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Brain and Salivary Gland Tumors and Mobile Phone Use: Evaluating the Evidence from Various Epidemiological Study Designs

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Abstract

Mobile phones (MPs) are the most relevant source of radiofrequency electromagnetic field (RF-EMF) exposure to the brain and the salivary gland. Whether this exposure implies a cancer risk has been addressed in several case-control and few cohort studies. A meta-analysis of these studies does not show increased risks for meningioma, pituitary, and salivary gland tumors. For glioma and acoustic neuroma, the results are heterogeneous, with few case-control studies reporting substantially increased risks.

However, these elevated risks are not coherent with observed incidence time trends, which are considered informative for this specific topic owing to the steep increase in MP use, the availability of virtually complete cancer registry data from many countries, and the limited number of known competing environmental risk factors. In conclusion, epidemiological studies do not suggest increased brain or salivary gland tumor risk with MP use, although some uncertainty remains regarding long latency periods (>15 years), rare brain tumor subtypes, and MP usage during childhood.

INTRODUCTION

Exposures from Mobile Phones

The first cellular network (1G) introduced in 1979 in Japan and in 1981 in the Nordic countries used mobile phones (MPs) with antennae mounted on a car or a bag. Handheld MPs with antennae on the handset were introduced in 1983 in the United States and in 1987 in the Nordic countries. With the deployment of the Global System of Mobile Communication (GSM, 2G) in the early 1990s, the number of MP subscribers started to increase steeply, reaching a penetration rate of 50% in Europe in 2000, in the United States in 2005, in developing countries in 2008, and even in the least developed countries in 2010 (54). The overall number of MP subscriptions exceeded the worldwide population in 2016 (54).

Second-, third-, and fourth-generation MPs and cordless phones emit radiofrequency electromagnetic fields (RF-EMF) in the frequency range of 700–2,700 MHz, and 5G is expected to use the frequency spectrum up to 80 GHz. Wireless phones, i.e. MPs and cordless phones, used close to the body produce a near-field exposure situation, and the specific absorption rate (SAR, in W/kg tissue weight) is the most relevant exposure metric (48). In general, the SAR decreases with the square of the distance to the source. MPs are relatively strong transmitters because they have to reach longer distances than do other common RF-EMF sources [e.g., wireless local area networks (WLAN), cordless phones]. Thus, for MP users, the most significant exposure contribution to the brain arises from these devices when held to the head during voice calls (94). Exposure contributions from RF-EMF far-field sources such as WLANs, MP base stations, or broadcast transmitters to the brain and to the whole body are typically below 10% (32, 94).

Epidemiologic research on the carcinogenicity of RF-EMF has focused mainly on tumors developing in the head, in which organs and tissues are more exposed than other parts of the body. For earlier studies of MP use, cumulative call time was shown to be a good predictor of exposure (12, 117), but the validity of this exposure proxy lessened with more recent applications (61) and technologies. The main reason is the adaptive power control in response to the network quality, which has become very efficient for Universal Mobile Telecommunications System (UMTS, 3G) technology (34). Minimum emission levels of a UMTS phone used with optimal network quality can be more than 100,000 times lower than under the worst-case situation of bad network quality and maximum power emission. In real-world situations, the average output power differences between GSM calls and UMTS calls are between a factor of 100 and 500 (34, 83). Consequently, although the amount of MP use has increased over time as MP-related costs have decreased, cumulative RF-EMF exposure among people mainly using their phone in the UMTS era is expected to be considerably lower than in those with long durations of MP use in the GSM era, as well. Additional exposure uncertainty comes from the changing usage patterns: Users tend to hold the

phone to the head less frequently now, as compared with the early decades of MP use, but they attend to the screen more when using various phone applications.

Biological Plausibility for Carcinogenicity

Although MP batteries also produce extremely low-frequency electromagnetic fields (15), RF-EMF emissions are of more significant concern for potential health risk. Because RF-EMF belongs to the nonionizing part of the EMF spectrum, the photon energy is too weak to directly ionize molecules (18) and thereby cause direct DNA damage. Absorption of RF-EMF is known to heat biological tissue owing to its electrical conductivity. Apart from the thermal interaction, despite considerable research efforts, no other mechanism relevant for carcinogenesis has been consistently established (91). Oxidative stress was seen to be increased after RF-EMF in some in vitro and in vivo studies (23). However, no convincing evidence of changes in protein and gene expression induced by low-level RF-EMF was obtained from cell culture or rodent brain tissue experiments (68). In a pooled analysis of 15 in vitro and microarray studies of RF-EMF exposure, investigators observed no strong link to any known pathway of human diseases, including cancer (81).

Among the numerous animal studies conducted, some results indicated an increased cancer risk (31, 79) or tumor promotion in mice coexposed to carcinogenic chemicals (64, 111). The large-scale US National Toxicology Program (NTP) experiment investigated the carcinogenicity of lifetime exposure to RF-EMF in rats (79) and mice (78). Whole-body SAR values up to 6 W/kg were applied in rats and up to 10 W/kg in mice, which is far higher than the whole-body standard for the public (0.08 W/kg) but within the range of the regulatory limits for localized sources such as MP handsets for the public (2 W/kg) and for workers (10 W/kg) (48). For male rats, the NTP concluded that there is "clear evidence of tumors in the hearts of male rats" for the incidence of heart schwannoma, with 5 cases in the highest GSM exposure group and 6 cases in the highest CDMA (code-division multiple access) exposure versus 0 cases in the sham-exposed group. Further, they concluded "some evidence of tumors in the brains and in the adrenal glands of male rats." Only "equivocal evidence" of carcinogenicity was seen for all outcomes in female rats as well as in male and female mice. Thus, the observed carcinogenicity may be causal or a chance finding due to multiple testing. Alternatively, it may be the consequence of temperature-induced metabolic changes in male rats, where a measurable increase in core temperature was registered. The latter might also explain the unexpected significantly longer lifetime of exposed male rats compared with their sham controls.

Epidemiology of Intracranial and Salivary Gland Tumors

Intracranial tumors are rare diseases, with incidence rates below 10 per 100,000. They are a heterogeneous family of neoplasms, including tumors occurring in the brain, cerebral meninges, cranial nerves, and pituitary gland, with more than 100 histologically distinct types (87). Overall, the most frequently reported histology is meningioma (37%), followed by gliomas (25%), pituitary gland tumors (16%), and nerve sheath tumors (8%). The vast majority of nerve sheath tumors are vestibular schwannomas (also known as acoustic neuromas) (80).

Gliomas account for 70% of adult malignant primary brain tumors (92). The role of environmental factors in the etiology of glioma is not well understood (80, 90). High-dose ionizing radiation, as applied for cancer treatment, is an established risk factor (80, 90). Radiation risk decreases with age, and the observed median interval between exposure and diagnosis of a radiation-induced glioma is between 9 and 18 years (69). The evidence concerning other exposures—such as

smoking and other lifestyle factors, organic chemicals, N-nitroso compounds including passive smoking, pesticides, extremely-low-frequency magnetic fields, and estrogen-only menopausal hormone therapy—is too inconsistent to ascribe causation (9, 21, 80, 90).

Also poorly understood is the etiology of meningioma, a slow-growing, mostly benign tumor originating from the meninges. High-dose ionizing radiation is a causal factor for meningioma, with a median latency period ranging between 17 and 23 years (69). Meningioma is much more common in women than men (ratio about 2:1), whereas glioma is somewhat more common in men.

Acoustic neuroma is a slow-growing benign tumor of the myelin-forming cells of the VIII cranial nerve. Apart from the inherited disorder neurofibromatosis type 2 and high-dose radiation, no other risk factors are clearly established, although chronic noise exposure is suspected to be a risk factor (20). Tumors of the pituitary gland are usually benign neoplasms, and the most common histological type is pituitary adenoma (77). Salivary gland tumors include neoplasms of the parotid and of other salivary glands. Most salivary neoplasms are benign (70). Epidemiological research on the etiology of childhood CNS tumors came to similar conclusions as did studies on CNS tumors in adults, with no established environmental factors other than high-dose ionizing radiation (86).

STRENGTHS AND LIMITATIONS OF EPIDEMIOLOGICAL STUDY DESIGNS IN THIS RESEARCH CONTEXT

Case-Control Studies

In a case-control study, a group of individuals with the disease under investigation (cases) and a group of subjects without the disease (controls) are compared with respect to the exposure of interest. A crucial aspect of this study design is the selection of controls, which provides information about the exposure distribution in the population from which the cases arose without introducing selection bias. Selection bias may occur in case-control studies if not everybody who was initially sampled is willing to participate and if willingness to participate is related to both exposure and case-control status (95). Nonparticipation validation studies in the Interphone study, for example, found that non-MP users were less likely to participate than were MP users and that participation in controls was lower than in cases (51, 73); as a consequence, prevalence of MP use was more overestimated in controls than in cases, resulting in a downward bias of approximately 10% (118). Bias (in both directions) can be introduced if cases and controls differ in the completeness of answers to questions in interviews or questionnaires.

By design, in a case-control study, exposure information must be collected retrospectively, after identification of cases and controls. In case-control studies on MP use, this data collection has been done almost exclusively by self-completed questionnaires or interviews, which allows investigators to obtain detailed information about MP use histories and confounding factors. However, for both cases and controls, participants have found it very difficult to accurately recall MP use habits from many years prior, and misclassification inevitably occurs, as demonstrated in several validation studies (3, 35, 53, 56, 72, 82, 104, 112, 115). Misclassification entirely independent of the case status, i.e., nondifferential, usually leads to a dilution of the risk estimates toward unity. There is also evidence of systematic misclassification; light users tended to underestimate, and heavy users tended to overestimate, their amount of phone use (35, 116); this tendency, although nondifferential between cases and controls, would lead to an inflation of any association.

Additionally, some researchers are concerned that the disease affects the reporting of the exposure, resulting in recall bias. Cases may overestimate their previous MP use as a potential cause

of their disease, whereas controls may not have thought much about past MP use and will thus underestimate it. If cases overestimate, and/or controls underestimate, exposure, an overestimation of the risk or a spurious association will occur. The determination that this type of differential exposure misclassification is indeed relevant comes from a validation study, in which cases tended to overestimate their MP use further back in time; this behavior was not observed among controls (114). Indication for recall bias may also be derived from a Swedish study that included cases diagnosed between 2007 and 2009 (34). In this study, the proportion of MP users reporting to have started to use analog or digital MPs before the corresponding technology was actually implemented was significantly higher in cases than in controls.

One particular challenge is the reporting of the side of the head predominantly used for calling. A recent validation study in young people aged between 10 and 24 years from 12 countries demonstrated that correlation between self-reported and app-recorded side of use was moderate for right side users and almost nonexistent for left side users (35). For cases, retrospective assessment of the preferred head side for MP use may also be biased toward the side where a tumor occurred (101). In contrast, controls do not have any motivation to differently report the side of the head for making MP calls, which will ultimately produce a bias in laterality analyses (101).

Operator-recorded traffic data is assumed to be more reliable than self-reported MP use; some uncertainties remain, however, as people may use other phones or talk on voice-over-IP (e.g., Skype or WhatsApp), which is registered as data transfer and not counted as voice call duration. To date, only one case-control study on childhood brain tumors considered retrospectively collected operator-recorded MP use (5). When retrospectively collected, operator-recorded data have additional limitations: Not all operators retain traceable traffic data for long periods; the MP user may not be the subscriber, e.g., phones may be redistributed within families; and study participants may not remember their previous phone numbers, which are needed for record identification. The motivation to remember and share data from old subscriptions may depend on the case-control status, which could introduce bias.

Cohort Studies

Cohort studies start with a disease-free population and follow the cohort members over time for occurrence of the studied disease (or diseases), while the exposures of interest are collected at baseline and ideally on a continual basis during the follow-up period. Comparability between exposed and unexposed must be ensured, e.g., through control of confounding. Selection bias is usually not a problem in cohort studies, but it is crucial to have mechanisms in place for follow-up of the cohort members. Otherwise, if loss to follow-up is related to exposure status, bias might be introduced. For cancer outcomes that are usually rare, the cohort needs to be very large, which often leads to the collection of less detailed exposure information than in case-control studies. Too crude exposure information may hamper the ability to detect effects restricted to small subgroups with specific exposure characteristics. Only a few cohort studies on tumors of the head and wireless phone use have been conducted so far (10, 11, 30, 33, 103, 105), and a large international study (COSMOS) is still ongoing (102, 112). Some of the cohort studies have used only register-based exposure information, with few details about MP use. In contrast, other studies have used self-reported information about MP use at baseline, which may change over time and is thus subject to nondifferential exposure misclassification and may yield a bias toward the null in the case of a true association. An important difference compared with case-control studies is that when exposure information is collected before the occurrence of the disease, the likelihood of differential exposure misclassification, i.e., recall bias, is minimized.

Ecological Studies

In an ecological study, disease incidence or prevalence is compared in space and/or over time. Data are usually retrieved from routine statistics, such as cancer registers. Such comparisons of aggregated data are often affected by confounding or ecological fallacy (95), and thus ecological studies are usually considered weak and useful only for hypothesis generation. For the specific question of carcinogenicity of MP use, analyses of cancer incidence time trends may be valuable for several reasons.

First, prior to the MP era, RF-EMF exposure of the head was negligible except for a few specific working environments; this level of exposure has changed dramatically since the mid-1990s. If indeed MP use will increase the risk of developing a tumor, the corresponding cancer incidence rates worldwide should have increased substantially, unless compensated by just as sudden changes in exposures to other, currently unknown, strong protective or risk factors for head tumors. Second, such analyses do not need individual and complex exposure assessment because they capitalize from the marked change in exposure on the population level. MP use spread very distinctly in different age and sex groups; i.e., measurable incidence increases should be seen first and be stronger in men compared with women and among those who were in their 30s to 50s when MP technology began to be used more frequently. Third, time trends of incidence are not prone to participation bias as seen in case-control studies.

A prerequisite for an evaluation of time trends of tumors of the head is the availability of high-quality registry data with virtually complete tumor registration over long time periods. Moreover, one must take into consideration that incidence rates of many brain tumors have been increasing in many countries since the introduction and more frequent use of magnetic resonance imaging and computer tomography (71). However, this rise began in the 1980s before MP use had become widely prevalent. Similarly, changes over time in the registration of benign intracranial tumors (67), in histology coding practice due to improved diagnostics, or in the population acceptance rate for autopsy will affect incidence rates of brain tumor subtypes. These caveats should be considered when interpreting incidence time trends, but such studies are nevertheless informative for hazard identification in this specific context.

Case-Case Studies

Radiofrequency exposure during MP use is highly localized and declines rapidly with distance from the exposure source. The energy absorption reaches only a few centimeters into the brain. Thus, tumors in MP users, if directly caused by the RF-EMF, would be expected to be located more often close to the exposure source. A few case-case studies have been conducted to test this hypothesis using different methods.

A case-case analysis may reduce various types of biases, in particular control-selection bias. However, depending on the method applied, bias may be introduced owing to underlying assumptions about the spatial distribution of tumors in the head. In addition, recall bias may be of concern if some of the exposure information used in such analyses is collected retrospectively by interview or questionnaire.

STUDY RESULTS

In the following section, we present an overview of study results on MP use and risk of intracranial and salivary gland tumors, including a meta-analysis of case-control and cohort studies published up to December 31, 2017. Meta risk (mRR) estimates are shown for "ever versus never use"

and "long-term use" (i.e., time since first use of at least 10 years). For multicountry studies [i.e., Interphone (51, 52)] or studies of the same protocol but in different phases [i.e., Swedish Örebro (40, 46)], inclusion in the meta-analyses was restricted to the most comprehensive analyses (for details, see **Supplemental Data**).

Supplemental Material >

Glioma

Glioma is the most frequently studied type of tumor in relation to MP use (25 case-control and 3 cohort studies on adults; **Supplemental Data**). Some investigations involved shared populations; therefore, the meta-analysis was restricted to 12 unique, nonoverlapping studies (2, 7, 11, 22, 33, 40, 46, 50, 51, 74, 109, 120). The Interphone international analysis (51) and the Swedish Örebro study (40, 46) contribute most of the cases.

On the basis of 4,197 exposed glioma cases, an mRR of 1.00 [95% confidence interval (CI) 0.89–1.13] was obtained for ever users compared with nonusers with substantial heterogeneity across studies ($I^2 = 60\%, p = 0.003$) (**Supplemental Figure 1**). Two studies reported a statistically significantly decreased glioma risk (11, 51), and two studies demonstrated increased risks (2, 40).

The mRR for long-term use (>10 years) was nonsignificantly elevated (mRR = 1.11, 0.85–1.46) on the basis of 1,018 exposed cases (**Figure 1**) with considerable heterogeneity across studies ($I^2 = 82\%$, $p < 0.001$). One cohort study reported a significantly decreased odds ratio (OR) of 0.77 (0.62–0.96) (11) and one case-control study reported an increased OR of 1.69 (1.40–2.03), which is the pooled estimate of all latency categories >10 years presented in Hardell & Carlberg (40). **Supplemental Figure 2** shows the glioma risk in relation to cumulative duration of MP use. In 4 out of 7 studies, investigators observed a significant increased risk in the highest category of MP use: >896 h (OR = 2.89, 1.41–5.93) in the French study (22), >1,640 h (OR = 1.40, 1.03–1.89) in Interphone (51), and >2,001 and >2,377 h (OR = 3.7, 1.7–7.7 and OR = 2.8, 1.6–4.8) in the two Swedish studies, respectively (41, 43). No upward trend in OR with increasing cutoffs of the highest exposure category is derivable from these estimates.

To check the implications of a potential glioma risk from MP use, several studies have assessed how much the incidence of glioma or brain cancer would increase over time under various risk and latency time scenarios. The incidence time trends in the United States (66), the Nordic countries (26, 27), and Australia (19) are not consistent with substantially increased risk from MP use as observed in some of the studies in **Figure 1**. A comprehensive analysis of global trends in brain and CNS tumors, including data from 1993 to 2007 from 96 registries in 39 countries, did not find an overall pattern supporting the hypothesis of increasing incidence rates following, with some latency, the time period of MP uptake in different populations, as outlined in the first paragraph of this article (71). Increases in brain cancer incidences over time were observed in some studies. However, in most instances the increase did not follow the dissemination of MPs but rather started earlier (28, 57, 76, 98) or was limited to the elderly (29, 55, 93), among whom MP use was uncommon until recently. In other publications, the increase was limited to specific topographic or morphologic subtypes of brain cancer and compensated by a decrease in complementary diagnoses, as seen in Israel (8), England (24, 85), Sweden (39), or the United States (65). Thus, the findings may be explained by changes in the availability of information and coding practices, particularly related to brain and CNS tumors of unknown type (D43) and brain cancers with unknown intracerebral location (ICD-O-3 code C71.9) or morphology (e.g., glioma malignant NOS, ICD-O-3 code 9380) (1, 58).

A case-case analysis of a subset of Interphone data from 7 European countries was performed to assess whether gliomas of 888 cases occurred more often in brain areas closest (<5 cm) to a MP held to the ear and areas most exposed to RF-EMF emitted by the device (63). However, no such

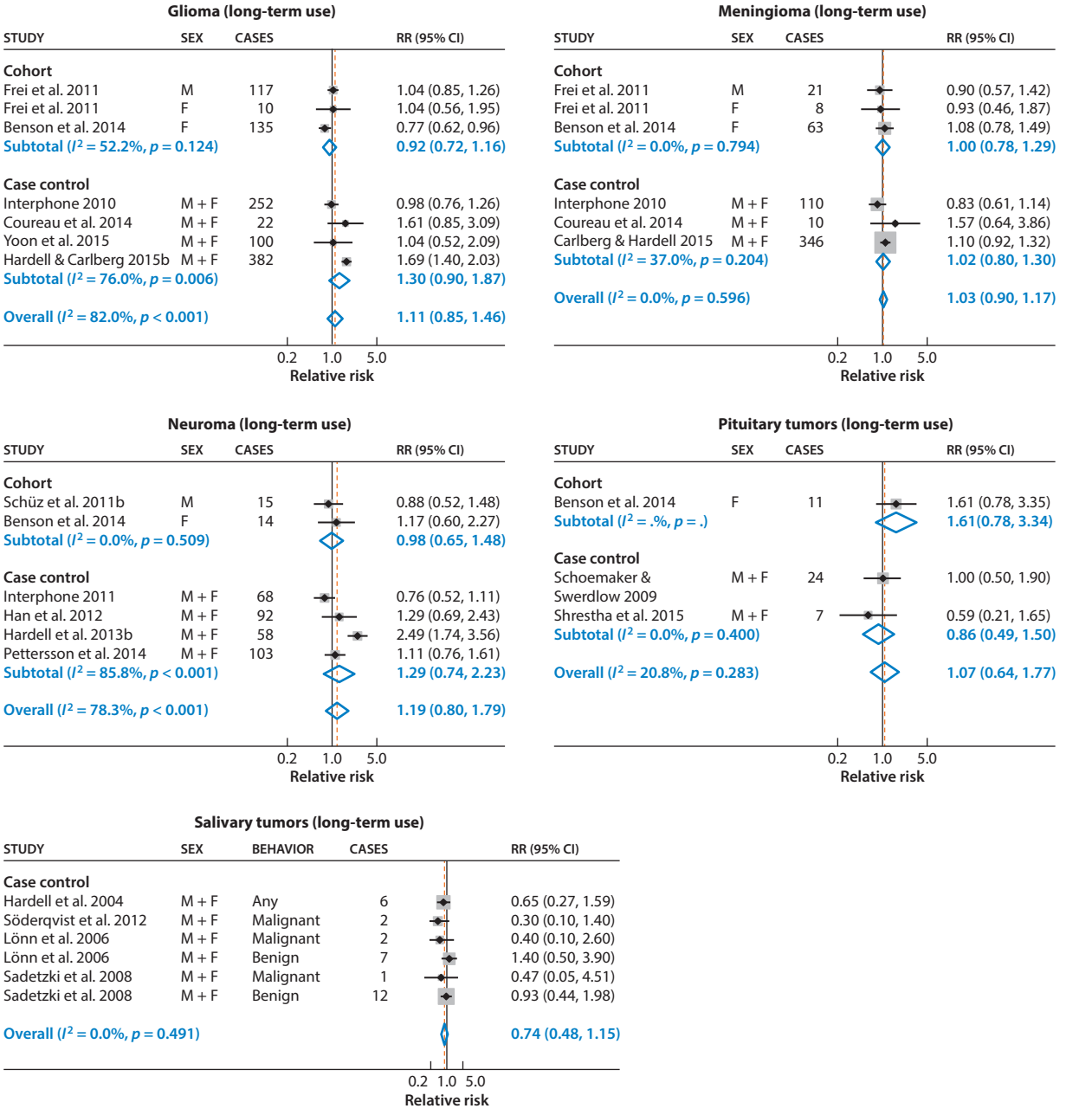

Figure 1

Meta-analyses of tumors of the head and long-term (>10 years) mobile phone use. Note, odds ratios for Hardell & Carlberg 2015 (40) (glioma) and Hardell et al. 2013 (44) (neuroma) have been derived by pooling their odds ratios of all latency categories >10 years for mobile phone use. The orange dashed line represents the mean meta risk (mRR) of all studies of the corresponding graph. Where only one study is shown, no measure of heterogeneity can be provided. Abbreviations: CI, confidence interval; F, female; I^2, percentage of variation across studies that is due to heterogeneity rather than chance; M, male; p, p-value of the heterogeneity test; RR, relative risk.

pattern was found, and the mean distance between tumor midpoint and the phone axis at the ear was similar among regular MP users and never or nonregular users. This study did not use any of the self-reported exposure data except usage status and is therefore unlikely to be affected by recall bias, although nondifferential exposure misclassification cannot be avoided. In an additional case-case study of a subset of Interphone data from five other countries, the duration and amount of MP use among people with tumors in highly exposed areas of the brain were compared with the corresponding characteristics in patients with tumors located in other parts of the brain (16). On the basis of 11 exposed cases, this study found some indications that people with gliomas in the most exposed brain areas are more likely to be long-term MP users. Self-reported duration of use in this paper may be subject to recall bias for more distant use, as indicated in an Interphone validation study (114). In another analysis of 792 gliomas from the Interphone study, investigators observed a statistically significant association between the intracranial distribution of gliomas and the self-reported location of the phone (36). However, as acknowledged by the authors, this type of analysis is potentially influenced by recall bias with respect to the laterality of MP use.

Meningioma

Overall, 18 case-control studies and 2 cohort studies on meningioma have been conducted (see **Supplemental Data**). In the meta-analysis of 9 unique, nonoverlapping studies with a total of 2,686 exposed cases (2, 7, 11, 17, 22, 33, 46, 50, 51) ever use of MP was inversely associated with meningioma risk (mRR = 0.91; 95% CI 0.84–0.98) (**Supplemental Figure 1**) and not associated with long-term use of >10 years (mRR = 1.03, 0.90–1.17) on the basis of 558 exposed cases, with no heterogeneity between studies in both meta-analyses (**Figure 1**). In a French study (22), cumulative duration of >896 h resulted in an OR of 2.57 (1.02 to 6.44), and in a Swedish study >1,486 h of cumulative MP use yielded an OR of 1.3 (1.1–1.6). In the Interphone study, meningioma risk for >1,640 h of cumulative MP use was not significantly elevated [OR = 1.15 (0.81–1.62)]. The few published time trend analyses do not indicate an increased incidence among men since the introduction of MP, whereas an increase in meningioma incidence in women started before the introduction of MP (27). The only case-case study to date did not observe that MP use was more common in people with a meningioma in the most exposed brain regions (16).

Supplemental Material >

Acoustic Neuroma

Nineteen case-control studies and 2 cohort studies on acoustic neuroma have been conducted, and 11 studies with 1,546 exposed cases were included in the meta-analysis (see **Supplemental Data**). The pattern of results is similar to that observed for glioma. Neither ever MP use (mRR = 1.02, 95% CI 0.84–1.24, number of exposed cases: 1,546) (**Supplemental Figure 1**) nor long-term use (mRR = 1.19, 0.80–1.79, n = 350) (**Figure 1**) was associated with acoustic neuroma risk. The heterogeneity across studies is substantial in both meta-analyses. In relation to the cumulative duration of MP use, four studies found increased risk estimates for the highest usage category, although the estimates were not always statistically significant (**Supplemental Figure 3**): >680 h (OR = 1.46, 0.98–2.17), >1,001 h (OR = 3.1, 1.5–6.4), >1,487 h (OR = 2.6, 1.5–4.4) in three Swedish studies (42, 44, 84), and >1,640 h (OR = 1.32, 0.88–1. 97) in Interphone (52). Like for glioma, no upward trend in OR with increasing cutoffs was seen.

Sparse data available on trends in acoustic neuroma incidence do not indicate an increase since MP use became widespread (62, 75). A case-case analysis of 787 acoustic neuroma cases from Japan found some indication of increased risk for ipsilateral use (97), in particular among heavy users (>20 min/day). Cases with ipsilateral frequent use were found to have tumors with smaller

diameters, which may suggest a detection bias because hearing capacity decreases with progressing disease. Thus, people using the ear with the tumor may realize sooner that they might have a unilateral hearing loss. Such detection bias would explain the seeming association between the side of MP use and occurrence of the tumor. A Swedish case-control study also indicated that laterality analysis for this specific type of tumor could be biased (84).

Pituitary Tumors

Only 4 case-control studies (45, 100, 106, 110) and 1 cohort study (10) addressed the risk of pituitary tumor from MP use, contributing 375 exposed cases to the meta-analysis. Overall, ever use of MPs was not associated with pituitary tumor risk (mRR = 0.86; 95% CI 0.56–1.31), although between-study heterogeneity was high (**Supplemental Figure 1**). Risk for long-term use was 1.07 (0.65–1.77) on the basis of 3 studies with 42 exposed cases (**Figure 1**).

Supplemental Material >

Salivary Gland Tumors

Seven case-control studies and one cohort study on the risk of salivary gland tumors were included in the meta-analysis. On the basis of 657 exposed benign or malignant salivary gland tumor cases, no risk increase (mRR = 0.92, 0.80–1.06) among ever MP users was observed (**Supplemental Figure 1**), with little heterogeneity between studies. Similarly, there was no indication of a long-term risk (mRR = 0.74, 0.48–1.15) (**Figure 1**). No increase in incidence of malignant parotid gland tumors was observed in Swedish and Nordic adults between 1970 and 2009 (107).

Childhood Brain Tumors

So far, results on the association between wireless phone use and childhood brain tumors in children and adolescents are available from only one case-control study. Participants were aged 7–19 years and diagnosed with a brain tumor between 2004 and 2008 in Denmark, Norway, Sweden, and Switzerland (CEFALO study) (5). Overall, the results of the CEFALO study do not suggest a causal association because the brain tumor risk was not elevated in brain regions that are most exposed when using a MP, and no consistent exposure–response association was observed in relation to several self-reported and operator-recorded exposure measures, despite some sporadic statistically significant associations. Another study in 10- to 24-year-old individuals (MOBI-Kids) is ongoing (96).

Notable increases in astrocytoma risk among persons who started to use wireless phones before age 20 years (fivefold for MP and fourfold for cordless phones) were observed in a Swedish case-control study (38). Now, most young adults have started to use MPs before the age of 20, and therefore risks of such magnitude are not compatible with incident time trends in Sweden or other countries for this age group (26, 66). Other case-control studies have not found increased risks in the youngest age group (60).

A time trend study of brain tumor incidence in children and adolescents (5 to 19 years) found decreasing rather than increasing rates between 2000 and 2008 in Sweden (4). Stable trends were observed in the Nordic countries for children aged 0–10 years between 1985 and 2006 (99) and for individuals aged 5–19 years between 1990 and 2008 (108), in England among individuals aged 10–20 years between 1998 and 2007 (25), in Australia for individuals aged 0–19 years between 2000 and 2008 (29), and in the United States for individuals aged 0–19 years between 1977 and 2006 (49) and for those aged 5–19 years between 1990 and 2007 (13).

DISCUSSION AND CONCLUSION

In 2011, the IARC (International Agency for Research on Cancer) classified RF-EMF as "possibly carcinogenic to humans" (Group 2B) based on limited evidence in humans and in experimental animals (6, 47). The epidemiology IARC Working Group based their evaluation mainly on findings from the Interphone and Swedish Örebro case-control studies of glioma and acoustic neuroma and stated, "While both of these are susceptible to bias, the Working Group concluded that these findings could not be dismissed as reflecting bias alone, and that a causal interpretation was possible" (47, p. 410). Since then, several new studies or study updates have been conducted (see cumulative meta-analysis in **Supplemental Figure 4**). In our meta-analysis of long-term MP users, no indication emerged for an increased risk of meningioma, pituitary, and salivary gland tumors, whereas meta-estimates of glioma and acoustic neuroma risk were slightly above 1, with confidence intervals including the null effect (**Figure 1**) and considerable across-study heterogeneity. A sensitivity analysis using different data sets of unique and nonoverlapping studies shows that our findings are robust to the choice of data set as long as they do not overlap (**Supplemental Figure 5**). The observed absence of risk is in line with earlier meta-analyses (59, 91), whereas some recent meta-analyses reported significantly increased brain tumor risk from long-term MP use (14, 88, 119). However, they paid less attention to avoid multiple counting of the same individual data or combined different disease entities.

Supplemental Material >

In light of the inconsistent epidemiological study results for glioma and acoustic neuroma, the most relevant question is whether some of the studies showing no association missed a true risk or whether some of the studies showing an association are, in fact, falsely positive. The risk might have been underestimated owing to nondifferential exposure misclassification, in particular by the cohort studies lacking detailed exposure information, relying on subscriber status before a given time point (33), or relying on answers to a few basic questions on how often (daily versus less often) and how long a MP had been used (10). This misclassification is expected to dilute any exposure–response relation if there is a true association. The ongoing COSMOS study is collecting operator data prospectively and will not suffer from this type of bias (102). In case-control studies, bias to null from substantial nondifferential exposure misclassification may overcompensate some recall bias (73, 116). Thus, it is theoretically conceivable that a real risk went undetected.

However, the mRR estimates of glioma and acoustic neuroma in long-term users were driven mainly by the pooled Örebro studies with average ORs for all MP latency categories >10 years of 1.69 (1.40–2.03) for glioma (40) and of 2.49 (1.74–3.56) for acoustic neuroma (44). Simple calculations demonstrate that such excess risks would not have been unnoticed in clinical practice by now. The populations from the Nordic countries were among the first to use MPs regularly, and a 50% penetration rate was achieved in Europe in 2000. Now, in Sweden substantially more than 50% of the population is a long-term MP user, and an excess glioma risk on the order of 60–70% would yield an increase of at least 30% in glioma incidence rates, which has not been observed in Swedish people aged <70 years (**Supplemental Figure 6**). An observed excess risk of about 150% for acoustic neuroma would produce an even stronger increase in incidence rates. Published time trend analyses do not indicate any noticeable increase in brain tumor incidence since the introduction of MPs. Nevertheless, these studies cannot prove the absence of risk, as they are not sensitive to small increases in incidence of rare histologic subtypes. Current time trend analyses would not yet pick up a risk increase occurring at latency periods of more than 15–20 years. However, assuming a similar latency for nonionizing radiation as observed for ionizing radiation, one would expect that any relevant risk should already have started to emerge by now (26, 66, 71, 98).

These inconsistencies should encourage investigators to revisit those case-control studies with significant excess risk to investigate what design or conduct feature led to the overestimation of risk. False-positive findings could be produced by recall bias, as discussed above. Thus, a comparison of the exposure distribution in the controls with public statistics is another cross-check to evaluate the plausibility of self-reported MP use. In the four Örebro case-control studies including cases diagnosed between 1994–2003 and 2007–2009, the proportion of MP users in controls has not increased at the same pace as in the Swedish population according to the Swedish Post and Telecom Agency (89). Because of the rapid uptake of MP use over time, it is important that MP exposure is evaluated up to the same calendar period for cases and controls in order to avoid bias (113).

Recall bias is also a likely explanation for the increased risk for ipsilateral use observed in some studies because in these studies contralateral use tended to be protective, which is biologically implausible (101). For acoustic neuroma, this type of analysis is particularly vulnerable to bias owing to potential diagnostic detection bias.

In summary, current evidence from all available studies including in vitro, in vivo, and epidemiological studies does not indicate an association between MP use and tumors developing from the most exposed organs and tissues. Given the large amount of research on this topic, any potentially undetected risk is expected to be small from an individual perspective and might concern long latency periods (>15 years), rare brain tumor subtypes, and MP usage during childhood. To address such small risks, high-quality research with accurate exposure assessment is needed, taking into account that MP call duration alone is not expected to adequately reflect RF-EMF exposure to the brain.

DISCLOSURE STATEMENT

M.F. is vice chairman of the International Commission on Non-Ionizing Radiation Protection, an independent body setting guidelines for nonionizing radiation protection. She has served as advisor to a number of national and international public advisory and research steering groups concerning the potential health effects of exposure to nonionizing radiation, including the World Health Organization. M.R. is a member of the International Commission on Non-Ionizing Radiation Protection. From 2011 to 2018, M.R. was an unpaid member of the foundation board of the Swiss Research Foundation for Electricity and Mobile Communication, a non-profit research foundation at ETH Zurich. Neither industry nor nongovernmental organizations are represented on the scientific board of the foundation.

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