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ORIGINAL REPORT

Mobile Phone Use and Risk of Tumors: A Meta-Analysis

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Case-control studies have reported inconsistent findings regarding the association between mobile phone use and tumor risk. We investigated these associations using a meta-analysis.

Methods
We searched MEDLINE (PubMed), EMBASE, and the Cochrane Library in August 2008. Two evaluators independently reviewed and selected articles based on predetermined selection criteria.

Results
Of 465 articles meeting our initial criteria, 23 case-control studies, which involved 37,916 participants (12,344 patient cases and 25,572 controls), were included in the final analyses. Compared with never or rarely having used a mobile phone, the odds ratio for overall use was 0.98 for malignant and benign tumors (95% CI, 0.89 to 1.07) in a random-effects meta-analysis of all 23 studies. However, a significant positive association (harmful effect) was observed in a random-effects meta-analysis of eight studies using blinding, whereas a significant negative association (protective effect) was observed in a fixed-effects meta-analysis of 15 studies not using blinding. Mobile phone use of 10 years or longer was associated with a risk of tumors in 13 studies reporting this association (odds ratio = 1.18; 95% CI, 1.04 to 1.34). Further, these findings were also observed in the subgroup analyses by methodologic quality of study. Blinding and methodologic quality of study were strongly associated with the research group.

Conclusion
The current study found that there is possible evidence linking mobile phone use to an increased risk of tumors from a meta-analysis of low-biased case-control studies. Prospective cohort studies providing a higher level of evidence are needed.

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INTRODUCTION

The worldwide use of mobile phones has rapidly increased over the past decade. According to data from the International Telecommunication Union, the number of worldwide mobile cellular subscribers was 12.2 per 100 inhabitants in 2000 but grew to 49.5 per 100 inhabitants in 2007.[1] With the increasing use of mobile phones (ie, cellular phones and cordless phones), concern has been raised about the possible carcinogenic effects as a result of exposure to radiofrequency electromagnetic fields (EMFs) emitted from cellular phones ranging from 800 to 2,000 MHz,[2,3] which fall in the microwave spectrum. Although some in vitro studies reported the potential effects of high-frequency EMFs on cell proliferation and activation of oncogene transcription,[4-6] those biologic effects and mechanisms in developing neoplasm remain unclear. Over the past decade, epidemiologic studies (mainly case-control) also have reported the relationships between the use of mobile phones and malignant or benign tumors such as brain tumors, head and neck tumors, non-Hodgkin's lymphoma, and testicular cancer.[7-28]

Some case-control studies have suggested a positive (ie, harmful) association between the use of mobile phones and the risk of tumors,[7,10-12,15-18,23,25,27] whereas other case-control studies have reported no significant association.[8,9,11,13,14,19-22,24,26,28] Also, the only retrospective cohort study reported no evidence for the association among either short-term or long-term users.[29,30]

Regarding the conflicting scientific evidence, three meta-analyses reported no association or a slight increased risk.[31-33] However, these meta-analyses involved only brain tumors. In the current study, we investigated the associations between the use of mobile phones and the risk of tumors, including both malignant and benign conditions, via a meta-analysis of case-control studies.

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METHODS

Literature Search

We searched MEDLINE (PubMed; 1968 to August 2008), EMBASE (1977 to August 2008), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (1953 to August 2008) using common keywords related to mobile phones and tumor or cancer. The keywords were as follows: "mobile phones," "cellular phones," or "cordless phones" and "tumors" or "cancer." We also reviewed the bibliographies of relevant articles to locate additional publications. The language of publication was not restricted.

Selection Criteria

We included epidemiologic studies that met all of the following criteria: case-control study (to date, no randomized controlled trials and only one retrospective cohort study published in four different articles have been reported; therefore, we included only case-control studies in this study); investigated the associations between the use of mobile phones, cellular phones, or cordless phones and malignant or benign tumors; reported outcome measures with adjusted odds ratios and 95% CIs, crude odds ratios and 95% CIs, or values in cells of a 2×2 table (from which odds ratios could be calculated). If data were duplicated or shared in more than one study, the first published or more comprehensive study was included in the analysis.

Selection of Relevant Studies

Two of the authors (S.-K.M. and W.J.) independently evaluated eligibility of all studies retrieved from the databases based on the predetermined selection criteria. Disagreements between evaluators were resolved by discussion or in consultation with a third author (D.D.M.).

Assessment of Methodologic Quality

We assessed the methodologic quality of included studies based on the Newcastle-Ottawa Scale (NOS) for quality of case-control studies in meta-analyses.[34] A star system of the NOS (range, 0 to 9 stars) has been developed for the assessment. In the current study, we considered a study awarded 7 or more stars as a high-quality study because standard criteria have not been established. The mean value for the 23 studies assessed was 6.3 stars.

Main and Subgroup Analyses

We investigated the association between the use of mobile phones (use *v* never or rarely use, if possible) and the overall risk of all tumors by using adjusted data as a main analysis. We also performed subgroup analyses by whether the status of patient cases and controls was blinded at interview (blinded or not blinded/no description), research group (adjusted or crude data), methodologic quality (high or low quality), type of tumor, malignancy of tumor (malignant or benign), type of mobile phone (analog or digital), laterality of tumor (ipsilateral or contralateral), and type of case-control study (hospital based or population based). Furthermore, we investigated the association between long-term mobile phone use ($\geq$ 10 years) and the risk of tumors, including subgroup analyses by the factors listed earlier.

Statistical Analyses

To compute a pooled odds ratio with 95% CI, we used the adjusted odds ratio and 95% CIs reported in each article whenever possible. We examined heterogeneity in results across studies using Higgins I^2, which measures the percentage of total variation across studies.[35] We considered an I^2 value of greater than 50% as indicative of substantial heterogeneity.

When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using the Woolf's (inverse variance) method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian and Laird method.[36]

We evaluated publication bias of the studies included in the final analysis using Begg's funnel plot and Egger's test. If publication bias exists, Begg's funnel plot is asymmetric or the *P* value is less than .05 by Egger's test. Also, a meta-regression analysis was performed to assess the effect of subgroups and study characteristics, such as research group, year of publication, type of tumor, and study design, on the study results. Blinding and methodologic quality were excluded because of multicollinearity with research group. We used Stata SE version 10.0 software package (StataCorp, College Station, TX) for statistical analysis.

RESULTS

Identification of Relevant Studies

Figure 1 shows a flow diagram of how we identified relevant studies. A total of 465 articles were identified by searching three databases and hand-searching relevant bibliographies. We excluded 135 duplicate articles and an additional 287 articles that did not satisfy the selection criteria. After reviewing the full texts of the remaining 43 articles, 21 articles[37-57] were excluded because of several reasons, as shown in Figure 1. The remaining 23 case-control studies from 22 articles[7-28] were included in the final analysis (the study by Auvinen et al[11] was considered as two individual case-control studies).

Characteristics of Studies Included in the Final Analysis

In the 23 case-control studies, we identified a total of 37,916 participants (12,344 patient cases and 25,572 controls). For studies reporting age and sex, the mean age was 52.6 years (range, 18 to 90 years), and 51% of the participants were women.

Appendix Table A1 (online only) shows the general characteristics of the 23 case-control studies (22 articles) included in the final analysis. The percentage of study participants who reported having used a mobile phone was 43.5% among the patient cases and 45.2% among the controls (data not shown in Appendix Table A1).

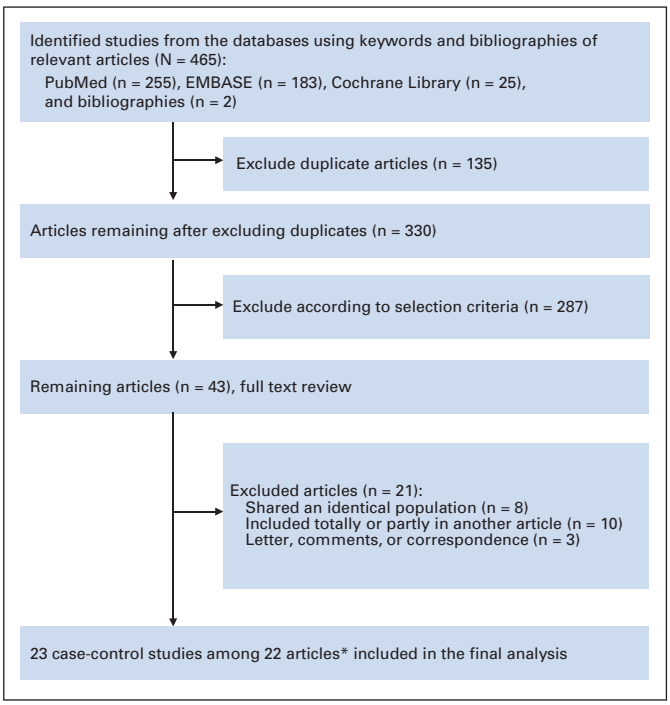


Fig 1. Flow diagram for identification of relevant case-control studies. (*) One article (Auvinen et al[11]) was divided into two studies because it involved two different types of tumors.

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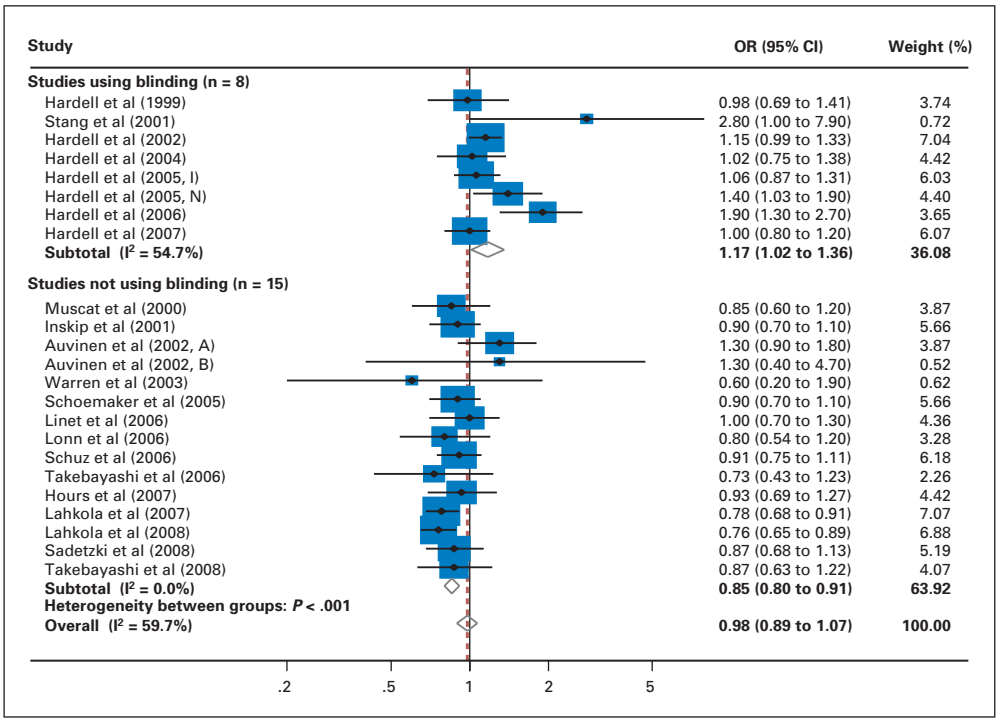


Fig 2. Overall use of mobile phones and the risk of tumors in a random-effects model meta-analysis of case-control studies[7-28] by the use of blinding at an interview for exposure measurements (n = 23). OR, odds ratio; Hardell et al (2005, I) indicates reference 15; Hardell et al (2005, N) indicates reference 16.

Overall Use of Mobile Phones and Risk of Tumors

As shown in Figure 2, the overall use of mobile phones (use *v* never or rarely use) was not significantly associated with the risk of tumors in a random-effects model meta-analysis of all 23 case-control studies (odds ratio = 0.98; 95% CI, 0.89 to 1.07). However, a significant positive association (ie, harmful effect) was observed in eight studies [7,12,14-16,18,23] and one study by another group[10]) using blinding (odds ratio = 1.17; 95% CI, 1.02 to 1.36), whereas a significant negative association (ie, protective effect) was observed in 15 studies (nine INTERPHONE-related studies[17,20-22,24-28] and six studies by other groups[8,9,11,13,19]) not using blinding (odds ratio = 0.85; 95% CI, 0.80 to 0.91). No publication bias was observed in the selected studies (Begg's funnel plot was symmetric; Egger's test, *P* for bias = .21; Fig 3).

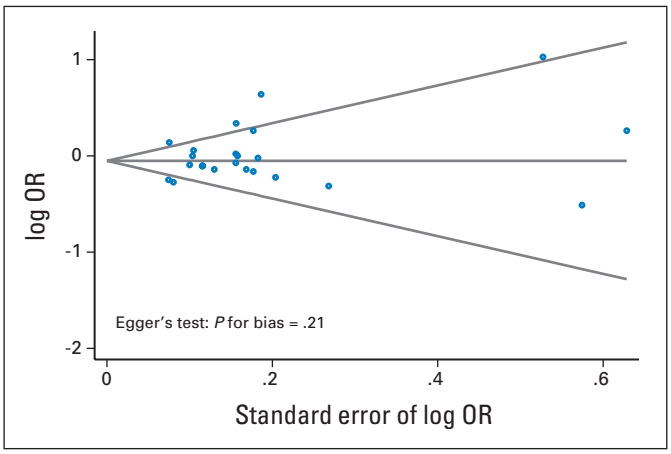


Fig 3. Begg's funnel plots and Egger's test for identifying publication bias (*P* = .21) in a meta-analysis of case-control studies[7-28] (n = 23). OR, odds ratio.

Table 1 shows the methodologic quality of studies included in the final analysis. The range of quality scores was 5 to 8; the average score was 6.3. The high-quality studies (score of ≥ 7) included all seven of the studies by Hardell et al, one INTERPHONE-related study, and two studies by other groups. The low-quality studies (score of < 7) included eight INTERPHONE-related studies and six studies by other groups.

A subgroup meta-analysis by research group showed a significant positive association for the seven studies reported by Hardell et al but a significant negative association for nine INTERPHONE-related studies (Table 2). When using crude data, a significant association was not found in any of the 23 studies or in subgroup analyses by research group.

Subgroup meta-analyses by methodologic quality of study revealed a significant positive association in the high-quality studies (odds ratio = 1.09; 95% CI, 1.01 to 1.18), whereas a negative association was observed in the low-quality studies. In subgroup meta-analyses by malignancy of tumor, no significant association was observed for malignant tumors. However, a significant negative association was observed for benign tumors. Neither the use of analog phones nor the use of digital phones was associated with the risk of tumors. The ipsilateral use of mobile phones (ie, on the same side of the head where the tumor exists) was marginally associated with the risk of tumors in the 12 studies reporting tumor laterality.

Mobile Phone Use of 10 Years or Longer and Risk of Tumors

Among the 23 studies, there was a significant positive association between mobile phone use of 10 years or longer and the risk of tumors in a fixed-effects meta-analysis of 13 studies reporting this association (odds ratio = 1.18; 95% CI, 1.04 to 1.34; Fig 4; Appendix Table A2, online only). As for blinding, a fixed-effects

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Table 1. Methodologic Quality of Studies Included in the Final Analysis Based on the Newcastle-Ottawa Scale for Assessing the Quality of Case-Control Studies

	Selection (score)				Comparability (score)	Exposure (score)			
Study	Adequate Definition of Patient Cases	Representativeness of Patient Cases	Selection of Controls	Definition of Controls	Control for Important Factor or Additional Factor	Ascertainment of Exposure (blinding)	Same Method of Ascertainment for Participants	Nonresponse Rate*	Total Score†
Hardell et al[7]	1	1	1	0	1	1	1	1	7
Muscat et al[8]	1	0	0	1	2	0	1	0	5
Inskip et al[9]	1	0	0	1	2	0	1	0	5
Stang et al[10] (hospital based)	1	1	0	0	2	1	1	0	6
Stang et al[10] (population based)	1	1	1	0	2	1	1	0	7
Auvinen et al[11] (1)	1	1	1	1	1	0	1	0	6
Auvinen et al[11] (2)	1	1	1	1	1	0	1	0	6
Hardell et al[12]	1	1	1	0	2	1	1	0	7
Warren et al[13]	1	1	0	1	1	0	1	0	5
Hardell et al[14]	1	1	1	0	1	1	1	1	7
Hardell et al[15]	1	1	1	0	2	1	1	1	8
Hardell et al[16]	1	1	1	0	2	1	1	0	7
Schoemaker et al[17]	1	1	1	1	2	0	1	0	7
Hardell et al[18]	1	1	1	0	2	1	1	1	8
Linet et al[19]	1	1	1	1	2	0	1	0	7
Lönn et al[20]	1	1	1	0	2	0	1	0	6
Schüz et al[21]	1	1	1	0	2	0	1	0	6
Takebayashi et al[22]	1	1	1	0	2	0	1	0	6
Hardell et al[23]	1	1	1	0	2	1	1	1	8
Hours et al[24]	1	1	1	0	2	0	1	0	6
Lahkola et al[25]	1	1	1	0	2	0	1	0	6
Lahkola et al[26]	1	1	1	0	1	0	1	0	5
Sadetzki et al[27]	1	1	1	0	1	0	1	0	5
Takebayashi et al[28]	1	1	1	0	2	0	1	0	6

*When there was no significant difference in the response rate between both groups by using a χ^2 test ($P > .05$), one point was awarded.
†Total score could range from 0 to 9 points.

meta-analysis of the seven blinded studies showed a positive association, whereas a fixed-effects meta-analysis of the six unblinded studies showed no significant association.

In the subgroup meta-analyses by methodologic quality, a significant positive association was found in the eight high-quality studies but not in the seven low-quality studies. With regard to tumor malignancy, mobile phone use of 10 years or longer was significantly positively associated with the risk of benign tumors but not with the risk of malignant tumors.

The use of analog phones for 10 years or longer was positively associated with the risk of tumors. However, further subgroup analyses by research group showed a significant association only in the studies by Hardell et al.[7,12,14-16,18,23] Regarding the laterality of tumors and mobile phone use of 10 years or longer, a significantly increased odds ratio was identified for ipsilateral use but not for contralateral use.

Overall Mobile Phone Use and the Risk of Brain Tumors

As shown in Appendix Table A3 (online only), no significant association was observed in a meta-analysis of 15 studies involving brain tumors. For meningiomas, a preventive effect was observed, and this effect was largely a result of a decreased odds ratio in INTERPHONE-related studies.

A significant negative association was found in a meta-analysis of studies involving benign brain tumors, and this was largely a result of a decreased odds ratio in the INTERPHONE-related studies. No association between mobile phone use and tumor risk was observed in both analog phone users and digital phone users. With regard to research group, blinding, and methodologic quality, similar findings to those of the subgroup analyses were observed (ie, a significant association in the studies by Hardell et al, a negative association in INTERPHONE-related studies, and no association in the studies by other groups).

Overall Mobile Phone Use and the Risk of Other Tumors

Appendix Table A4 (online only) shows the findings of the subgroup analyses of studies involving tumors other than brain tumors. Unlike brain tumors, all of the subgroup meta-analyses based on various factors showed no significant associations between overall mobile phone use and the risk of other tumors.

Meta-Regression Analysis

A meta-regression analysis showed that only the variable indicating research group was significantly associated with the study results ($P = .001$). No significant association was observed for year of publication, type of tumor, or study design.

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Table 2. Mobile Phone Use (*v* never or rarely use) and the Risk of Tumors in Subgroup Meta-Analyses

Factor	No. of Studies	Summary OR	95% CI of OR	Heterogeneity, I^2 (%)	Model Used
All	23	0.98	0.89 to 1.07	59.7	Random effects
Research group					
Hardell et al*	7	1.15	1.01 to 1.32	52.1	Random effects
INTERPHONE†	9	0.83	0.77 to 0.89	0	Fixed effects
Other groups	7	0.99	0.86 to 1.14	30.6	Fixed effects
Research group (crude data)	23	0.97	0.87 to 1.08	73.6	Random effects
Hardell et al	7	1.14	0.96 to 1.35	71.0	Random effects
INTERPHONE	9	0.88	0.75 to 1.03	79.8	Random effects
Other groups	7	0.90	0.79 to 1.03	22.6	Fixed effects
Methodologic quality					
High (low bias: ≥ 7 points)*	10	1.09	1.01 to 1.18	46.3	Fixed effects
Hardell et al*	7	1.15	1.00 to 1.32	52.1	Random effects
INTERPHONE	1	0.90	0.70 to 1.10	NA	NA
Other group	2	1.02	0.75 to 1.38	0	Fixed effects
Low (high bias: < 7 points)†	14	0.85	0.79 to 0.91	5.7	Fixed effects
INTERPHONE†	8	0.82	0.76 to 0.88	0	Fixed effects
Other groups	6	0.97	0.83 to 1.14	24.2	Fixed effects
Malignancy of tumor					
Malignant	15	1.00	0.89 to 1.13	52.0	Random effects
Hardell et al	6	1.11	0.96 to 1.29	50.5	Random effects
INTERPHONE†	4	0.78	0.67 to 0.91	0	Fixed effects
Other groups	5	0.97	0.80 to 1.18	19.6	Fixed effects
Benign	15	0.87	0.80 to 0.95	20.7	Fixed effects
Hardell et al	4	1.17	0.97 to 1.42	3.8	Fixed effects
INTERPHONE†	8	0.81	0.73 to 0.90	0	Fixed effects
Other groups	3	0.82	0.61 to 1.11	0	Fixed effects
Type of mobile phone					
Analog	12	0.96	0.87 to 1.07	49.9	Fixed effects
Hardell et al	7	1.04	0.89 to 1.22	34.5	Fixed effects
INTERPHONE†	3	0.84	0.72 to 0.96	0	Fixed effects
Other groups*	2	1.55	1.08 to 2.2	0	Fixed effects
Digital	14	0.95	0.84 to 1.08	55.8	Random effects
Hardell et al	7	1.10	0.97 to 1.24	12.7	Fixed effects
INTERPHONE†	5	0.78	0.71 to 0.85	0	Fixed effects
Other groups	2	0.93	0.55 to 1.59	0	Fixed effects
Laterality of tumor					
Ipsilateral	12	1.22	0.99 to 1.51	85.9	Random effects
Hardell et al*	4	1.80	1.24 to 2.62	84.9	Random effects
INTERPHONE	8	1.00	0.91 to 1.10	37.0	Fixed effects
Contralateral	11	0.94	0.77 to 1.15	82.3	Random effects
Hardell et al	3	1.31	0.74 to 2.31	93.0	Random effects
INTERPHONE†	8	0.81	0.74 to 0.89	48.2	Fixed effects
Type of case-control study					
Hospital based (all other groups)	4	0.89	0.74 to 1.07	0.0	Fixed effects
Population based	20	0.99	0.89 to 1.09	61.8	Random effects
Hardell et al*	7	1.15	1.01 to 1.32	52.1	Random effects
INTERPHONE†	9	0.83	0.77 to 0.89	0	Fixed effects
Other groups	4	1.14	0.91 to 1.43	0	Fixed effects

Abbreviations: OR, odds ratio; NA, not applicable.
*Statistically significant positive association.
†Statistically significant negative association.

DISCUSSION

We found that the use of mobile phones was associated with a mild increased risk of tumors, when compared with never or rare use of mobile phones, in the meta-analyses of case-control studies that used blinding or had a high methodologic quality, whereas no significant association was observed in a meta-analysis of all included studies. Also, mobile phone use of 10 years or longer increased the risk of tumors in a meta-analysis of all the studies reporting this association. Furthermore, in the subgroup meta-analyses by research group, a distinct pattern of the findings was observed as follows: a positive association (ie, harmful effect) in the Hardell et al studies, a negative association (ie, protective effect) in the INTERPHONE-related studies, and no association in other research groups' studies.

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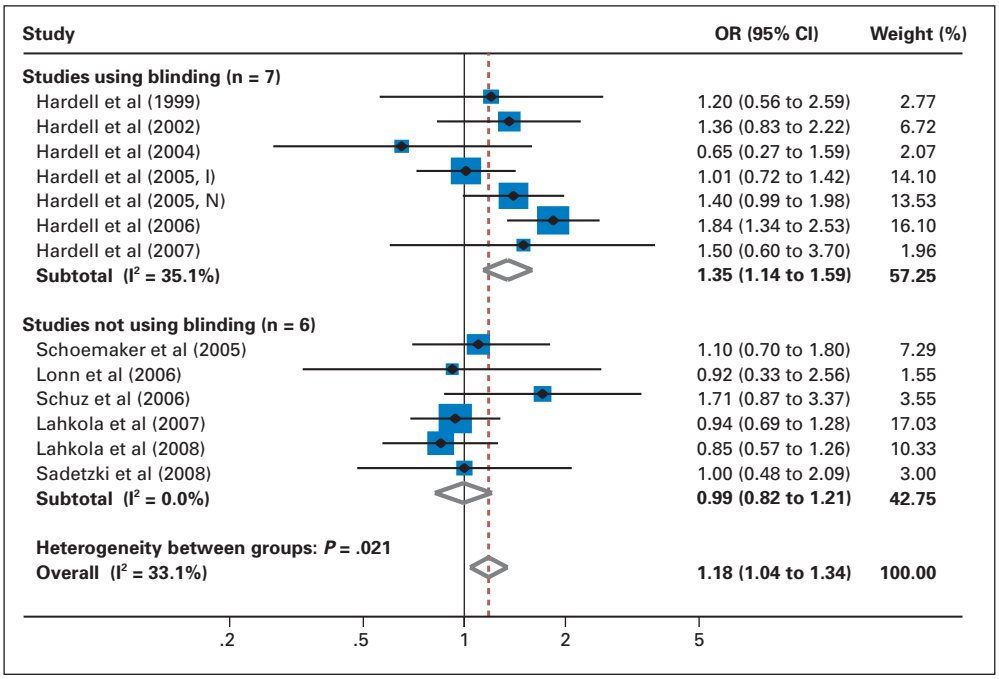


Fig 4. Mobile phone use of 10 years or longer and the risk of tumors in a fixed-effects model meta-analysis of case-control studies[7,12,14-18,20,21,23,25-27] by the use of blinding at an interview for exposure measurements (n = 13). OR, odds ratio; Hardell et al (2005, l) indicates reference 15; Hardell et al (2005, N) indicates reference 16.

These findings were strongly related to the fact that all of the studies by Hardell et al used blinding to the status of patient cases or controls at the interview and were categorized as having a high methodologic quality when assessed based on the NOS, whereas most of the INTERPHONE-related studies and studies by other groups did not use blinding and were thus categorized as having low methodologic quality. The blinding item is one of the eight items in the NOS. Nevertheless, we also used the blinding item independently as well as the NOS as a kind of indicator of the quality assessment for the studies because the NOS has not been fully validated and the blinding item was considered an important factor that affects the findings of each study.

Also, similar findings concerning the research group were observed in subgroup analyses by malignancy of tumor, type of laterality, type of case-control study, and type of tumor. Regarding type of brain tumor, a negative association was observed for meningiomas but not for gliomas and acoustic neuromas, and this negative association was largely a result of a decreased odds ratio in INTERPHONE-related studies.

Besides blinding and methodologic quality of studies, we should consider two potential biases regarding the differences we found by research groups—recall bias and selection bias, both of which have been described in detail elsewhere.[57] In a validation study of short-term recall for mobile phone use, Vrijheid et al[58] reported that substantial random errors could reduce the power of the INTERPHONE study to detect an increased risk of brain and parotid gland tumors. Furthermore, they found that random errors and selection bias could lead to finding a decreased risk of brain cancer through Monte-Carlo simulation using the INTERPHONE data.[57] These findings may explain why a significant decreased risk for tumor was observed among mobile phone users in the INTERPHONE-related studies.

To reduce recall and selection biases, a prospective cohort study is needed. A large nationwide Danish retrospective cohort study,[29,30,59,60] which is the only cohort study published so far, reported that there was no evidence for an association between cellular telephone use and tumor risk based on standardized incidence ratios for cancer that were calculated from the cancer prevalence among cellular telephone subscribers compared with the rates expected among the general population. However, this study relied on phone subscription information and did not evaluate actual exposure to mobile phones.

If we do not consider subgroup meta-analyses by research group or blinding/methodologic quality of studies, our overall results are similar to the previous three meta-analyses[31-33] evaluating mobile phone use and the risk of brain tumor, which reported no overall increased risk of brain tumors among cellular phone users and slightly increased risk of brain tumors for use of 10 years or longer.

Unlike the previous meta-analyses, however, we found significant associations between mobile phone use and risk of tumors in low-biased, case-control studies, which were mostly studies by Hardell et al, when performing subgroup analyses by use of blinding or the methodologic quality of studies. That is, the methodologic quality of study and blinding were strongly related to both the research group and the studies' findings. In particular, among the items of the NOS for assessing the quality of case-control studies, blinding and response rates between patient cases and controls were the major contributing factors to differentiate a high-quality study from a low-quality study. All seven studies by Hardell et al[7,12,14-16,18,23] used blinding, and five of them showed no significant difference in response rates between patient cases and controls, whereas INTERPHONE-related studies and the other studies, except for the study by Stang et al,[10] did not use blinding and showed a significant difference in response rates.

We feel the need to mention the funding sources for each research group because it is possible that these may have influenced the respective study designs and results. According to the acknowledgments that appeared in the publications, the Hardell et al group was supported by grants from the Swedish Work Environment Fund, Orebro Cancer Fund, Orebro University Hospital Cancer Fund, and

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so on. Most of the INTERPHONE-related studies were mainly supported by the Quality of Life and Management of Living Resources program of the European Union and the International Union Against Cancer; the International Union Against Cancer received funds for those studies from the Mobile Manufacturers Forum and the Global System for Mobile Communication Association.

The association between mobile phone use and tumor risk also remains unresolved in experimental studies using in vivo animal models or in vitro cancer cell lines. Although it has been established that low-frequency EMF (microwave) exposure induces biologic change of cytoplasmic membranes, nuclear levels, and specific gene levels,[6,61-63] the effect of high-frequency EMF exposure on health is still controversial.[64-70]

Our study has several limitations. First, it does not provide the highest level of evidence because only case-control studies were involved. As mentioned previously, recall bias and selection bias might reduce the quality of mobile phone exposure data and, therefore, cause a spurious association. Second, we did not explore potential confounding factors in the studies by Hardell et al[7,12,14-16,18,23] that reported positive results not found by other study groups. Those issues need to be explored in future studies.

In sum, in our meta-analyses of case-control studies, we found evidence linking mobile phone use to an increased risk of tumors, especially among users of 10 or more years. Furthermore, we found a large discrepancy in the association between mobile phone use and tumor risk by research group, which is confounded with the methodologic quality of the research. Our findings should be confirmed in prospective cohort studies to provide a higher level of evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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