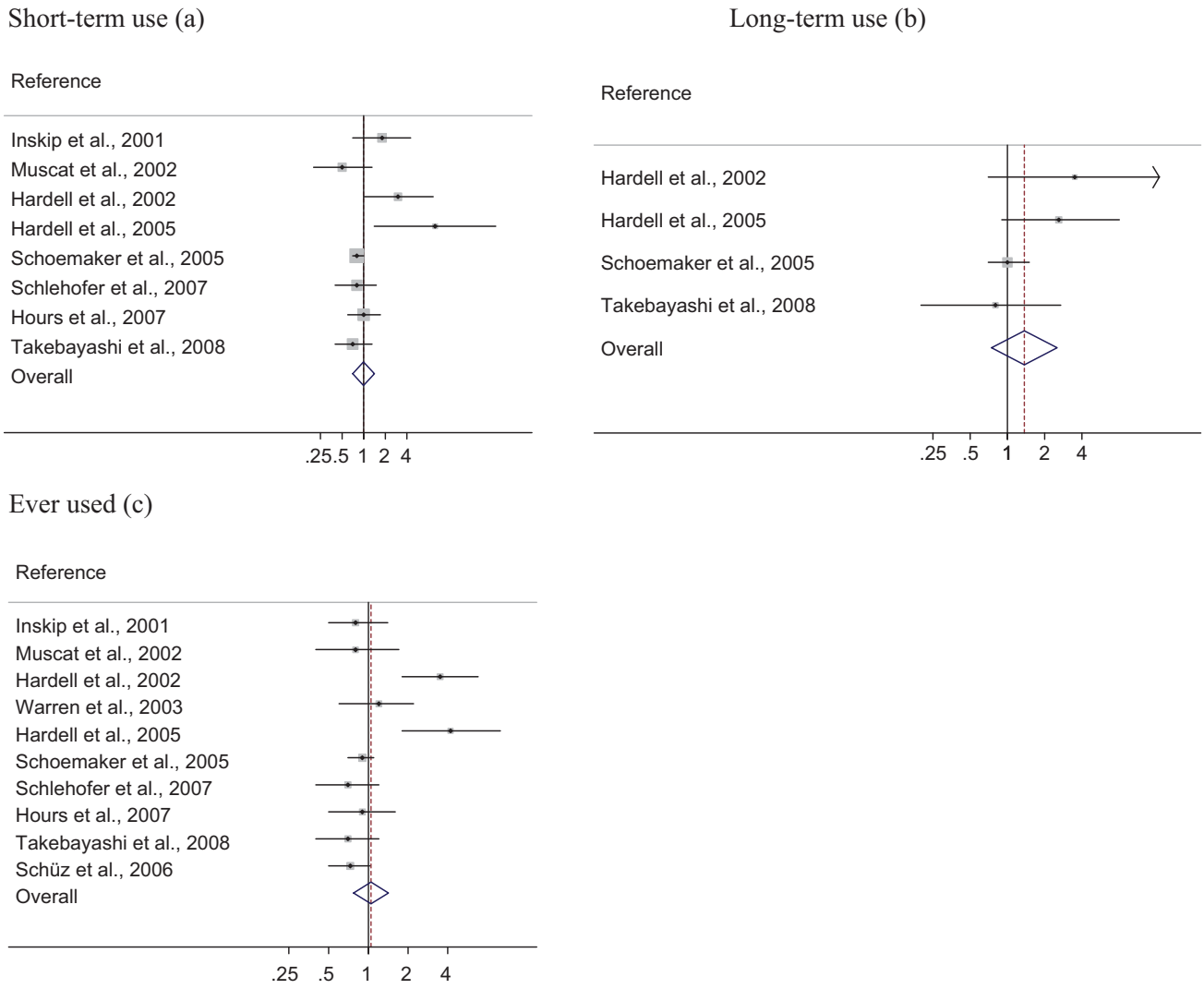

Fig. 3. Plots of the ORs (points) and their CIs (bars) of acoustic neuroma risk for short-term use (**a**), long-term use (**b**) and ever used (**c**) a cell phone. The diamond symbol gives the combined ORs and CIs, and the arrow indicates that the CI value extends past the limit of the OR axis.

uninformative. Inskip et al. [2010] also examined brain cancer trends in the USA. Their study had limitations but the results were accorded more weight than Lehrer et al. based on our study quality criteria. Inskip et al. used data collected by the US National Cancer Institute (Bethesda, MD) for both the period preceding widespread cell phone use (1977–1991) and the period including widespread use (1992–2006), and they included approximately 10% of the US population. They found a statistically significant increase in glioma incidence among women aged 20–29 but not in men. The trend for women was driven by a rising incidence in frontal lobe tumors, and no increases were apparent for temporal or parietal lobe cancers or cancers of the cerebellum, which involve those parts of the brain that would be more highly exposed to RF fields from cell phones. The authors concluded that "overall, the data do not provide support for the view that use of cell phones causes brain cancer." Altogether, the ecological studies of trends in disease do not support a relationship between brain tumors or acoustic neuromas and wireless phone use.

Cordless Phones

The German component of the Interphone Study included an additional examination of cordless phone use and exposure to cordless phone base stations to determine if they were associated with an increased risk of gliomas or meningiomas. Face-to-face interviews determined the length of time that study participants owned a cordless phone, whether

TABLE 4. Results of Studies on Time Since First Cell Phone Use and Risk of Parotid Gland Tumors, and Variation in Effect Estimates Attributable to Heterogeneity

	Short-term use[a]		Long-term use[a]		Ever used[a]	
Study	Exposed cases (exposure period)[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)	Exposed cases[b]	OR (95% CI)
Auvinen et al. [2002]	3 (1–2 years)	1.7 (0.4–7.5)	—	—	4	1.3 (0.4–4.7)
Hardell et al. [2004] [b]	31 (>1 year) analog)	0.9 (0.6–1.4)	6	0.7 (0.3–1.7)	31 (analog)	0.9 (0.6–1.4)
Schüz et al. [2006]			—	—	26	0.9 (0.6–1.3)
Lönn et al. [2006] (malignant)	14 (1–4 years)	0.7 (0.3–1.3)	2	0.4 (0.1–2.6)	25	0.7 (0.4–1.3)
Lönn et al. [2006] (benign)	47 (1–4 years)	1.0 (0.6–1.8)	7	1.4 (0.5–3.9)	77	0.9 (0.5–1.5)
Sadetzki et al. [2008] (malignant)	21 (1–4 years)	1.3 (0.6–2.7)	1	0.5 (0.1–4.5)	33	1.1 (0.5–2.1)
Sadetzki et al. [2008] (benign)	335 (1–4 years)	0.8 (0.6–1.1)	22	0.9 (0.4–2.0)	252	0.9 (0.6–1.1)
Combined OR	—	0.88 (0.72–1.08)	—	0.83 (0.52–1.33)	—	0.87 (0.73–1.04)
I^2	—	0.0%	—	0.0%	—	0.0%
Heterogeneity P	—	0.73	—	0.69	—	0.97

[a]Short-term use is a regular phone user (defined as at least 1 call/week for ≥6 months) for 1–6 years (depending on study); exposure period given in parentheses refers to the considered exposure window prior to diagnosis; Long-term use is start of mobile phone use ≥10 years ago or occasionally ≥10 years of cumulative mobile phone use; Ever used is defined as ever having been a regular user.
[b]Only analog data used in Hardell et al. study.

they were regular users, and the location of the base station with respect to the bedroom in their home. Exposure categories were then based on years since first use of their phone. No statistically significant association between glioma or meningioma risk and cordless phone use or exposure to base stations was found [Schüz et al., 2006a,b]. These studies were well reported, standard statistical methods were used for data analysis, and selection/participation bias was considered low. A weakness in the studies was that time since first regular use of a cordless phone was self-reported, but some validation of number and duration of calls was performed in a previous study and could be applied to this study [Schüz et al., 2006a]. Overall, the studies were given almost full additional weight.

Hardell et al. have conducted a number of studies on cordless phones and the risk of brain cancer or head tumors. No significantly increased risk was observed for acoustic neuromas [Hardell et al., 2005] or salivary gland tumors [Hardell et al., 2004]. However, Hardell et al. [2006] reported an increased risk of malignant brain tumors associated with cordless phone use. Hardell et al. [2006a] investigated the association between cordless phone use and malignant brain tumors in a pooled analysis of two case–control studies with 905 patients diagnosed between 1997 and 2003 and 2162 controls aged 20–80 years. Cumulative lifetime use of cordless phones for >2000 h yielded an OR of 2.3 and a CI of 1.5–3.6. They reported an OR of 2.2 and a CI of 1.3–3.9 for high-grade astrocytomas using a >10-year latency period for cordless phone use.

Hardell et al. [2010] posed questions on cordless phone use to next-of-kin in a case–control study of deceased cases of malignant brain tumors. Unadjusted risk estimates were not reported. Unconditional logistic regression was used and no justification for using it was provided. Exposures were based on reports by next-of-kin, which have less validity than exposures reported by cases, and there was no validation of the exposure data. Therefore, this study received only partial additional weight. It reported no statistically significant risk of malignant brain tumors from cordless phone use, even for the most hours of use (>2000 h) and the longest latency period (>10 years). Overall, there is a similar pattern across studies for cordless phones and cell phones. Most of the studies from the Hardell group report an association whereas other studies do not. The reason for this is unclear.

In Vivo Studies

Our search identified 45 in vivo studies published since 1 January 2000. Excluding reviews, editorials and commentaries, 22 provided original research results directly related to our review. These consisted of 10 genotoxicity studies and 12 tumor and tumor promotion studies.

Genotoxicity. In vivo genotoxicity studies were reviewed to determine whether RF exposure produces genotoxic effects in brain cells. Study endpoints included breaks in DNA or gene mutations, which are necessary steps in the process of carcinogenesis that could lead to brain cancer. To determine whether

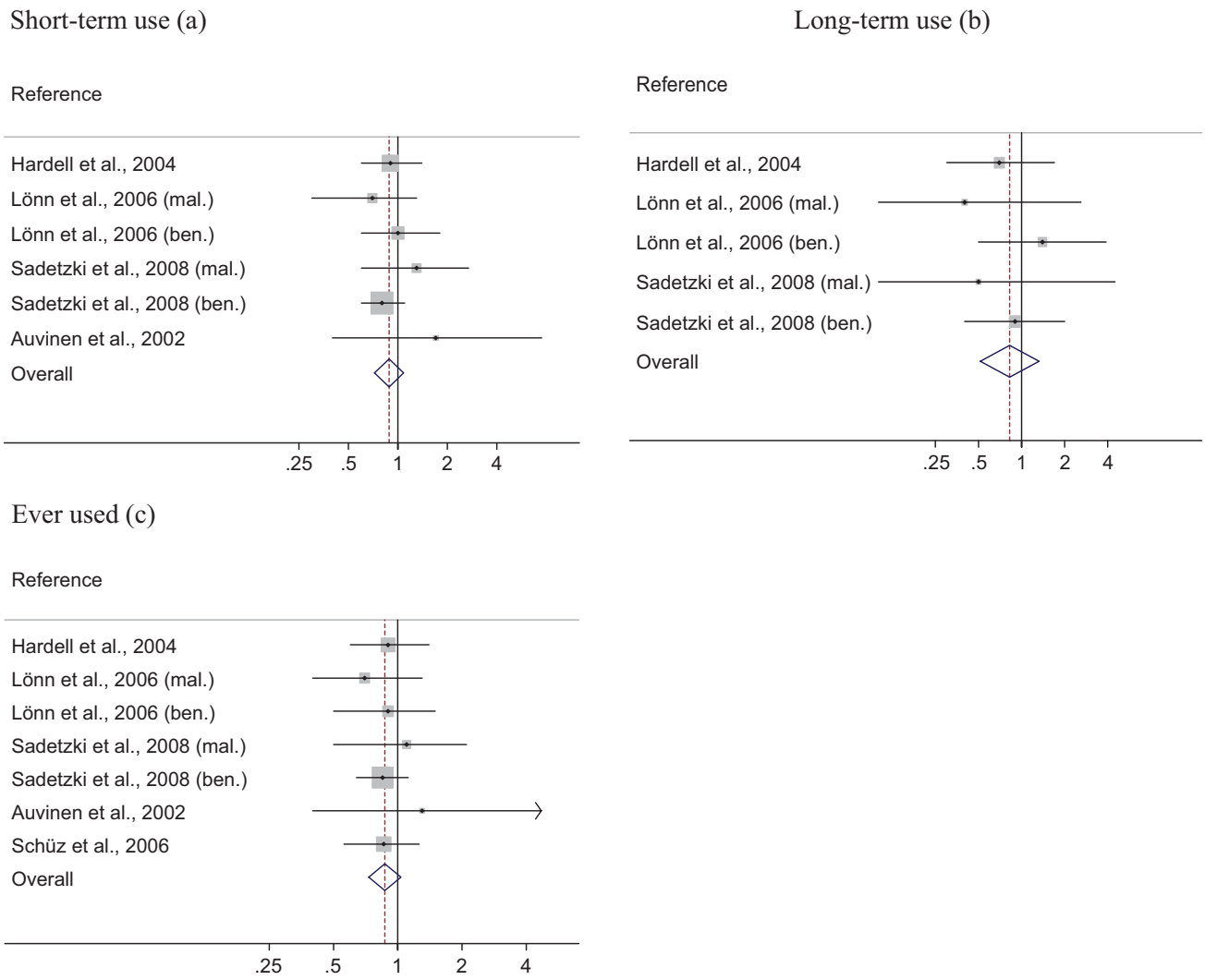

Fig. 4. Plots of the ORs (points) and their CIs (bars) of parotid gland risk for short-term use (**a**), long-term use (**b**) and ever used (**c**) a cell phone. The diamond symbol gives the combined ORs and CIs, and the arrow indicates that the CI value extends past the limit of the OR axis.

breaks in DNA have occurred, the studies used comet assays or other genotoxicity assays. For assays to be free of observational or other biases, it is important that data collection and management be blinded as to whether the cells were in the exposed or sham-exposed group. In this regard, assay results provided by recording instrumentation are much more reliable than those provided from personal observation, which inherently involve an increased risk of observational bias. Subsequent examination of the results of the analyses by an independent panel should improve the chance for bias-free results.

Six of the 10 genotoxicity studies were given less additional weight for poor dosimetry and particularly because the researchers were not blinded as to which were the exposed and control groups, and were not blinded during data management [Takahashi et al., 2002; Gadhia et al., 2003; Ono et al., 2004; Lai and Singh, 2005; Belyaev et al., 2006; Paulraj and Behari, 2006]. In two other studies, the dosimetry was completely inadequate and did not satisfy most of our quality criteria [Guler et al., 2010; Kesari et al., 2010]. Accordingly, the results of those studies received little or no additional weight. The remaining two studies received almost full additional weight because they satisfied all or most of our quality criteria. Particularly important was that they were conducted in a fully blinded manner and the results of their analyses were reviewed by a panel of experts independent of the researchers, substantially increasing confidence in their results. These two studies found no genotoxic effects [Lagroye et al., 2004;

Verschaeve et al., 2006]. Some studies that received little additional weight reported positive results. Overall, the studies do not support the conclusion that RF exposure causes genotoxic effects.

Tumor and tumor promotion. In the quality evaluation, many studies were accorded almost full additional weight because they satisfied most of our quality criteria [Adey et al., 2000; Zook and Simmens, 2001, 2006; La Regina et al., 2003; Shirai et al., 2005, 2007; Heikkinen et al., 2006]. Saran et al. [2007] received less additional weight because data management was not blind. The most additional weight was accorded to the following studies because they satisfied all or substantially all of our quality criteria: Anderson et al. [2004], Smith et al. [2007], and Tillmann et al. [2007, 2010]. None of the 12 studies found any effect of RF exposure on the incidence of brain tumors or brain tumor promotion.

The results of the pooled analyses for the in vivo tumor and tumor promotion studies are shown in forest plots (Figs. 5a,b and 6). For both spontaneous brain tumors and tumors promoted by chemical carcinogens, there was no evidence of a significantly increased risk with exposure, with ORs close to unity. A statistically significant decrease in the promotion of brain tumors occurred at RF exposures below 2.0 W/kg (Fig. 5b), but as explained in the Discussion, that result appears to be spurious. Similarly, a statistically significant increase in the incidence of pituitary tumors was only found at RF exposures below 2 W/kg (Fig. 6) but this also appears to be a spurious result (as discussed below). For the other studies that investigated the effects on spontaneous pituitary tumors and the single study on promoted pituitary tumors, the ORs were very close to unity. Overall, our pooled analyses showed no relationship between RF exposure and the incidence of brain tumors or brain tumor promotion.

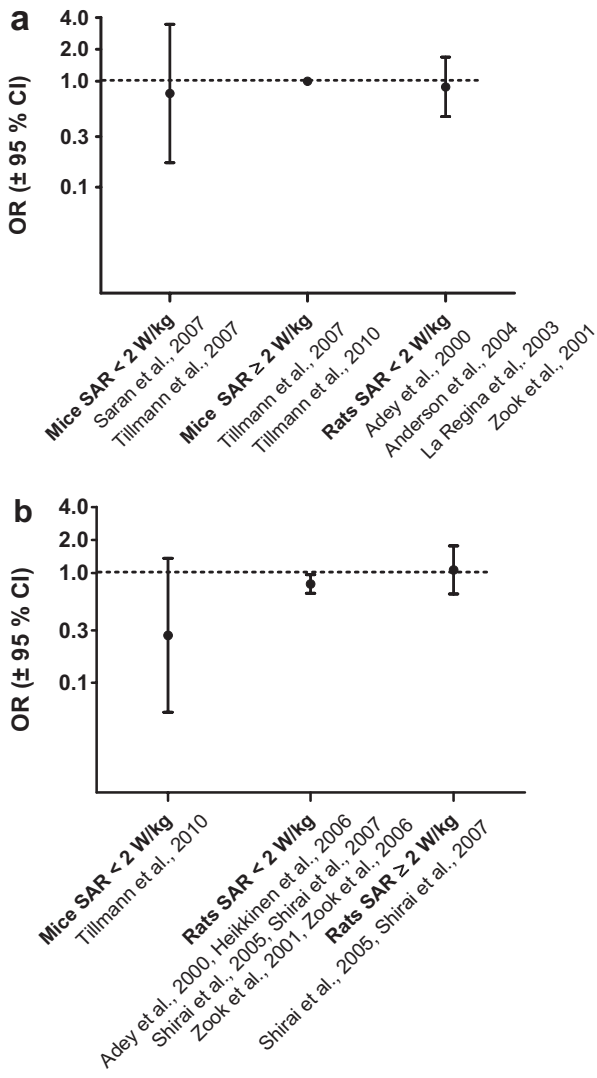

Fig. 5. **a**: Plots of spontaneous brain tumor results. **b**: Plots of brain tumor promotion results.

DISCUSSION

Mechanisms and In Vitro Studies

Mechanistic considerations can be the key in determining whether RF fields cause or contribute to disease because living organisms are governed by the same physical laws that govern all systems [Durney and Christensen, 2000]. Identification of one or more putative mechanisms of action is not essential to support the conclusion that exposure to an agent may be associated with a specific disease outcome. However, in cases where data are equivocal and/or an association has not been clearly demonstrated, identification of a relevant mechanism of action increases the probability that any observed association does indeed represent cause and effect. For RF fields to cause or contribute to diseases in living organisms there must be a mechanism by which their physical forces can cause or contribute to the alteration of the structure or function of cells or their molecules (including nucleic acids and proteins) [Parkinson, 1985; Durney and Christensen, 2000; Valberg et al., 2007]. While many theoretical nonthermal mechanisms have been proposed and considerable effort has been devoted to evaluating them, the only established mechanism of action of RF fields that has been established to cause adverse health consequences is delivery of enough energy to heat tissue [Foster and Repacholi, 2004; Sheppard

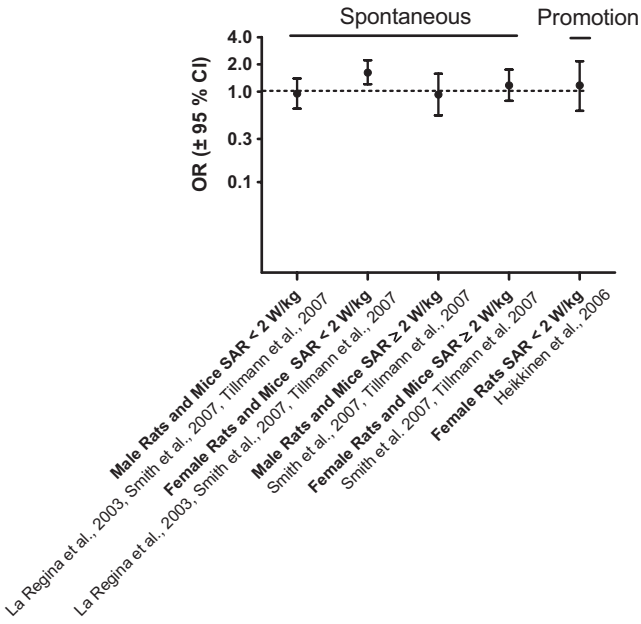

Fig. 6. Plot of pituitary tumor results.

et al., 2008; EFHRAN, 2010]. No reproducible evidence of non-thermal health effects of RF exposure has been demonstrated. Accordingly, the thermal mechanism is the basis for the international RF exposure guidelines that, with a large safety margin, limit the local SAR in the head to 2 W/kg from devices such as wireless phones [ICNIRP, 1998, 2009b; IEEE, 2005].

In vitro studies can provide information on the actions of agents on simplified biological systems (cells and tissues) and identify possible mechanisms of action, but whole living organisms often have mechanisms that compensate for effects occurring in vitro. Thus, for in vitro study findings to be of material value in an assessment of human health risks, observed effects must be shown to lead to adverse health effects in vivo.

Reviews of early in vitro studies conducted by the WHO [1993], the ICNIRP [1998], Repacholi [1998], the Royal Society of Canada [1999], the IEGMP [2000] and the AGNIR [2003] highlighted the variability of results, almost certainly caused by poor dosimetry, while consistently concluding that RF fields have not been shown to be genotoxic. Despite intensive additional research, the ICNIRP Standing Committee on Biology, after considering studies with substantially improved dosimetry, reached the same conclusion in 2010: ''Overall, however, the evidence for low-level genotoxic effects is very weak'' [Verschaeve et al., 2010]. The same conclusion has been reached by all recent reviews [ICNIRP, 2009a; SCENIHR, 2009; SSM, 2009; EFHRAN, 2010; Juutilainen et al., 2011]. In summary, the results of the in vitro studies are consistent with the results of the mechanistic studies, and despite extensive research they have failed to establish any relationship between exposure to RF fields and cancer. No clear pattern of evidence identifying a non-thermal mechanism that could underlie any adverse health effects of RF exposure has been identified.

Epidemiology Studies

For gliomas, the combined results (from eight studies, Table 1) show a close to symmetric dispersion across unity for short-term use (OR = 1.03, CI = 0.86–1.24) and for those who had ever used a cell phone (OR = 1.07, CI = 0.89–1.29). ORs of unity indicate no increased risk from exposure. For long-term use, the combined OR is above unity (OR = 1.40, CI = 0.84–2.31), although not statistically significant. Combined risk estimates for acoustic neuroma were similar to glioma (though with a skewed distribution of results with elevated risks reported from studies by Hardell et al. [2002, 2006]), and they were somewhat lower for meningioma. The inconsistency between studies is substantial, as statistically significant heterogeneity was found in all analyses involving eight or more studies. No indication of increased risks was found for parotid gland tumors.

Our results are comparable with those of earlier meta-analyses including cohort studies [Lahkola et al., 2006; Ahlbom et al., 2009], though with more precise risk estimates owing to the substantially larger number of subjects due to inclusion of the combined Interphone Study results. The meta-analyses involving only case–control studies have provided higher risk estimates, particularly for long-term use [Hardell et al., 2008; Myung et al., 2009]. However, the results of Myung et al. were affected by the higher weighting given to studies reporting blinding of interviewers regarding case–control status. Blinding may not be an effective quality indicator in case–control studies (compared to randomized trials) because disease status is often apparent to the interviewer despite attempts to conceal it. Another methodological concern in the Myung et al. study was the use of a fixed effects analysis assuming a common effect across all studies, thus yielding a narrower CI than with the random effects model used in other meta-analyses including those presented here.

Furthermore, a meta-analysis is inherently prone to the same biases that affect primary studies. By combining the results of several studies, precision

is increased but bias in the primary data is unaffected (unless biases in opposite directions in the various studies cancel each other out). Recall bias is a major concern in case–control studies, while selection bias can affect both case–control and cohort studies. The most extensive evaluation of biases and sources of error was conducted within the Interphone Study, although it is unclear to what extent their results are applicable to other studies with different protocols [Vrijheid et al., 2006, 2009a,b]. In the Interphone Study, lower participation among non-users of cell phones was observed to a larger extent for controls than for cases [Vrijheid et al., 2009b], which results in a downward bias of the risk estimates. According to sensitivity analyses, it appears unlikely that these biases account entirely for the risk estimates below unity in the Interphone Study Group [2010]. However, all risk estimates significantly below unity in the meta-analysis were from the Interphone Study.

Exposure assessment in the case–control studies relies almost entirely on retrospective self-reported exposure so recall bias is a concern. Several studies have compared the amount of cell phone use reported by volunteers with objective data based on either traffic records from network operators or records from a software-modified phone [Vrijheid et al., 2009a]. Most have reported substantial overestimation of call-time, which can bias the results if overestimation differs between cases and controls. In the Interphone Study, self-reported cell phone use was compared with operator-recorded data in a sample of study participants from Australia, Canada and Italy. On average, little differential exposure misclassification between cases and controls was found. However, in the highest category of cumulative number of calls, exposure overestimation was more pronounced in cases than in controls [Vrijheid et al., 2009a]. Furthermore, the ratio of self-reported to recorded phone use increased with increasing time before the interview in cases but not in controls. Such a pattern could explain an increased risk in the most extreme exposure categories for duration of use.

For this reason, we considered only the crude exposure surrogate "regular use" in our meta-analyses. This proxy exposure measure is expected to be less prone to recall bias. Most importantly, as duration between exposure and occurrence of disease is a relevant parameter, we put a particular focus on long-term effects, i.e., cell phone use at least 10 years before tumor diagnosis.

No validation studies have been reported by the Hardell group, which makes it impossible to assess the magnitude and direction of biases that could affect their results, and potentially explains the consistently increased risks reported—all reported risk estimates >1.3 and all statistically significant elevated findings in our meta-analysis were from their studies. All the studies by the Hardell group used a similar protocol and therefore could be consistently affected by bias.

Only a few studies [Dreyer et al., 1999; Auvinen et al., 2002; Schüz et al., 2006] utilized objective exposure data obtained from computerized records of phone operators. They are, however, limited by a lack of depth of information. Further, they included only private subscriptions, while at the time of data collection a substantial proportion of customers had been using phones covered by corporate subscriptions. Also, subscriptions for children are often held by their parents. Thus, subscription data cannot be considered a gold standard for assessing cell phone use. Therefore, misclassification of exposure remains a serious concern. If misclassification is similar in the compared groups (cases and controls, or across exposure levels in a cohort study), it is likely to attenuate any association if one exists.

Besides the lack of an exposure measure allowing quantification of the amount of energy absorbed from the phone, another limitation of epidemiological studies is the insufficient amount of evidence regarding long-term use beyond 10 years. Also, studies on childhood brain tumors are on-going but not yet reported.

Laterality. We considered performing an analysis of the side of the head the phone was used (laterality). This may be relevant as the maximum absorption of RF energy occurs on the side of the head where the cell phone is held. Various studies have reported conflicting results related to laterality. Several showed an increased risk, sometimes with a corresponding risk deficit in the opposite side, although some have reported an increased risk on the contralateral side [Hardell et al., 2003; Christensen et al., 2004; Lönn et al., 2004; Schoemaker et al., 2005; Takebayashi et al., 2006]. However, recall bias is of even greater concern for retrospectively reported side of the head for cell phone use [Schüz, 2009]. The Interphone Study conducted a sub-study of regular users to assess bias in reported laterality in 172 glioma and 160 meningioma cases and 340 controls. Participants were asked at the end of an interview to place the cell phone to their head in the usual fashion. The side where they placed it was compared with their reported preferred side for cell phone use. The concordance was substantially lower for cases (72% for glioma and 66% for meningioma) compared to controls (95%), with cases over-reporting use on the

side of the head where the tumor occurred [Interphone Study Group, 2010]. This recall bias creates the false appearance of an increased risk on the ipsilateral side (OR $>$ 1) and a protective effect on the contralateral side (OR $<$ 1), as observed in some of the studies cited above. This pattern suggests recall bias for reporting the preferred side of the head for mobile phone use.

Recall bias in studies cannot be removed in a meta-analysis and it renders the combined estimate unreliable; therefore, we did not conduct a laterality analysis. In a study on brain tumors in children and adolescents, published after our cut-off date, Aydin et al. [2011] conducted laterality analyses and did not find evidence for a laterality effect since ORs were higher for contralateral than ipsilateral use.

In Vivo Studies

Few cancer-related in vivo studies were reported before 1992 [WHO, 1993]. While a number of in vivo studies had been conducted by 1999, the Royal Society of Canada concluded that they did not produce any consistent relationship between RF exposure and cancer in animals [Royal Society of Canada, 1999]. Their conclusion was consistent with that of the WHO/ICNIRP international seminar the previous year: ''Although weak evidence exists, it fails to support an effect of RF exposure on mutagenesis or cancer initiation. There is scant evidence for a co-carcinogenic effect or an effect on tumor promotion or progression'' [Repacholi, 1998]. In 2003, the AGNIR published its detailed review on possible health effects from RF fields and concluded from the in vivo studies that: ''The evidence provided by the more recent studies ... clearly indicates that RF radiation does not increase the incidence of either spontaneous or induced tumors (for both mobile phone and other frequencies).'' In sum, the in vivo studies reviewed by the AGNIR [2003] did not support a relationship between exposure to RF fields and cancer.

As addressed above, while some genotoxicity studies reported some positive effects, they were the ones accorded the least weight in their quality assessment because they were either not performed in a fully blinded fashion, the dosimetry was incomplete, or they had other serious limitations. The two studies that did not have such limitations and were therefore accorded the most weight from our quality evaluation did not report any positive effects. Our results from evaluating the genotoxicity studies since 1 January 2000 do not show any consistent genotoxic effects from RF exposure. This conclusion is supported by several recent detailed reviews [SCENIHR, 2009; SSM, 2009; EFHRAN, 2010; Verschaeve et al., 2010].

Most of the tumor and tumor promotion studies were of high quality and received almost full additional weight in our quality assessment. Overall, the results of our pooled analysis of the in vivo data showed no relationship between RF exposure and either the incidence of brain tumors or their promotion in animals induced with chemical carcinogens. There was a statistically significant protective effect from RF exposures below 2 W/kg on tumor promotion (Fig. 5b). However, this result just reached significance and appears to be a spurious finding likely caused by an over-representation of tumors in the sham group because there was no effect from exposures above 2 W/kg.

Some of the in vivo studies included pituitary tumors and while they are not brain tumors and were not identified for examination in this review, they are tumors in the head so we examined the limited data available for any insights they might provide. Unlike humans, rats and mice have a high incidence of spontaneous pituitary tumors, which makes analysis more difficult. Our pooled analyses identified a statistically significant increase in pituitary tumors at SARs below 2.0 W/kg but not $\geq$2.0 W/kg, and in females but not males, as shown in Figure 6. The only study that investigated effects on tumor promotion in female rats did not find any statistically significant excess with exposures below 2.0 W/kg. The increase in pituitary tumor incidence occurred in only one rat and one mouse study. Subsequent investigation revealed that these results were almost certainly due to the abnormally high and variable incidence rates of pituitary tumors that typically occur in these animals (up to 54%), especially females [Charles River, 1989; La Regina et al., 2003], which could result in the underrepresentation of tumors in the sham group. Overall, our results from evaluating brain tumor and brain tumor promotion studies do not show a consistent relationship between RF exposure and the incidence of brain cancers or other head tumors, or their promotion in animals induced with chemical carcinogens. Our results are consistent with the results of previous reviews [HCN, 2008; SCENIHR, 2009; SSM, 2009; ICNIRP, 2009a; EFHRAN, 2010; Verschaeve et al., 2010; Juutilainen et al., 2011].

Overall Assessment

Hill [1965] identified key criteria or factors for assessing whether a causal relationship has or has not been established between an exposure and a disease [Schüz, 2008]. Hill explained most of his considerations using examples from single studies rather than

from collections of studies. Accordingly, we elaborated the Hill approach (as set out below) to our assessment of a collection of studies (slightly modifying the names of a couple of the criteria to make our elaboration clear and including his coherence factor in our elaboration of his consistency factor), and considered them in making our overall assessment about a causal relationship.

Strength. Neither our meta-analysis of the epidemiology study results nor our pooled analysis of the in vivo studies showed any statistically significant increased risk for the brain cancer glioma or the other three head tumors from wireless phone use. However, data on long-term use of cell phones (>10 years) are considered insufficient to make any determinations.

Consistency. The results of the epidemiology studies are inconsistent with each other—particularly for the Interphone and Hardell et al. studies, which may reflect differences in study design and potential biases. The results of the in vivo studies are generally consistent with each other and show no overall relationship between exposure to RF fields and the brain cancer glioma or the other three head tumors.

Dose–response relationship. The epidemiology studies show no clear increase in risk in relation to time since first use. That does not, however, exclude an association with long-term exposure (>10 years) because data is insufficient for that duration of use. No meaningful equivalent for a physical or biological concept of dose can be constructed based on the epidemiological studies included in the meta-analysis. The in vivo studies, where excellent exposure indicators are used, show no statistically significant dose–response relationship.

Specificity. We considered a limited range of tumor types so specificity does not provide a useful indicator of a causal relationship between wireless phone use and the brain cancer glioma or the other three head tumors.

Temporality. The epidemiology studies only considered wireless phone use occurring before the appearance of tumors. The in vivo studies do not show a statistically significant increase in the onset of either the brain cancer glioma or the other three head tumors after exposure to RF fields.

Biological plausibility. Despite extensive research over many years, no interaction mechanism has been established whereby exposure to low level RF fields (below the level where heating is the dominant mechanism) from wireless phones could cause or contribute to disease in living organisms. Overall, the lack of an appropriate mechanism and the results of the in vitro and in vivo studies do not provide any support for causality.

Experiment. As addressed above, neither the in vitro nor in vivo studies provide any overall support for a causal relationship between wireless phone use and the brain cancer glioma or the other three head tumors.

Analogy. There are no known analogous exposures that cause brain cancers or the other three tumors originating in the head. Both RF and extremely low frequency (ELF) fields are non-ionizing electromagnetic fields but ELF fields have not been shown to cause brain cancers or other tumors originating in the head. Because ionizing radiation is commonly equated with RF radiation, we note that ionizing radiation is not analogous to RF field exposure. That is because, unlike ionizing radiation, RF fields from wireless phones and other sources of exposure (e.g., radio and TV signals) do not have the capability to deliver enough energy to break DNA bonds or even the weakest chemical bonds within the molecules that make up the cells of the body.

CONCLUSION

We conducted a systematic review based on a pre-agreed methodology to assess whether a causal relationship has been established between the use of wireless phones and the brain cancer glioma and three other tumors originating in the areas of the head that most absorb the RF energy emitted by wireless phones. The results of the principal epidemiology studies, the Interphone Study and the studies by Hardell et al. are inconsistent. There are also insufficient data to make any determinations about risks for children and long-term use (≥10 years) by adults.

Both the in vivo and epidemiology studies that were accorded the most additional weight based on the quality assessment criteria by our independent evaluations found no consistent relationship between the brain cancer glioma or the other three head tumors and wireless phone use.

We also conducted a pooled analysis of all the in vivo tumor and tumor promotion studies and meta-analyses of all the epidemiology case–control and cohort studies (not according to any additional weight

to any study based on the quality assessment criteria). Overall, those analyses were also consistent in finding no statistically significant relationship between brain cancers or head tumors and wireless phone use.

In summary, none of the Hill criteria support a causal relationship between wireless phone use and brain cancers or other tumors in the areas of the head that most absorb the RF energy from wireless phones. Accordingly, the conclusions and recommendations of WHO [2011] provide adequate protective measures, and the ICNIRP guidelines limiting exposure to RF fields [ICNIRP, 1998, 2009b] continue to provide a sound, science-based standard for public health policy regarding the use of wireless phones by adults.

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