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Wireless Phone Use and Risk of Adult Glioma: Evidence from a Meta-Analysis

Peng Wang[1], Chongxian Hou[2], Yanwen Li[1], Dong Zhou[1]

■ BACKGROUND: **Wireless phone use has been increasing rapidly and is associated with the risk of glioma. Many studies have been conducted on this association without reaching agreement. The aim of this meta-analysis was to determine the possible association between wireless phone use and risk of adult glioma.**

■ METHODS: **Eligible studies were identified by searching PubMed and Embase up to July 2017. Random-effects or fixed-effects model was used to combine the results depending on the heterogeneity of the analysis. Publication bias was evaluated using Begg's funnel plot and Egger's regression asymmetry test. Subgroup analysis was performed to evaluate possible influence of these variables.**

■ RESULTS: **Ten studies on the association of wireless phone use and risk of glioma were included. The combined odds ratio of adult gliomas associated with ever use of wireless phones was 1.03 (95% confidence interval [CI], 0.92–1.16) with high heterogeneity ($I^2 = 54.2\%$, $P = 0.013$). In subgroup analyses, no significant association was found between tumor location in the temporal lobe and adult glioma risk, with odds ratios of 1.26 (95% CI, 0.87–1.84), 0.93 (95% CI, 0.69–1.24), and 1.61 (95% CI, 0.78–3.33). A significant association with risk of glioma was found in long-term users (≥10 years) with odds ratio of 1.33 (95% CI, 1.05–1.67).**

■ CONCLUSIONS: **Ever use of wireless phones was not significantly associated with risk of adult glioma, but there could be increased risk in long-term users.**

INTRODUCTION

The use of wireless phones has rapidly increased over the past 30 years. The exposure of wireless phone users to radiofrequency (RF) electromagnetic fields (EMFs) has raised widespread concern owing to potential negative effects on health. The International Agency for Research on Cancer classified RF EMFs associated with wireless phone use as possibly carcinogenic to humans (group 2B).[1] However, Morgan et al.[2] suggested that mobile phone radiation that causes brain tumors in humans should be classified as a probable human carcinogen (group 2A). In contrast, some studies indicated that RF could decrease the risk for brain tumor because of the introduction of adaptive response: cells that are exposed to a very low, nontoxic dose of a mutagen become resistant to the damage induced by subsequent exposure to high doses.[3,4]

Many studies have been conducted to explore the potential effects of exposure to RF, extremely low frequency, and EMF emitted from mobile phones leading to brain tumors among adults. However, the results are inconsistent.[5-14] In recent years, several meta-analyses[15-20] have been conducted to explore the relationship between wireless phone use and adult glioma risk. However, all these analyses derived their evidence from case-control studies. Based on the recent meta-analyses, 2 more cohort studies,[13,14] and 1 more case-control study,[11] we conducted our own meta-analysis. Furthermore, we analyzed the risk of glioma in the temporal lobe of adults. We conducted this meta-analysis to confirm the relationship between adult glioma risk and wireless phone use. This study was registered in PROSPERO (No. 42016041892).

MATERIALS AND METHODS

Search Strategy

A comprehensive search in PubMed and EMBASE was conducted. The following search terms were used: (cell phone) OR (mobile

Key words
- Cell phone
- Glioma
- Meta-analysis
- Mobile phone
- Wireless phone use

Abbreviations and Acronyms
CI: Confidence interval
EMF: Electromagnetic field
OR: Odds ratio
RF: Radiofrequency

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phone) OR (cellular phone) OR (wireless phone) OR (cordless phone) AND (glioma OR glioblastoma OR brain tumor OR brain cancer OR brain neoplasm). Reference lists of relevant articles were checked to identify additional studies. Two investigators (P.W. and C.H.) retrieved the literature and searched the articles independently. Disagreements were resolved by consensus or through discussion with a third reviewer (D.Z.).

Inclusion Criteria

All relevant studies on the association between wireless cell phone use and glioma risk were included. The inclusion criteria were as follows: 1) case-control or cohort design; 2) exposure of interest was wireless phone use; 3) outcome of interest was primary glioma in individuals >16 years of age; 4) odds ratio (OR) or relative risk with 95% confidence intervals (CIs) was available. Reviews and publications with duplicate data were excluded.

Data Extraction

The following information was extracted from the included studies: name of first author, year of publication, study design, study region, study period, sex and age range of study participants, time since the first use of wireless phone, tumor location, side of use (ipsilateral/contralateral), cumulative hours of use, number of cases, and OR or relative risk with corresponding 95% CIs. Data were extracted independently by 2 investigators (P.W. and C.H.), and disagreements were resolved by consensus or through discussion with a third reviewer (D.Z.).

Statistical Analysis

Because the incidence of glioma was low, the relative risk value was mathematically similar to the OR value in the studies. Thus, all results were reported as ORs for simplicity. The random-effects or fixed-effects model was used to quantify the relationship between wireless phone use and risk of adult glioma depending on the heterogeneity of analysis.[21] The Q and I^2 statistics were used to assess the heterogeneity among the studies included.[22] I^2 illustrates the proportion of total variation that was attributable to heterogeneity between studies as opposed to random error or chance; I^2 values of 0%, 25%, 50%, and 75% were defined as no, low, moderate, and high heterogeneity.[23] If heterogeneity existed, subgroup analysis was performed to evaluate variations that influenced these variables in overall results. The substantial impact on between-study heterogeneity of each study was estimated by influence analyses.[24] Begg's funnel plot[25] and Egger's[26] regression asymmetry test were used to evaluate publication bias. All analyses were 2-sided and performed by Stata 12.0 (StataCorp LLC, College Station, Texas, USA). $P < 0.05$ was considered to be statistically significant.

RESULTS

Search Results and Study Characteristics

In accordance with the search criteria, 10 studies (8 case-control studies[5-12] and 2 cohort studies[13,14]) were enrolled in this meta-analysis on the association between wireless phone use and risk of adult glioma. Of the included studies, 2 were pooled studies,[9,11] and 8 were primary studies.[5-8,10,12-14]

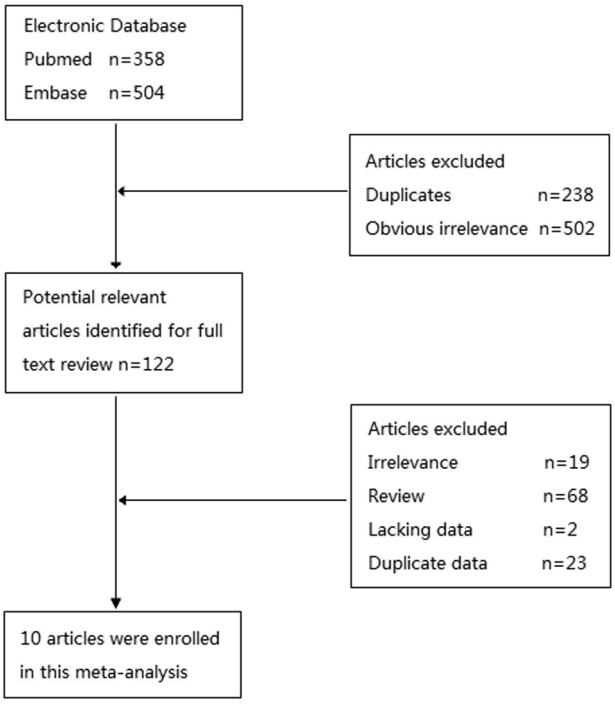

Figure 1. Detailed steps for selection of articles.

INTERPHONE is a multinational case-control study[9] and is the largest epidemiologic study in this field. The pooled analyses of case-control studies from all 13 participating countries were extracted. The INTERPHONE group drew the conclusions that 1) there was no increased risk of glioma with mobile phone use, and 2) there were suggestions of an increased incidence of glioma with heavy and long-term (phone use ≥10 years) use, with bias and error preventing a causal interpretation. However, a significant decrease in risk of glioma was observed (OR = 0.81; 95% CI, 0.70–0.94) in individuals who use mobile phones regularly (i.e., an average of at least 1 call per week for a period of ≥6 months). Furthermore, increased risk of glioma in the temporal lobe could be seen in individuals with the heaviest ipsilateral use (i.e., with a cumulative call time of ≥1640 hours).

Hardell et al. conducted a series of studies in this area. A pooled analysis conducted by Hardell and Carlberg[11] was included in this meta-analysis. The study by Hardell and Carlberg[11] clearly showed that wireless phone use increased the risk of glioma, especially with latency and cumulative use. Moreover, a higher risk for glioma in the temporal lobe was found (OR = 4.30; 95% CI, 2.00–9.30 for mobile phones; OR = 2.4; 95% CI, 0.60–9.50 for cordless phones). Also, Auvinen et al.[8] found a weak association between gliomas and analog cellular phone use (OR = 2.10; 95% CI, 1.30–3.40). However, other studies did not support the hypothesis of increased risk of glioma with wireless phone use.[5-7,10,12] Moreover, 2 cohort studies without recall bias showed no increased risk of glioma.[13,14] **Figure 1** shows the detailed steps for selection of articles. **Table 1** presents the characteristics of the studies included.

Table 1. Characteristics of Included Studies

Author, Year	Study Type	Years, Country	Age (Years), Sex	Tumor Type	Exposed Cases	OR (95% CI)	Comments
Hardell et al., 1999[5]	Case-control	1994—1996, Sweden	20—80, both	Astrocytoma, glioblastoma	36	1.09 (0.64—1.84)	>1 year
Muscat et al., 2000[6]	Case-control	1994—1998, United States	18—80, both	Astrocytoma Oligodendroglioma/ mixed glioma	354 55	0.80 (0.50—1.20) 0.90 (0.40—2.10)	Ever use of handheld cellular phone on a regular basis (regular defined as having a subscription to cellular telephone service)
Inskip et al., 2001[7]	Case-control	1994—1998, United States	≥18, both	Glioma	201	1.00 (0.70—1.40)	Ever use
Auvinen et al., 2002[8]	Case-control	1996, Finland	20—69, both	Glioma	198	1.50 (1.00—2.40)	Ever use
INTERPHONE Study Group, 2010[9]	Case-control	2000—2004, 13 countries	30—59, both	Glioma	1666	0.81 (0.70—0.94)	Regular use ≥1 year (had average of at least 1 call per week for period of ≥6 months)
Coureau et al., 2013[10]	Case-control	2004—2006, France	≥16, both	Glioma	142	1.24 (0.86—1.77)	Regular mobile phone user (at least once a week for ≥6 months)
Hardell et al., 2015[11]	Case-control	1997—2003, 2007—2009, Sweden	20—80, both	Glioma	1074	1.30 (1.10—1.60)	>1 year use of wireless phone
Yoon et al., 2015[12]	Case-control	2002—2007, Korea	15—69, both	Glioma	239	1.17 (0.63—2.14)	Regular use
Frei et al., 2011[13]	Cohort	1987—1995, Denmark	≥30, both	Glioma	324 (male) 32 (female)	1.08 (0.96—1.22) 0.98 (0.69—1.40)	Exposed persons (who had mobile phone subscriptions for at least 1 year)
Benson et al., 2013[14]	Cohort	1999—2005, United Kingdom	Middle-aged women	Glioma	334	0.91 (0.76—1.08)	Ever use

OR, odds ratio; CI, confidence interval.

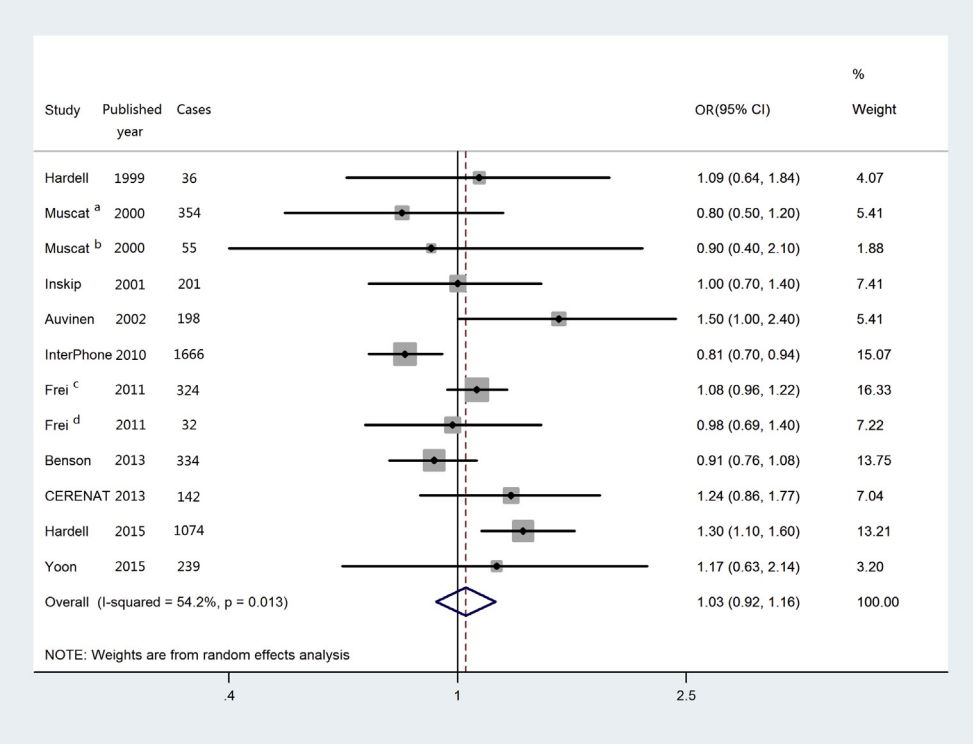

Figure 2. Forest plot of ever use of wireless phones and adult glioma risk. [a]Astrocytic. [b]Oligodendroglioma/mixed glioma. [c]Male users. [d]Female users. OR, odds ratio; CI, confidence interval.

Main Analyses

Ever Use of Wireless Phones. All 10 studies included in this meta-analysis estimated the risk of ever use of mobile phones. Pooled results suggested that ever use of wireless phones was not significantly associated with the risk of adult glioma (summary OR = 1.03; 95% CI, 0.92–1.16) and demonstrated high heterogeneity (I^2 = 54.2%; P = 0.013) (Figure 2). However, the heterogeneity was decreased when either the INTERPHONE

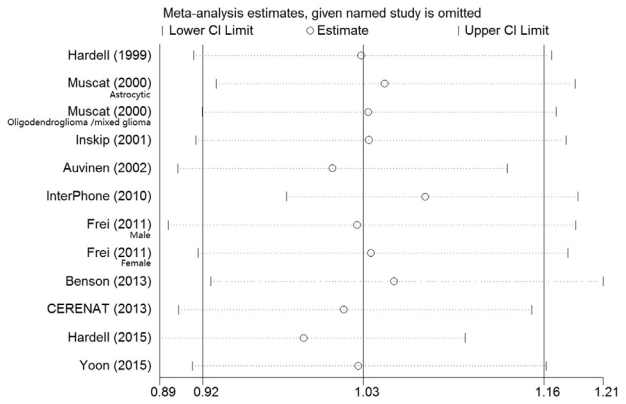

Figure 3. Influence analysis on ever use of wireless phones and adult glioma risk. Given name of the study is omitted. CI, confidence interval.

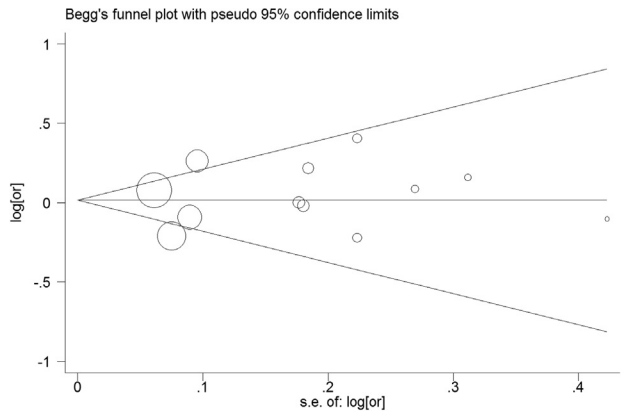

Figure 4. Begg's funnel plot to detect publication bias.

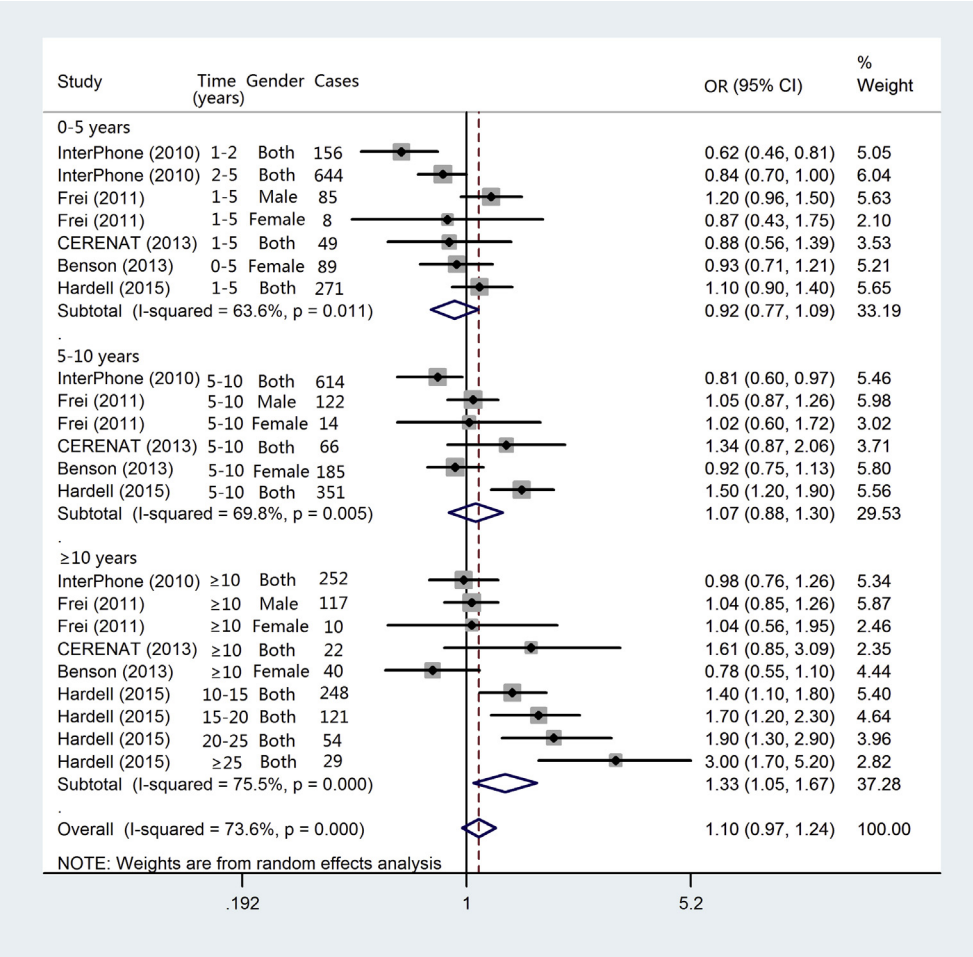

Figure 5. Forest plot from the time since first use of wireless phone and adult glioma risk. OR, odds ratio; CI, confidence interval.

study[9] (OR = 1.08; 95% CI, 0.98–1.09; I^2 = 21.1%; P = 0.148) or the study by Hardell and Carlberg[11] (OR = 0.99; 95% CI, 0.89–1.11; I^2 = 38.4%; P = 0.093) was removed from the meta-analysis.

Sensitivity Analysis and Publication Bias. Influence analysis (Figure 3) showed that removing 1 individual study had no excessive influence on the association between ever use of wireless phones and gliomas. Begg's funnel plot (Figure 4) and Egger's test detected no significant publication bias between ever use of wireless phones and the risk of gliomas (P = 0.624).

Subgroup Analysis

Subgroup analysis of ever use of wireless phones and adult glioma risk demonstrated heterogeneity (I^2 = 54.2%; P = 0.013) in the pooled results. Thus, subgroup analysis of time since first use of wireless phone, location of tumor, and laterality (ipsilateral/contralateral) was performed to explore the potential heterogeneity.

Time Since First Use of Wireless Phone. Of the 10 included studies, the data of time since the start of wireless phone use were shown in 7 studies. The categories of time since first use were classified as short-term (<5 years), midterm (5–10 years), and long-term (>10 years). In the INTERPHONE study, we combined 2 categories (1–2 years and 2–4 years) into 1 category (<5 years), making them more comparable to other studies. In the studies by Yoon et al.[12] and Auvinen et al.,[8] the time since first use was classified as 1–4 years, 4–7 years, and >7 years and <1 year, 1–2 years, and >2 years, respectively. Thus, the 2 studies were not included in this analysis. No significant association between short-term (OR = 0.92; 95% CI, 0.77–1.09) or mid-term (OR = 1.07; 95% CI, 0.88–1.30) wireless phone use and risk of glioma was observed (Figure 5). However, increased risk could be seen with long-term use (OR = 1.33; 95% CI, 1.05–1.67).

Laterality (Side of Wireless Phone Use and Tumor Location). Exposure was identified as ipsilateral if the phone was used mainly on the

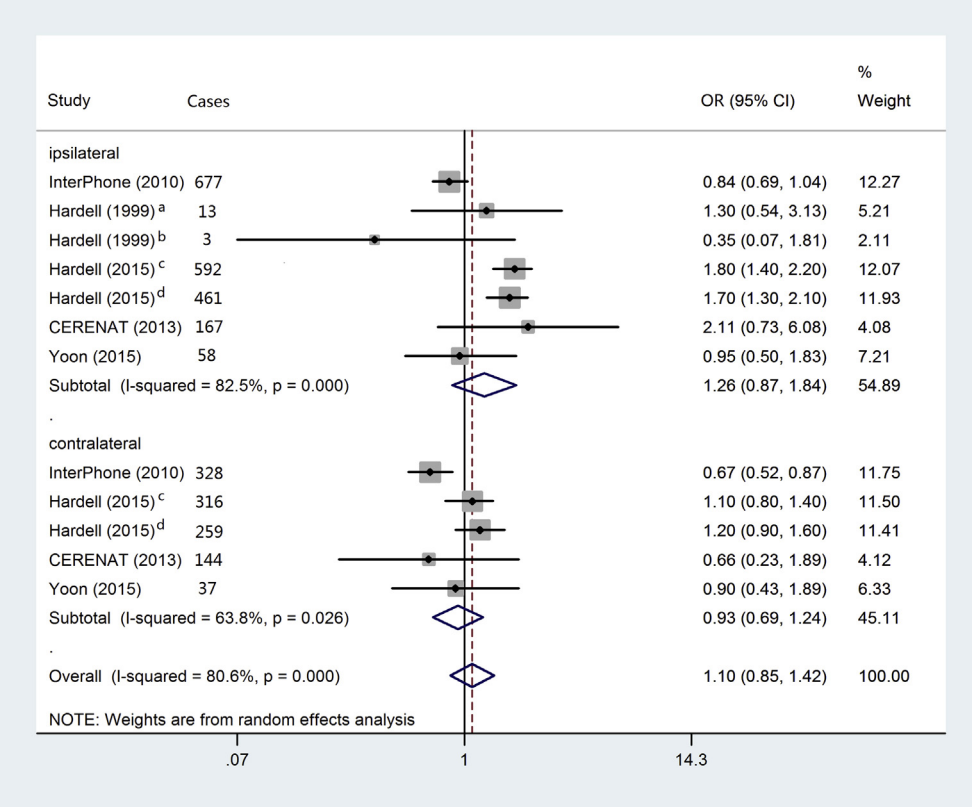

Figure 6. Forest plot for 1 side of wireless phone use and adult glioma risk. [a]Right side and right ear. [b]Left side and left ear. [c]Mobile phone use. [d]Cordless phone use (mobile phone and cordless phone both belong to wireless phone category). OR, odds ratio; CI, confidence interval.

same side as the location of the glioma and contralateral if the phone was used mainly on the side of the head opposite to the tumor. Data of the association between the side of wireless phone use (ipsilateral or contralateral) and glioma were reported in 4 studies. The pooled analyses suggested that neither ipsilateral (OR = 1.26; 95% CI, 0.87–1.84) nor contralateral (OR = 0.93; 95% CI, 0.69–1.24) wireless phone use was associated with adult glioma risk (Figure 6).

Temporal Lobe. Of the 10 included studies, data regarding tumor location in the temporal lobe were reported in 4 studies. The pooled analyses suggested that wireless phone use does not increase the risk of gliomas located in the temporal lobe (OR = 0.93; 95% CI, 0.69–1.24) (Figure 7).

DISCUSSION

In this meta-analysis, no statistically significant association was found between wireless phone use and adult glioma risk, but increased risk of adult glioma could be seen with long-term wireless phone use. No significant association was found in subgroup analyses. However, uncertainties about adult glioma risk still existed because of inconsistencies among the studies.

Several researchers hypothesized that damage induced by RF may lead to the development of cancer and/or cell death. However, the current data could not provide sufficient evidence that genotoxicity could be caused by RF exposure.[27,28] Some recent studies even indicated that nonionizing RF was capable of inducing adaptive response, which may play a role in the reduction of carcinogenesis.[3,4]

More than 50% of the maximum values of specific absorption rate are located at a distance <15 mm from the barycenter of the mobile phone. Moreover, the maximum specific absorption rate was always seen in the temporal lobe. The position of the mobile phone is of great importance in affecting the specific absorption rate.[29] In the included studies addressing laterality, all ipsilateral ORs were higher than contralateral ORs, although the CIs included 1. These results suggested that the use of wireless phones may play a role in risk of adult gliomas. However, the evidence is still weak.

This meta-analysis has some limitations. First, most of the studies included were case-control studies, and the data in the studies were extracted mostly by interviews or questionnaires. Moreover, patients may have changed their lifestyle after diagnosis. Thus, recall bias could not be avoided, which significantly

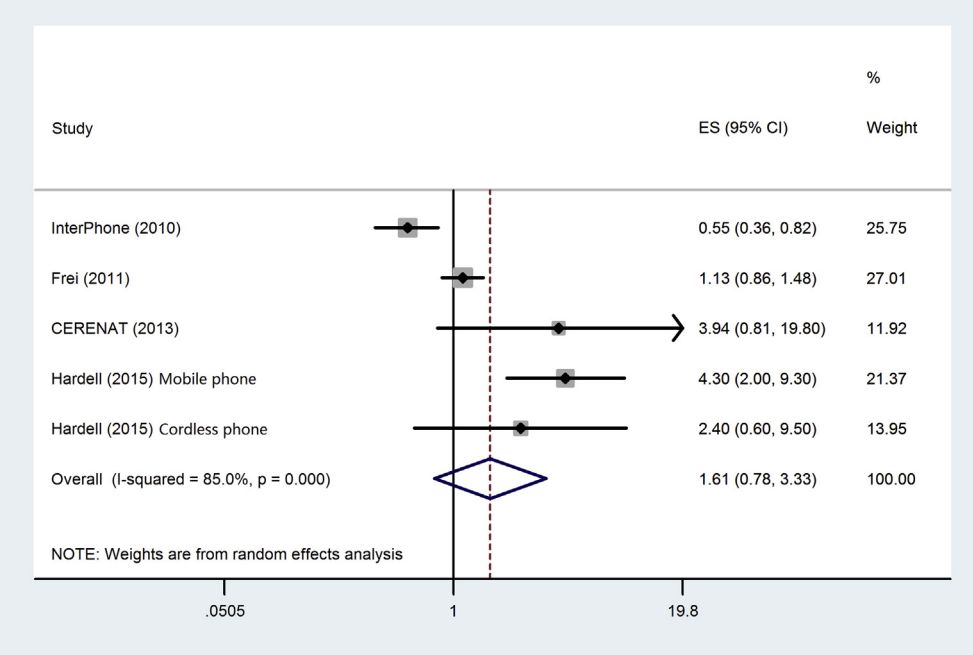

Figure 7. Forest plot for wireless phone use and adult glioma located in temporal lobe. ES, effect size; CI, confidence interval.

affect the results. More cohort studies should be investigated. Second, heterogeneity could be seen among the studies. Different protocols and different methods for classification of wireless phone use make it difficult to combine the data together precisely. The definition of wireless phone use and tumor information were also reported in varied forms. Furthermore, cases are not enough for subgroup analysis. Data on long-term heavy wireless phone use are still insufficient.

CONCLUSIONS

If cumulative RF EMF energy results in DNA double-strand breaks or gene mutations, the cumulative energy absorbed by the brain should also be evaluated. Therefore, the actual accurate calculation of RF EMF energy absorbed should be emphasized in future investigations. More studies and more cases are needed to explore the possible influence of long-term heavy wireless phone use. Meanwhile, 1 standard protocol is also needed for large-scale research.

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