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Relationship between radiofrequency-electromagnetic radiation from cellular phones and brain tumor: meta-analyses using various proxies for RF-EMR exposure-outcome assessment

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Abstract

Introduction The authors conducted meta-analyses regarding the association between cellular and mobile phone use and brain tumor development by applying various radiofrequency-electromagnetic radiation (RF-EMR) exposure subcategories. With changing patterns of mobile phone use and rapidly developing Wireless Personal Area Network (WPAN) technology (such as Bluetooth), this study will provide insight into the importance of more precise exposure subcategories for RF-EMR.

Methods The medical librarian searched MEDLINE (PubMed), EMBASE, and the Cochrane Library until 16 December 2020.

Results In these meta-analyses, 19 case-control studies and five cohort studies were included. Ipsilateral users reported a pooled odds ratio (OR) of 1.40 (95% CI 1.21–1.62) compared to non-regular users. Users with years of use over 10 years reported a pooled OR of 1.27 (95% CI 1.08–1.48). When stratified by each type of brain tumor, only meningioma (OR 1.20 (95% CI 1.04–1.39)), glioma (OR 1.45 (95% CI 1.16–1.82)), and malignant brain tumors (OR 1.93 (95% CI 1.55–2.39)) showed an increased OR with statistical significance for ipsilateral users. For users with years of use over 10 years, only glioma (OR 1.32 (95% CI 1.01–1.71)) showed an increased OR with statistical significance. When 11 studies with an OR with cumulative hours of use over 896 h were synthesized, the pooled OR was 1.59 (95% CI 1.25–2.02). When stratified by each type of brain tumor, glioma, meningioma, and acoustic neuroma reported the pooled OR of 1.66 (95% CI 1.13–2.44), 1.29 (95% CI 1.08–1.54), and 1.84 (95% CI 0.78–4.37), respectively. For each individual study that considered cumulative hours of use, the highest OR for glioma, meningioma, and acoustic neuroma was 2.89 (1.41–5.93) (both side use, > 896 h), 2.57 (1.02–6.44) (both side use, > 896 h), and 3.53 (1.59–7.82) (ipsilateral use, > 1640 h), respectively. For five cohort studies, the pooled risk ratios (RRs) for all CNS tumors, glioma, meningioma, and acoustic neuroma, were statistically equivocal, respectively. However, the point estimates for acoustic neuroma

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showed a rather increased pooled RR for ever-use (1.26) and over 10 years of use (1.61) compared to never-use, respectively.

Discussion In this meta-analysis, as the exposure subcategory used became more concrete, the pooled ORs demonstrated higher values with statistical significance. Although the meta-analysis of cohort studies yielded statistically inconclusive pooled effect estimates, (i) as the number of studies included grows and (ii) as the applied exposure subcategories become more concrete, the pooled RRs could show a different aspect in future research. Additionally, future studies should thoroughly account for changing patterns in mobile phone use and the growing use of earphones or headphones with WPAN technology.

Keywords Radiofrequency-electromagnetic radiation, Cellular phone, Mobile phone, Brain tumor, Meta-analysis

Introduction

A long debate about the relationship between RF-EMR exposure from cell phones and brain tumor incidence has existed since early 2000. Many researchers have conducted meta-analyses and subgroup analyses to clarify this relationship [1–4]. However, a definitive positive association was not observed in these studies. The Hardell group's studies reported moderate positive associations for glioma and acoustic neuroma incidence. In contrast, the Interphone group investigators could not find a statistically significant association for all types of brain tumors in light users. Only heavy cellphone users reported statistically significant associations for glioma and acoustic neuroma. The other third group, which pertains to neither the Hardell group nor the Interphone group, reported results that supported the Interphone group's results in general [5–7]. In particular, Coureau et al. reported an increased OR with statistical significance for glioma in heavy users [8].

In recent years, the pattern of mobile phone use has changed rapidly. With the introduction of 3G phones for data transmission (so-called 'smartphones' such as iPhones or Android phones), people started using their mobile phones for other purposes than mere calling: web surfing, watching movies and videos through YouTube or other applications, connecting to social network services like Facebook or Twitter, text messaging, morning alarm, recording schedules, catching a taxi, etc. This change increases the exposure time to RF-EMR from mobile phones and makes the exposure irregular according to a person's characteristics of mobile phone use. In addition, the widespread Wireless Personal Area Network (WPAN) technology, such as Bluetooth, is making mobile phone use more continuous and prolonged. In particular, this WPAN technology makes the distance between the head and the mobile phone farther. Therefore, RF-EMR exposure patterns are becoming more complicated for researchers to anticipate than before.

In consideration of these rapidly changing mobile phone technologies, the currently used proxies for RF-EMR exposure assessment are crude and insufficient to clarify the relationship between RF-EMR exposure from cell phones and brain tumor incidence. Auvinen et al. (2006) deeply discussed the difficulties in accurately measuring RF-EMR exposure dose from cellular phones in various real-world settings [9]. Theoretically, the accurate assessment of RF-EMR exposure should be based on (i) site-specific, (ii) time-integral of (iii) specific absorption rate (SAR). The usual exposure measures, such as the years of mobile phone use, the cumulative duration of calls, and the number of calls per week, are rough indicators of mobile phone use. As for the third 'SAR' component, the SAR consists of two proxy indicators of exposure, 'mobile phone use time' and 'power.' The output power range varies considerably across phone models, the network used, the location of use, and the technologies applied to the cellular or mobile phone. For example, if discontinuous transmission (DTX) technology were applied to a mobile phone, the power during a complete silent period would be reduced to about 10% of the emitted power when the DTX technology was not applied [10]. The calculation of power should consider these complex characteristics related to cellphone use. As for the first 'site-specific' component, the distance between the phone and the brain should be carefully considered. However, with advancing WPAN technology, the distance between the phone and the brain is becoming distant these days. Recently, more people have been using wireless Bluetooth headsets or earphones not only when they call people but also when they listen to music or watch a video or short clips on YouTube or TikTok. This important factor should be considered in future studies. Finally, as for the second 'time-integral' component, the appropriate exposure measure would be a weighted average of the cumulative time of cellphone use, weighted by the power at each time, stratified by the side of the head, also considering the use of WPAN (Bluetooth) hands-free devices. Today, nearly all essential life services are available through applications on mobile phones. Therefore, the time spent on mobile phones is becoming continuous and irregular, except for the time spent in mere calling. Therefore, the accurate exposure assessment of RF-EMR would become more difficult in future studies and should be carefully assessed by adequate experts. Strict rigor for

exposure assessment of RF-EMR should be adhered to in future cohort studies.

This study aims to synthesize evidence regarding the association between cellphone use and the risk of brain tumors. In particular, the authors conducted a series of meta-analyses and subgroup analyses using various exposure measuring categories, from crude to more precise ones. In consideration of crude exposure classifications used in previous meta-analyses, this study will give insight into the importance of more precise exposure subcategories in investigating this topic.

Methods

Literature search and inclusion criteria

A medical librarian in the medical library of the author's affiliation (Medical Library, the Catholic University of Korea, Seoul, Republic of Korea) conducted the search process. The medical librarian searched MEDLINE (PubMed), EMBASE, and the Cochrane Library (until 10 July 2024). The search terminologies and search queries used are provided in Supplementary material A.

The inclusion criteria were as follows: (i) The article should deal with the risk of brain tumors for analog (1G), digital (2G), and mobile phone (3G) users because of potential RF-EMR exposures. (ii) The article should be in English. (iii) The article should be an original research article. Review articles, conference abstracts, letters to the editor, and commentaries were excluded from the final article selection. (iv) Cohort studies were included but analyzed separately. Cordless phone users were excluded from the analysis because cordless phones are not being used currently, and individual home-based cordless phones are almost substituted with personal cellular or mobile phones. Cellular and mobile phone technologies are developing so fast, and the power of emitted RF-EMR is changing rapidly. Therefore, the old technology, cordless phones, was excluded from the analysis because of its low significance in future public health implications.

As for cordless phones, only several Hardell group studies included the RF-EMR from cordless phones as the exposure of interest. In these studies, the risk of malignant brain tumors and astrocytoma was increased. For meningioma, only the ipsilateral exposure increased the risk. The interphone group studies did not consider cordless phone use. This difference could lead to a bias in estimating risks: this could bias the results towards unity based on the increased risk shown by Hardell et al. [5]. However, we aim to estimate the brain tumor risks of RF-EMR exposure from cellular phones. Therefore, we excluded cordless phones from the RF-EMR exposure source.

Numerous studies have been conducted by researchers all over the world to examine the brain tumor risks due to the RF-EMR emitted from cellular and mobile phones until the present. Researchers sometimes reported the results from the same data to multiple articles. In several cases, they reported an outcome from a recent study together with the outcomes from previous studies. Therefore, carefully selecting included studies was paramount to conducting these meta-analyses with validity. The authors meticulously classified and summarized the included and excluded studies to avoid the inclusion of duplicated outcomes.

As for this duplicated outcome issue, two points should be clarified. First, one article could report multiple outcomes (two or three outcomes) if risk estimates for different types of brain tumors were reported simultaneously. In other words, even if 20 articles were included in the final selection, the number of synthesized risk estimates (outcomes) could be 30. Second, for ipsilateral/contralateral uses and years of use over/under 10 years, sometimes studies classified as duplicated can provide an unduplicated risk estimate because of different selection of reporting criteria (laterality and years of use). Therefore, we meticulously checked the studies with duplicated data to find unduplicated risk estimates. If these unduplicated risk estimates were found, these were included in the final meta-analyses.

The following items were summarized for the included and excluded studies: Each study was classified into three groups: (i) Interphone: the studies conducted as a part of the Interphone international study; (ii) Hardell: the studies conducted by the Hardell group; and (iii) The third group: the studies conducted by the other groups. The frequency bands of cellular or mobile phones, study period, study country, the number of cases and controls, and the types of brain tumors analyzed were recorded.

Selection and recall bias for the amount of cellphone use and misclassification and recall bias for ipsilateral/contralateral use

Instead of the typical rating of risk of bias for each included study, the authors analyzed the risk of bias regarding selection and recall bias for the amount of cell phone use and misclassification and recall bias for ipsilateral/contralateral use. A major reason was that typical risk of bias rating tools such as the National Toxicology Program Office of Health Assessment and Translation Risk of Bias rating tool (NTP OHAT RoB rating tool, Supplementary material B) were not appropriate for assessing individual studies regarding this topic. For example, the first and second questions were appropriate for assessing randomized controlled trials, not epidemiological studies, including cohort and case-control studies. The fifth, sixth, and seventh questions do not have a significant or practical meaning in this study topic. Regarding the ninth question, the reliability of the brain

tumor reporting system could be important. However, most studies usually used the national reporting system for brain tumors. Therefore, the ninth question could not have a practical significant meaning in this topic. Based on these reasons, the authors concluded that focusing on selection and recall bias for the amount of cell phone use and misclassification and recall bias for ipsilateral/contralateral use would be more practical and significant.

Examination for possible publication bias

To examine possible publication bias, the authors plotted Begg's funnel plot and conducted Egger's regression test with a significance level of 0.05 for the included risk estimates.

Data extraction

For each reported risk estimate, the type of brain tumor, laterality or duration of use, and the odds ratios (ORs) were provided in separate tables.

Main meta-analyses and subgroup analyses

For the selection between a fixed-effect or random-effect model, a random-effect model was selected considering the heterogeneity among included studies. A fixed or random effect model should be selected based on a theoretical understanding of the subject matter [11]. Therefore, Higgin's I-square statistic and Cochran's Q-test results were used only as supplementary indexes. Higgin's I-square statistics above 25% and Cochran's Q test results with a significance level of less than 0.1 were considered 'heterogeneous.'

The main meta-analyses and subgroup analyses were divided into four categories: (i) The first category was regular users vs. non-regular users. (ii) The second category was laterality (ipsilateral and contralateral vs. non-regular users, respectively). (iii) The third category was years of use (>10 and <10 years). (iv) The analyses regarding the first, second, and third categories were also conducted stratified by each type of brain tumor (glioma, meningioma, acoustic neuroma, pituitary tumor, malignant tumor). A pooled point estimate with a 95% confidence interval (CI) was provided for all meta-analyses.

For the second and third categories, a meta-ANOVA analysis was conducted. A meta-ANOVA analysis is a moderator analysis used in meta-analyses to find an effect difference among subgroups according to a study-level moderator variable (for example, study period, study country, publication type, etc.). If a moderator variable is a categorical variable, a meta-ANOVA analysis is used, and if a moderator variable is a continuous variable, a meta-regression analysis is used. Moderator analyses enable the examination of the difference in effect size between subgroups and the effect of a moderator variable on the effect size [12]. The statistical significance was set at 0.05 for meta-ANOVA analysis.

Meta-analysis for the total cumulative hours of use > 896 h

A separate meta-analysis was conducted for subjects with the cumulative hours of use > 896 h. If an OR for ipsilateral use with cumulative hours of use over 896 h was available in a study, the OR was used for the individual study for this meta-analysis.

Cumulative meta-analyses according to the publication year and the precision of each included study

Cumulative meta-analyses according to the publication year and the precision of each included study were conducted separately for regular users, ipsilateral/contralateral users, years of use > 10 years/<10 years, and total cumulative hours of use > 896 h.

Results of cohort studies

The results of cohort studies were provided separately. A detailed discussion was added to the discussion section.

Results

Screening and selection processes

Figure 1 provides the screening and selection processes for this meta-analysis. A total of 1,103 articles were identified from three databases, including PubMed, EMBASE, and the Cochrane Library. After the exclusion of 300 duplicate articles, 803 articles remained. Through primary screening using titles and abstracts, 502 articles were excluded. And then, for the remaining 301 articles, a full-text review was conducted, with an additional 271 articles excluded. After that, only 25 case-control and 5 cohort studies articles remained. Among these articles, six case-control studies that dealt with benign or malignant parotid tumors were excluded (6 articles). Finally, 19 case-control studies and 5 cohort studies remained. Relevant data were extracted for these 19 case-control studies and 5 cohort studies.

Included and excluded case-control studies

Supplementary materials C-1 and C-2 provide the summary table for included studies and that for excluded studies due to duplicated data, respectively. The types of brain tumors included were glioma, meningioma, acoustic neuroma, pituitary tumors, malignant tumors, all brain tumors, and benign brain tumors. Duplicated data were marked as 'Du' and excluded from meta-analyses.

Selection and recall bias for the amount of cellphone use and misclassification and recall bias for ipsilateral/contralateral use

Supplementary materials D-1 and D-2 provide the authors' bias rating regarding selection and recall bias for

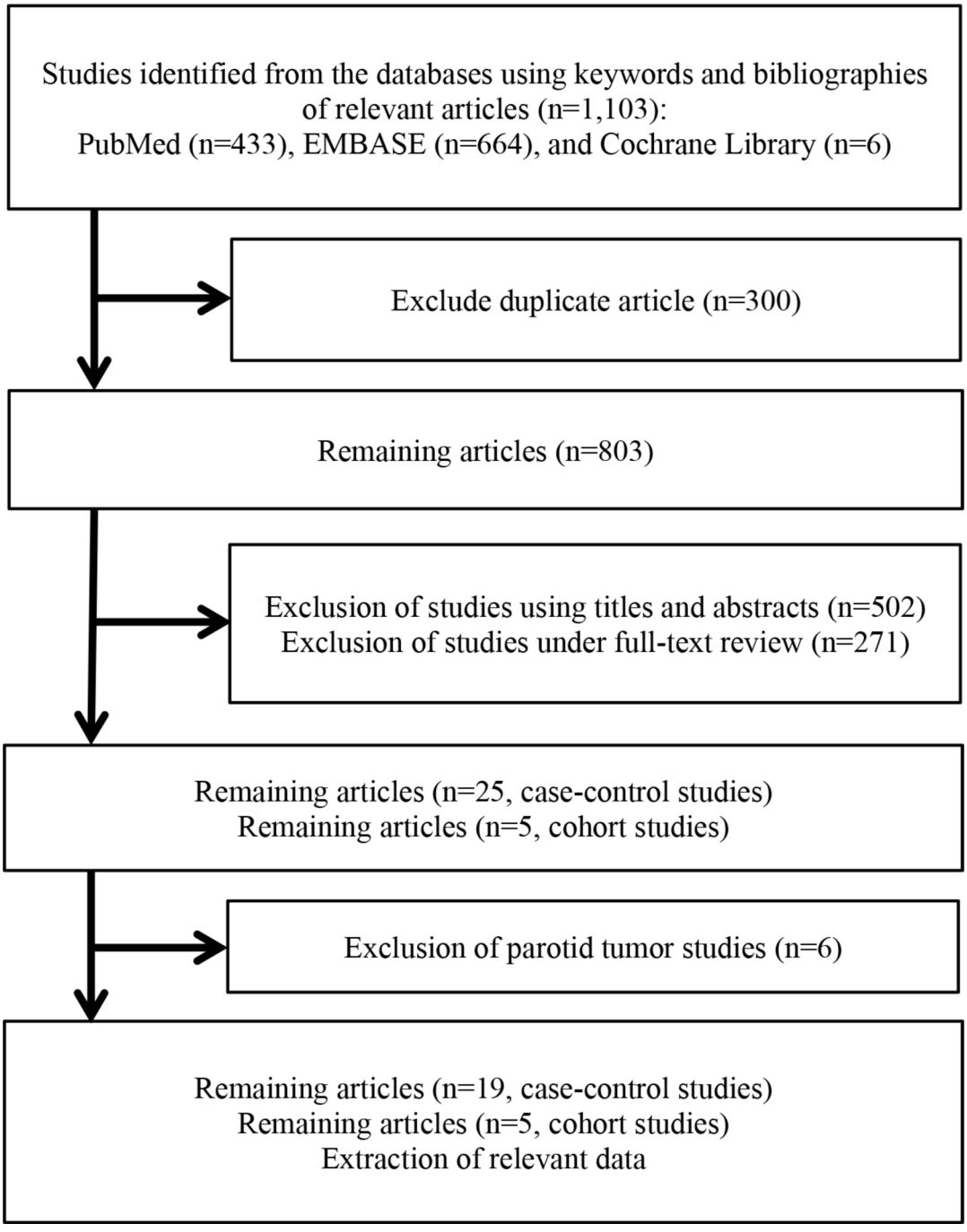

Fig. 1 Screening and selecting processes for this meta-analysis

the amount of cellphone use and misclassification and recall bias for ipsilateral and contralateral use for case-control and cohort studies, respectively.

Examination for possible publication bias (case-control studies)

Supplementary material E provides the funnel plot and Egger's regression test result. Egger's p-value was 0.38.

Selection between a fixed-effect and a random-effect model

All meta-analyses conducted in this study showed a statistically significant Cochran's Q test result. Therefore, a random-effect model was applied throughout all analyses of this study.

We applied a conventional meta-analysis model to this study and did not apply a multi-level meta-analysis model. This was because there was no interdependence

between risk estimates from each study. Supplementary materials F-1 and F-2 provide a summary of study populations for case-control studies and cohort studies, respectively. Because studies with duplicated data were checked meticulously, marked as 'Du' in Supplementary C-2, and excluded from the final evidence synthesis, we could confirm that there was no interdependence among the risk estimate from each study, as the reader could check in Supplementary material F-1.

Meta-analyses and subgroup analyses for regular users, ipsilateral/contralateral uses, and years of use over/under 10 years (case-control studies)

Supplementary material G provides the list of included effect estimates for meta-analyses and subgroup analyses from each included study. The ORs for these three categories, regular users/non-regular users, ipsilateral/contralateral uses, and years of use over/under 10 years, were summarized in Supplementary material G-1, G-2, and G-3, respectively.

Table 1 summarizes the results of meta-analyses and subgroup analyses for regular users, ipsilateral/contralateral uses, and years of use over/under 10 years. Supplementary material H provides the forest plots for these meta-analyses and subgroup analyses. The pooled OR for regular users was 0.98 (95% CI 0.90–1.07). The pooled OR for ipsilateral uses and contralateral uses was 1.40 (95% CI 1.21–1.62) and 1.04 (95% CI 0.93–1.16), respectively. The pooled OR for years of use over and under 10 years was 1.27 (95% CI 1.08–1.48) and 0.96 (95% CI 0.88–1.04), respectively. The Q-statistic and p-value were 9.02 and 0.002, respectively, for the laterality of use category. The Q-statistic and p-value were 10.43 and 0.001, respectively, for the years of use category.

Table 1 Summarized results of meta-analyses and subgroup analyses (case-control studies)

Category	Subcategory	The number of outcomes	Odds Ratio (95% CI)	Meta-ANOVA analysis
Regular user	Regular users	30	0.98 (0.90–1.07)	None
	Non-regular users		1.00	
Laterality of use	Ipsilateral uses	25	1.40 (1.21–1.62)*	Q = 9.02, $p = 0.002$*
	Contralateral uses	25	1.04 (0.93–1.16)	
Years of use	Over 10 years	19	1.27 (1.08–1.48)*	Q = 10.43, $p = 0.001$*
	Under 10 years	34	0.96 (0.88–1.04)	

*Statistically significant

Meta-analyses and subgroup analyses stratified by tumor types (case-control studies)

The results of meta-analyses and subgroup analyses stratified by tumor types are provided in Table 2. For regular users, the pooled OR for meningioma was 0.86 (95% CI 0.77–0.95). For ipsilateral uses, the pooled OR for meningioma, glioma, and malignant tumors was 1.20 (95% CI 1.04–1.39), 1.45 (95% CI 1.16–1.82), and 1.93 (95% CI 1.55–2.39), respectively. For years of use over 10 years, the pooled OR for glioma was 1.32 (95% CI 1.01–1.71). All other pooled ORs were statistically equivocal.

Meta-analysis of total cumulative hours of use over 896 h (case-control studies)

The characteristics of included studies for the meta-analysis of cumulative hours of use over 896 h are provided in Table 3. Of eleven effect estimates, seven were an increased OR with statistical significance. The remaining four effect estimates were statistically equivocal. Of these seven increased ORs with statistical significance, three were from glioma, the other two were from meningioma, and the remaining two were from acoustic neuroma. Figure 2 provides the forest plots for this meta-analysis. The pooled OR was 1.59 (95% CI 1.25–2.02). When stratified by each type of tumor, the pooled OR for glioma, meningioma, and acoustic neuroma was 1.66 (95% CI 1.13–2.44), 1.29 (95% CI 1.08–1.54), and 1.84 (95% CI 0.78–4.37), respectively.

Results of cumulative meta-analyses according to publication year and precision of each included study (case-control studies)

Figure 3 provides the results of cumulative meta-analyses according to the publication year, and the precision of each included study for ipsilateral users, years of use > 10 years, and total cumulative use > 896 h. The results of cumulative meta-analyses for regular users, contralateral users, and years of use < 10 years are provided in Supplementary material I.

For the cumulative meta-analysis according to publication year for ipsilateral users (Figs. 3−1), from 2005 to 2007 (k = 11), the pooled OR decreased from 2.90 (95% CI 1.38–6.10) to 1.40 (95% CI 1.08–1.82). After 2007 (k = 11), even though further studies were added, the point estimate of pooled OR did not change. However, the 95% CI was narrowed from (1.08–1.82) to (1.21–1.62). This phenomenon reflects that the reported individual OR was stabilized since 2007 after the formerly reported rather larger ORs for ipsilateral users.

For the cumulative meta-analysis according to precision for ipsilateral users (Figs. 3−2), until the 15th addition (k = 15), the pooled OR showed a rather stabilized estimate (1.71 (95% CI 1.49–1.96)). However, from then to the 25th addition (k = 25), the pooled OR decreased

Table 2 Results of meta-analyses and subgroup analyses according to tumor types (case-control studies)

Category	Subcategory	Tumor type	Number of outcomes	Odds ratio (95% CI)
Regular user	Regular vs. non-regular users	All brain tumor	3	1.13 (0.84–1.51)
		Meningioma	6	0.86 (0.77–0.95)*
		Acoustic neuroma	7	1.01 (0.79–1.31)
		Glioma	6	1.08 (0.86–1.35)
		Malignant tumor	5	0.91 (0.71–1.16)
		Pituitary tumor	3	0.74 (0.26–2.13)
Laterality of use	Ipsilateral	All brain tumor	1	1.74 (0.91–3.33)
	Contralateral	All brain tumor	1	2.07 (0.95–4.52)
	Ipsilateral	Meningioma	6	1.20 (1.04–1.39)*
	Contralateral	Meningioma	6	1.03 (0.87–1.23)
	Ipsilateral	Acoustic neuroma	8	1.38 (0.91–2.08)
	Contralateral	Acoustic neuroma	8	1.14 (0.87–1.51)
	Ipsilateral	Glioma	8	1.45 (1.16–1.82)*
	Contralateral	Glioma	8	0.96 (0.77–1.19)
	Ipsilateral	Malignant tumor	2	1.93 (1.55–2.39)*
	Contralateral	Malignant tumor	2	1.03 (0.83–1.28)
Years of use	Over 10 years	Meningioma	5	1.08 (0.90–1.30)
	Under 10 years	Meningioma	7	0.90 (0.79–1.02)
	Over 10 years	Acoustic neuroma	6	1.38 (0.93–2.05)
	Under 10 years	Acoustic neuroma	11	1.04 (0.88–1.23)
	Over 10 years	Glioma	4	1.32 (1.01–1.71)*
	Under 10 years	Glioma	7	0.98 (0.77–1.26)
	Over 10 years	Malignant tumor	3	1.35 (0.68–2.70)
	Under 10 years	Malignant tumor	7	0.92 (0.76–1.11)
	Over 10 years	Pituitary tumor	1	1.00 (0.53–1.90)
	Under 10 years	Pituitary tumor	2	0.89 (0.67–1.19)

*Statistically significant

For all analyses, the comparison group was non-regular users with an odds ratio of 1.00

to 1.40 (95% 1.21–1.62). This indicates the studies with a lower precision had a lower OR estimate, and this could have biased the pooled OR downwards.

For the cumulative meta-analysis according to the precision for years of use>10 years group (Fig. 3–3), the pooled OR increased from 1.10 (95% CI 0.86–1.40) to 1.46 (95% CI 1.16–1.85) until the 11th addition (k=11). However, from then, the pooled OR decreased to 1.27 (95% CI 1.08–1.48) until the 19th addition (k=19). This phenomenon indicates that the addition of the studies with a lower precision could have biased the pooled OR downwards.

For the cumulative meta-analysis according to publication year for the total cumulative hours of use>896 h group (Figs. 3–4), after the stabilization of the pooled point OR in the 6th addition (k=6) with 1.59 (95% CI 1.19–2.12), the pooled point OR did not change significantly until the 11th addition (k=11). However, the 95% CIs were narrowed continuously from the 6th addition to the 12th addition, from (1.19–2.12) to (1.27–1.91). This phenomenon indicates that the included studies showed a moderate increased OR with statistical significance since 2013.

For the cumulative meta-analysis according to precision for the total cumulative hours of use>896 h group (Figs. 3–5), the pooled OR increased until the 7th addition (k=7) to 1.90 (95% CI 1.39–2.59). After that, the pooled OR decreased until the 11th addition (k=11) to 1.59 (95% CI 1.25–2.02). This phenomenon indicates that the addition of the studies with a lower precision could have biased the pooled OR downwards.

Included cohort studies and evidence synthesis

Supplementary material J provides the characteristics of included cohort studies. The study period spread from 1982 to 2012. Two studies were conducted in Denmark [21, 22], and the other two studies were conducted in the UK [23, 24]. Another study was conducted in six countries, including Denmark, Finland, France, Sweden, the Netherlands, and the UK [25]. Supplementary material F-2 provides the summary of the study population for each cohort study. Based on this summary, we could confirm that there is no interdependence among the risk estimates from each study.

Supplementary material K provides the summary of risk ratios (RRs) reported in each cohort study. An increased RR with statistical significance (2.46 (95%

Table 3 Characteristics of included case-control studies for the meta-analysis with cumulative use over 896 h

Study	Group	Publication year	Period	Country	Laterality	Cumulative hours	Case	Control	Tumor type	Odds Ratio (95% CI)
Hardell et al. (2015) [13]	Hardell	2015	1997–2003, 2007–2009	Sweden	both	> 1486	367	618	glioma	2.00 (1.60–2.60)*
Yoon et al. (2015) [14]	The third group	2015	2002–2008	South Korea	ipsilateral	> 900	68	60	glioma	0.77 (0.32–1.84)
Carlberg et al. (2015) [15]	Hardell	2015	1997–2003, 2007–2009	Sweden	both	> 1486	336	618	meningioma	1.30 (1.10–1.60)*
Coureau et al. (2014) [8]	The third group	2014	2004–2006	France	both	> 896	131	233	glioma	2.89 (1.41–5.93)*
Coureau et al. (2014) [8]	The third group	2014	2004–2006	France	both	> 896	127	216	meningioma	2.57 (1.02–6.44)*
Hardell et al. (2013) a [16]	Hardell	2013	1997–2003, 2007–2009	Sweden	both	> 1486	56	618	acoustic neuroma	2.20 (1.50–3.40)*
The INTERPHONE Study Group (2011) [17]	Interphone	2011	2000–2004	13 Countries	ipsilateral	> 1640	815	1421	acoustic neuroma	3.53 (1.59–7.82)*
The INTERPHONE Study Group (2010) [18]	Interphone	2010	2000–2004	13 Countries	both	> 1640	1277	1281	meningioma	1.15 (0.81–1.62)
The INTERPHONE Study Group (2010) [18]	Interphone	2010	2000–2004	13 Countries	both	> 1640	1252	1232	glioma	1.40 (1.03–1.89)*
Takebayashi et al. (2006) [19]	Interphone	2006	2000–2004	Japan	both	> 900	166	53	acoustic neuroma	0.67 (0.25–1.83)
Hardell et al. (1999) [20]	Hardell	1999	1994–1996	Sweden	both	> 968	138	277	all tumors	1.06 (0.33–3.40)

*Statistically significant

¶For the number of cases and controls, only the numbers of the reference group and corresponding cumulative hours group were included

CI 1.07–5.64)) was reported only once in Benson et al. (2013) for acoustic neuroma in the over 10 years of use vs. never-use category [23]. On the contrary, the RR for the ever-use vs. never-use category for glioma from Schuz et al. (2022) showed a decreased RR with statistical significance (0.89 (95% CI 0.80–0.99)) [24]. All other RRs were statistically equivocal.

Table 4 provides the summary of pooled RR for each tumor for ever-use vs. never-use and over 10 years of use vs. never-use categories, respectively. An increased point RR was reported only for acoustic neuroma in ever-use vs. never-use and over 10 years of use vs. never-use categories, respectively (1.26 (95% CI 0.98–1.61) and 1.61 (95% CI 0.91–2.85), respectively). However, the CI for these two RRs were statistically equivocal, including 1. The pooled RRs for all other categories were statistically equivocal. Supplementary material L provides the forest plots for each analysis.

Discussion

In this meta-analysis regarding the association between cellular phone use and brain tumors, 19 case-control studies and five cohort studies were included. For regular users, the pooled OR was statistically equivocal compared to non-regular users. Ipsilateral users showed an increased pooled OR with statistical significance compared to non-regular users. Users with years of use over 10 years showed an increased pooled OR with statistical significance. When stratified by each type of brain tumor, all types of brain tumors showed a statistically equivocal pooled OR except for meningioma, with a decreased OR with statistical significance. For ipsilateral users, only meningioma, glioma, and malignant brain tumors showed an increased OR with statistical significance. For users with years of use over 10 years, only glioma showed an increased OR with statistical significance. When 11 studies with an OR with cumulative hours of use over 896 h were synthesized, the pooled OR was increased by 59% with a 95% CI from 25 to 102%. In particular, the risk of glioma was increased by 66%, with a 95% CI from 13 to 144%. For five cohort studies, the pooled RRs for all CNS tumors, glioma, meningioma, and acoustic neuroma, were statistically equivocal, respectively. However, the point estimates for acoustic neuroma showed a rather increased pooled RR for ever-use and over 10 years of use compared to never-use, respectively.

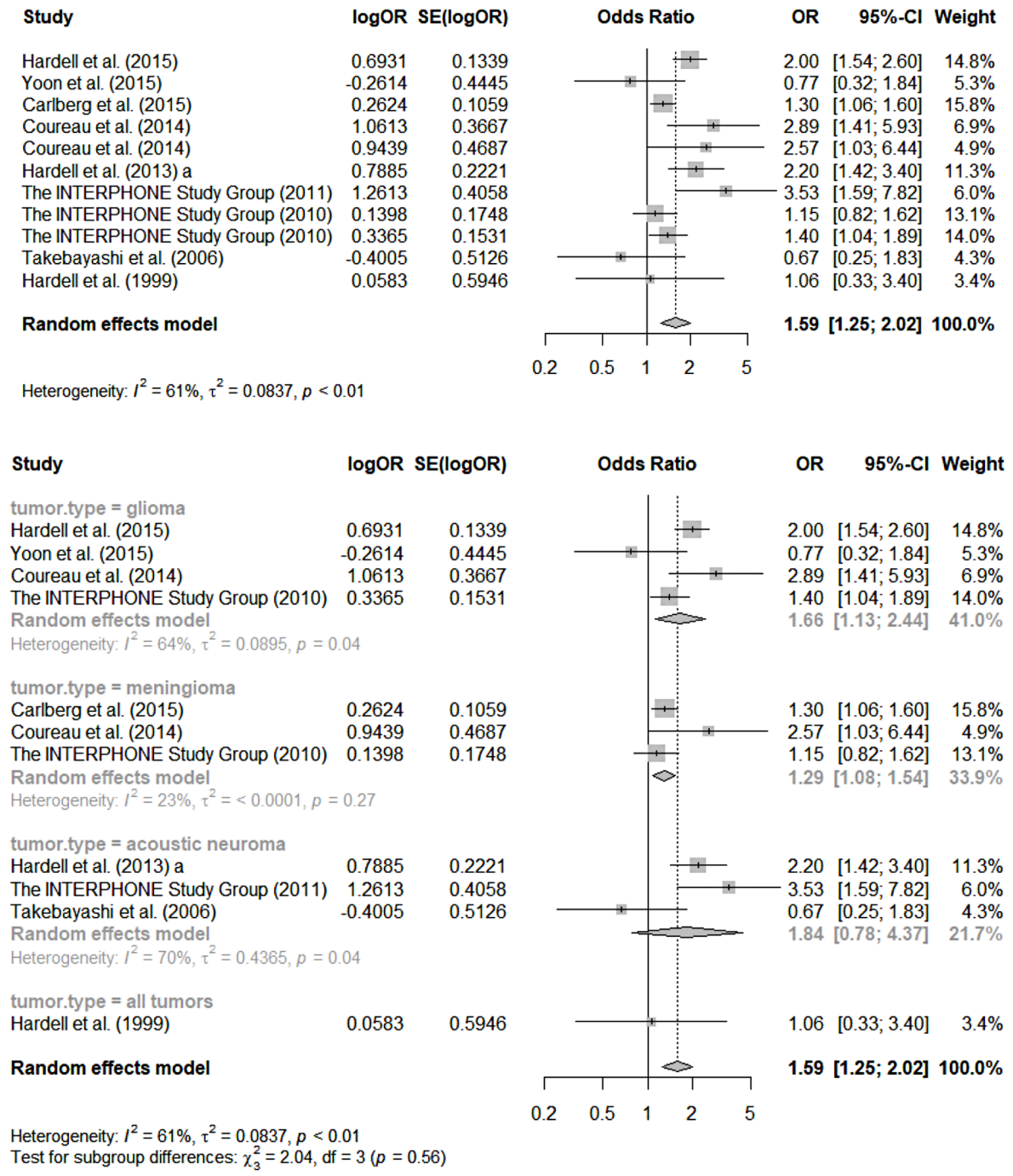

Fig. 2 Forest plots for meta-analysis of total cumulative use over 896 h (case-control studies)

Non-stratified results by types of brain tumor: Table 1

The results reported in Table 1 are already well-known from other meta-analyses [1, 3]. The pooled OR was statistically equivocal (0.98 (95% CI 0.90–1.07)) for simple regular users compared to non-regular users. However, the pooled OR for ipsilateral uses (1.40 (95% CI 1.21–1.62) and over 10 years of uses (1.27 (95% CI 1.08–1.48)) were increased with statistical significance, respectively. As the authors commented on in the introduction, Auvinen et al. insisted that the accurate assessment of RF-EMR exposure should be based on (i) site-specific, (ii) time-integral of (iii) specific absorption rate (SAR) [9]. Even though we cannot apply the most accurate exposure assessment method at this time, as the results in Table 1 indicate, a more accurate exposure subcategory (ipsilateral use and years of use over 10 years) can reveal

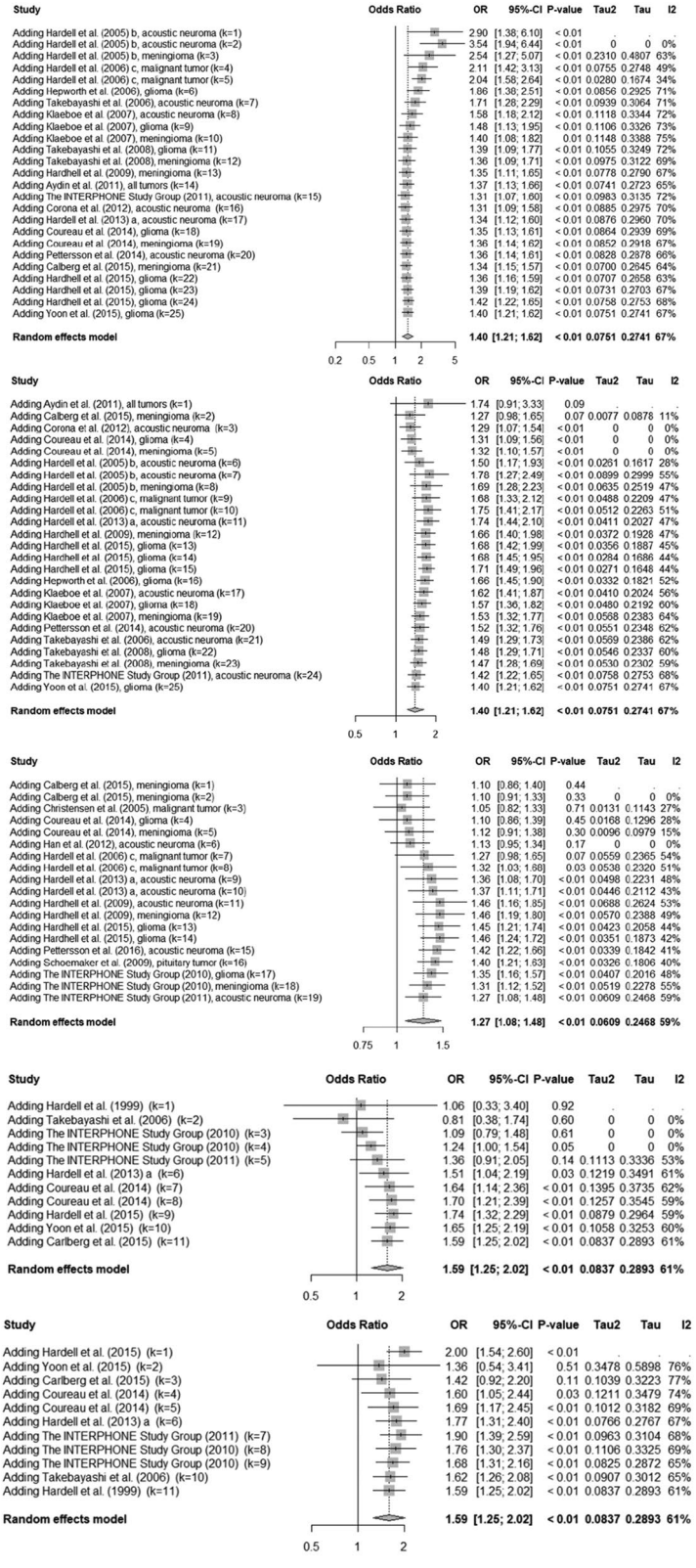

Fig. 3 Results of cumulative meta-analyses according to publication year and precision for ipsilateral users, years of use > 10 years, and total cumulative use > 896 h (case-control studies)

Table 4 Summary of pooled risk ratio (cohort studies)

Pooled RR (95% CI)	All CNS tumors	Meningioma	Acoustic neuroma	Glioma
Ever-use vs. never-use	1.00 (0.95–1.04)	0.98 (0.88–1.10)	1.26 (0.98–1.61)	0.96 (0.86–1.08)
Over 10 years of use vs. never-use	1.00 (0.92–1.08)	0.98 (0.85–1.14)	1.61 (0.91–2.85)	0.92 (0.82–1.02)

Pooled RR, Pooled Risk Ratio, 95% CI, 95% Confidence Interval

a previously unobserved association when a less accurate exposure subcategory (regular users vs. non-regular users) was applied.

Stratified results by types of brain tumor: Table 2

In Table 2, the results of meta-analyses and subgroup analyses stratified by tumor types are provided. For regular users, the pooled OR for meningioma showed a decreased pooled OR with statistical significance (0.86 (95% CI 0.77–0.95)). Similarly, in a recent meta-analysis published in 2020, the authors reported that a decreased pooled risk estimate was observed in the 0–5 years of use subgroup when stratified by laterality and years of use [26]. Other subgroups in this study reported a statistically equivocal pooled risk estimate. However, this protective effect for meningioma should be interpreted cautiously. In our study, when stratified by laterality of use and years of use over or under 10 years, any decreased pooled OR with statistical significance was not observed at all. Rather, an increased pooled OR with statistical significance for meningioma was observed for ipsilateral uses (1.20 (95% CI 1.04–1.39)). These contrasting results could be understood as a type of Simpson's paradox [27]. Therefore, we can understand that the stratified results, increased pooled ORs with statistical significance, would be correct compared to the unstratified result, a decreased pooled OR with statistical significance.

When stratified by types of brain tumors, meningioma, glioma, and malignant tumors showed an increased pooled OR with statistical significance for ipsilateral users, and glioma showed an increased pooled OR with statistical significance for users with years of use over 10 years.

Results for cumulative hours of use over 896 h: Table 3; Fig. 2

When ORs for cumulative hours of use over 896 h were combined (regardless of tumor type), the pooled OR showed 59% increased odds of brain tumor. In particular, the pooled OR for glioma and acoustic neuroma showed 66% and 84% increased odds, respectively, even though the 95% CI for acoustic neuroma was not statistically significant. Even though the number of included studies was relatively small, the used exposure subcategory was improved compared to the previously used two exposure subcategories (consideration of laterality of use and years of use over/under 10 years) because cumulative hours of use were considered.

Results of cumulative meta-analyses: Fig. 3

The results of cumulative meta-analyses according to publication year indicated that the ORs for ipsilateral users were relatively higher in initial studies from 2005 to 2006 but have stabilized since 2007. On the contrary, the ORs for cumulative hours of use over 896 h were relatively lower in initial studies from 1999 to 2006 but have stabilized since 2010. This indicates a possibility that initial studies could report rather biased results. The results of cumulative meta-analyses according to precision indicated that the pooled OR was biased downwards with the addition of studies with lower precision. This indicates that the results of studies with a lower precision should be interpreted cautiously.

Results for cohort studies: Table 4

Because exposure is determined before the outcome, cohort studies have a temporal structure that allows them to evaluate causality, making them capable of providing more reliable scientific evidence [28]. In the meta-analysis of cohort studies, all CNS tumors, meningioma, acoustic neuroma, and glioma showed a statistically equivocal pooled RR. Only the pooled point RR for acoustic neuroma showed an increased estimate.

For this meta-analysis of cohort studies, first, the number of included studies was too small to conclude on this topic. For each type of brain tumor, from two to five study outcomes were included. Second, the applied exposure subcategory needs to be more accurate in light of the aforementioned i) site-specific, (ii) time-integral of (iii) specific absorption rate (SAR) (in the introduction). At least cumulative hours of use should be applied in future cohort studies.

Influence of changing patterns of mobile phone use on RF-EMR exposure dose

With the conversion from 2G cellular phones through 3G and 4G mobile phones to current 5G mobile phones, transmission of large data became possible. With the introduction of 3G technology, all aspects of our society and daily lives have changed drastically. Currently, we are using mobile phones nearly continuously and putting mobile phones near our bodies even when we are not using them. For example, if people use their mobile phone for morning-alarming purposes, they might put their mobile phone near the bed, sometimes even beside their head, all night. These changed patterns of mobile phone use could increase exposure to RF-EMR from cellular and mobile phones. Therefore, precise exposure

assessment for RF-EMR from mobile phones would become more complex in future studies.

Influence of WPAN technology on the RF-EMR exposure dose

WPAN technology, such as Bluetooth, has been applied to smartphones in recent years. Among many devices, wireless earphones or headphones can be connected to smartphones without cords due to this WPAN technology. After the introduction of these devices with WPAN technology, there was no need to attach smartphones to the ear during calls. This technology reduced the RF-EMR dose to the head in general compared to the period before this technology.

Possible under-estimation due to the relatively short observation spans

Because brain tumors require a latency period to develop [29], an accurate assessment of brain tumor risk associated with RF-EMR exposure requires a long observation span. However, each included study did not consider a sufficient latency period in their study design. This could have led to a possible underestimation of brain tumor risk. Future studies with long observation spans might resolve this problem.

Age as a confounder: starting age of exposure and age of diagnosis

For accurate assessments of brain tumor risks from RF-EMR exposure, both the starting age of exposure and the age of brain tumor diagnosis should be considered at the same time. However, these types of information are not reported or considered unanimously in all individual studies. Because age is an essential confounder in the development of brain tumors, the starting age of exposure and age of diagnosis should be considered in future studies.

Previous studies that adjusted for selection and recall bias for the amount of cellphone use and misclassification and recall bias for ipsilateral/contralateral use

Momoli et al. adjusted for recall and selection bias due to low and unrepresentative participation data using billing records from network operators and non-participation questionnaires in the Canadian Interphone study [30]. In this study, the OR changed from 1.0 (95% CI 0.7–1.5) and 2.0 (95% CI 1.2–3.4) to 1.1 (95% CI 0.7–1.6) and 2.2 (95% CI 1.3–4.1) for regular users and cumulative hours of use over 558 h, respectively, for glioma. The OR changed from 1.3 (95% CI 0.8-2.0) and 1.0 (95% CI 0.4–2.4) to 1.4 (95% CI 0.8–2.2) and 1.4 (95% CI 0.5–3.6) for regular users and cumulative hours of use over 558 h, respectively, for meningioma. The OR changed from 0.7 (95% CI 0.4–1.2) and 0.7 (95% CI 0.3–1.6) to 0.7 (95% CI 0.4–1.2) and 0.7 (95% CI 0.3–1.8) for regular users and cumulative hours of use over 558 h, respectively, for acoustic neuroma. Based on these results, Momoli et al. concluded that adjustments for selection and recall biases did not materially affect the interpretation of results.

Vrijheid et al. re-analyzed the results of the Interphone study, considering possible recall errors and selection bias [31]. In this study, most results showed that the original results could have been underestimated under varying scenarios of recall errors and selection bias, except for when selection bias resulting from underselection of unexposed controls applied.

Conclusion

In this meta-analysis, as the applied exposure subcategories became more concrete, the pooled ORs showed more increased values with statistical significance. Even though the meta-analysis of cohort studies showed statistically equivocal pooled effect estimates, (i) as the number of included studies increases and (ii) as the applied exposure subcategory becomes more concrete, the pooled RRs could show a different aspect in future studies. Furthermore, changing patterns of mobile phone use and increasing use of earphones or headphones with WPAN technology should be sufficiently considered in future studies. Relatively short observation spans for brain tumor incidence and age of starting exposure and brain tumor diagnosis should also be considered in future studies. Previous studies that adjusted for selection and recall bias for the amount of cellphone use and misclassification and recall bias for ipsilateral/contralateral use showed possible underestimations of previous risk estimates. Future studies should try to adjust for these biases in their study design.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-024-01117-8.

Supplementary Material 1

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Author contributions

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Data availability
This research is a meta-analysis. Therefore, anyone can find the data used in the included individual research paper.

Declarations

Competing interests
The authors declare no competing interests.

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