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# Brain and salivary gland tumours and mobile phone use: evaluating the evidence from various epidemiological study designs

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**ABSTRACT**

Mobile phones (MP) are the most relevant source of radiofrequency electromagnetic fields (RF-EMF) exposure of the brain and the salivary gland. Whether this 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 tumours. For glioma and acoustic neuroma 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 due 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 tumour risk with MP use although some uncertainty remains regarding long latency period (>15 year), rare brain tumour subtypes and MP usage during childhood.

## INTRODUCTION

### *Exposures from mobile phones*

The first cellular network (1G) introduced in 1979 in Japan and 1981 in the Nordic countries used mobile phones (MP) with antennae mounted on a car or a bag. Handheld MP with antennae on the handset were introduced 1983 in the US and 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 US in 2005, in developing countries in 2008, and even in the least developed countries in 2010 (53). The overall number of MP subscriptions exceeded the worldwide population in 2016 (53).

Cordless phones and MP of the 2$^{nd}$ to 4$^{th}$ generation emit radiofrequency electromagnetic fields (RF-EMF) in the frequency range of 700 to 2,700 MHz and 5G is expected to use the frequency spectrum up to 80 GHz. Wireless phones and other devices which are 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 (47). In general, the SAR decreases with the square of the distance to the source. MPs are relatively strong transmitters since they have to reach longer distances than other common RF-EMF sources (e.g. W-LAN, cordless phones). As a consequence, for users of MPs, the far largest exposure contribution to the brain arises from these devices when held to the head during voice calls (92). Contributions from RF-EMF far-field sources such as W-LANs (wireless local area networks), MP base stations or broadcast transmitters to the brain and to the whole body exposure is typically below 10% (32, 92).

Since the head is the most exposed body part, epidemiologic research on the carcinogenicity of RF-EMF has mainly focused on tumours developing in these most exposed organs and tissues using cordless and/or MP use as a proxy for RF-EMF exposure. For earlier studies of MP use,

cumulative call time was shown to be a good predictor of exposure (12, 115), but the validity of this proxy lessened with more recent applications (60) and technologies. The main reason is the adaptive power control in response to the network quality, which has become very efficient for UMTS (3G) technology (34). Minimum emission levels of an UMTS phone used with optimal network quality can be more than 100,000 times lower than under worst case situation. In real use situations average output power differences between GSM and UMTS calls are between a factor of 100 to 500 (34, 81). Consequently, although the amount of use increased over time as MP use has become less costly, 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 use durations already in the GSM era. Additional exposure uncertainty comes from the changing usage patterns with holding the phone less frequently to the head but watching the screen when using various phone applications.

***Biological plausibility for carcinogenicity***

Although the battery of MP also produces extremely low frequency electromagnetic fields (15) emissions of RF-EMF are mostly of concern for potential health risk. Since RF-EMF belongs to the non-ionizing 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 due to its electrical conductivity. Apart from the thermal interaction, despite considerable research efforts, no other mechanism relevant for carcinogenesis has been consistently established (89). 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 (66). In a pooled analysis of 15 in vitro and microarrays studies of RF EMF

exposure, no strong link to any known pathway of human diseases, including cancer was observed (79).

Among the numerous animal studies conducted, some indicated an increased cancer risk (31, 77) or tumour promotion in mice co-exposed to carcinogenic chemicals (63, 109). The large scale US National Toxicology Program experiment investigated the carcinogenicity of life-time exposure to RF-EMF in rats (77) and mice (76). 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 in the range of the regulatory limits for localized sources like MP handsets for the public (2 W/kg) and for workers (10 W/kg) (47). For male rats the NTP concluded that there is "some evidence of carcinogenic activity" for the incidence of heart schwannoma with 5 cases in the highest GSM exposure group and 6 cases in the highest CDMA exposure vs 0 cases in the sham-exposed group. No other tumour types were significantly associated with RF-EMF exposure ("no" or "equivocal evidence"). No or only equivocal evidence of carcinogenicity was seen for all outcomes in female rats as well as in male and female mice. Thus, apart from a causal link the observed carcinogenicity may be a chance finding due to multiple testing or the consequence of temperature-induced metabolic changes in male rats, where 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 tumours***

All tumours of interest are rare diseases, with incidence rates below 10 per 100,000. Intracranial tumours are a heterogeneous family of neoplasms including tumours occurring in the brain, cerebral meninges, cranial nerves and pituitary gland, with over 100 histologically distinct types (85). Overall, the most frequently reported histology is meningioma (37%), followed by gliomas

(25%), pituitary gland tumours (16%), and nerve sheath tumours (8%). The great majority of nerve sheath tumours are vestibular schwannomas (alias acoustic neuromas) (78).

Gliomas account for 70% of adult malignant primary brain tumours (90). The role of environmental factors in the aetiology of glioma is not well understood (78, 88). High-dose ionizing radiation, as applied for cancer treatment, is an established risk factor (78, 88). 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 (67). 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, estrogen-only menopausal hormone therapy, is too inconsistent to ascribe causation (9, 21, 78, 88).

Similarly poorly understood is the aetiology of meningioma, a slow-growing, mostly benign tumour originating from the meninges. High-dose ionising radiation is a causal factor for meningioma, with a median latency period ranging between 17 to 23 years (67). Meningioma is much more common in women than men (ratio about 2:1), while glioma is somewhat more common in men.

Acoustic neuroma is a slow-growing benign tumour of the myelin-forming cells of the VIII cranial nerve. Apart from the inherited disorder neurofibromatosis II and high-dose radiation, no other risk factors are clearly established, although chronic noise exposure is suspected to be a risk factor (20). Tumours of the pituitary gland are usually benign neoplasms, and the most common histological type is pituitary adenoma (75). Salivary gland tumours include neoplasms of the parotid and of other salivary glands. The majority of salivary neoplasms are benign (68).

Epidemiological research on the aetiology of childhood CNS tumours came to similar conclusions as for adult studies with no established environmental factors other than high-dose ionizing radiation (84).

## 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 providing 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 (93). Non-participation validation studies in the Interphone Study for example found that non-MP users were less likely to participate than MP users and that participation in controls was lower than in cases (50, 71); as a consequence prevalence of MP use was more overestimated in controls than in cases, resulting in a downward bias of approximately 10% (116). 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 has to be collected retrospectively, after identification of cases and controls. In case-control studies on MP use, this has been done almost exclusively by self-completed questionnaires or interviews. This allows collecting detailed information about MP use histories and confounding factors. However, for both cases and controls it has been shown to be very difficult to accurately recall MP use habits many years earlier, and misclassification inevitably occurred as demonstrated in several validation studies (3, 35, 52, 55, 70, 80, 102, 110, 113). Misclassification entirely independent of the case-status, i.e. non-differential, usually leads to a dilution of the risk estimates towards 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, 114), which – although non-differential between cases and controls – would lead to an inflation of any association.

Additionally, there is concern 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, while controls may not thought much about past MP use and thus underestimate it. If cases overestimate and/or controls underestimate exposure, an overestimation of the risk or a spurious association will occur. That such type of differential exposure misclassification is indeed relevant comes from a validation study, where cases tended to overestimate their MP use more the further back in time, which was not observed among controls (112). Indication for recall bias may also be derived from a Swedish study including cases diagnosed between 2007 and 2009 (34). In this study the proportion of MP users reporting to have started to use analogue or digital MP before the corresponding technology was actually implemented, was significantly higher in cases than controls.

A particular challenge is 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 non-existent for left side users (35). There is also indication that for cases the retrospective assessment of the preferred head-side for MP use, is biased towards the side where a tumour occurred (99). 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 (99).

Operator-recorded traffic data is assumed to be more reliable than self-reported MP use, although some uncertainties remain 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 tumours 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 is 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 is collected at baseline and ideally continuously 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 lead to 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 tumours of the head and wireless phone use have been conducted so far (10, 11, 30, 33, 101, 103) and a large international study (COSMOS) is still on-going (100, 103). Some of the cohort studies have only used register-based exposure information, with few details about MP use, while others have used self-reported information about MP use at baseline which may change over time and is thus subject to non-differential exposure misclassification yielding a bias towards the null in 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 minimised.

***Ecological studies***

In an ecological study, disease incidence or prevalence are compared in space and/or over time. Data is usually retrieved from routine statistics, such as cancer registers. Such comparisons of aggregated data are often affected by confounding or ecological fallacy (93), and thus ecological studies are usually considered as weak and only useful for hypotheses 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, and this has been dramatically changed since the mid-nineties. If indeed MP use will increase the risk of developing a tumour, the corresponding cancer incidence rates worldwide should have increased substantially, unless compensated by just as sudden changes in exposure to other, currently unknown, strong protective or risk factors for head tumours. Second, such analyses do not need individual and complex exposure assessment since they capitalize from the marked change in exposure on the population level. Actually, MP use spread very distinctly in different age and sex groups, i.e. measurable incidence increases should be first seen 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 like case-control studies.

A prerequisite for an evaluation of time trends of tumours of the head is the availability of high-quality registry data with virtually complete tumour registration over long time periods. Moreover, one has to take into consideration that incidence rates of many brain tumours have been increasing in many countries since the introduction and more frequent use of magnetic

resonance imaging and computer tomography (69). However, this rise started already in the 80ties before MP had become widely used. Similarly, changes over time in registration of benign intracranial tumors (65), in histology coding practice due to improved diagnostics or changes in the acceptance rate for autopsy in the population will affect incidence rates of brain tumour subtypes. Taking this caveat into consideration when interpreting incidence time trends, 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 centimetres into the brain. This means that tumours 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 due to underlying assumptions about the spatial distribution of tumours 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 an overview of study results on MP use and risk of intracranial and salivary gland tumours is presented, including a meta-analysis of case-control and cohort studies published up to 31 December 2017. Meta risk (mRR) estimates are shown for "ever *vs* never use" and "long-term use" (i.e., time since first use of at least 10 years). For multi-country studies (i.e. Interphone (50, 51)) or studies of the same protocol but in different phases (i.e. Swedish Örebro

(39, 45)), inclusion in the meta-analyses was restricted to the most comprehensive analyses (for details see online supplementary 1).

***Glioma***

Glioma is the most studied type of tumour in terms of MP use (26 case-control and 3 cohort studies on adults, see online supplementary 1). Some investigations involved shared populations; therefore the meta-analysis was restricted to 12 unique, non-overlapping studies (2, 7, 10, 22, 33, 39, 45, 49, 50, 72, 107, 118). The INTERPHONE international analysis (50) and the Swedish Örebro study (39, 45) contribute most of the cases.

Based on 4,197 exposed glioma cases, a mRR of 1.00 (95% CI 0.89-1.13) was obtained for ever users compared with non-users with substantial heterogeneity across studies ($I^2$=60%, p=0.003) (eFigure 1). Two studies reported a statistically significantly decreased glioma risk (10, 50), and two studies increased risks (2, 39).

The mRR for long-term use (>10 years) was non-significantly elevated (mRR=1.11, 0.85-1.46) based on 1,018 exposed cases (Figure 1) with considerable heterogeneity across studies ($I^2$=82%, p<0.001), with one cohort study reporting a significantly decreased OR of 0.77 (0.62-0.96) (10) and one case-control study an increased OR of 1.69 (1.40-2.03), which is the pooled estimate of all latency categories >10 years presented in (39). eFigure 2 shows the glioma risk in relation to cumulative duration of MP use. In four out of seven studies, a significant increased risk in the highest category of MP use was observed, which were >896 hours (OR=2.89, 1.41-5.93) in the French study (22), >1640 hours (OR=1.40, 1.03-1.89) in Interphone (50) and >2001 and >2377 hours (OR=3.7, 1.7-7.7 and OR=2.8, 1.6-4.8) in the two Swedish studies (41, 42). No upward trend of OR with increasing cut-offs 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 (64), 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 very comprehensive analysis of global trends of brain and central nervous system (CNS) tumours 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 paper (69). Increases of brain cancer incidences over time were observed in some studies. However, in most instances the increase did not follow the dissemination of MP but rather started earlier (28, 56, 74, 96) or was limited to the elderly (29, 54, 91) 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 of complementary diagnoses as seen in Israel (8), England (24, 83) or Sweden (38). This suggests that the findings may be explained by changes in availability of information and coding practices, particularly related to brain and CNS tumours 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, 57).

A case-case analysis of a subset of Interphone data from seven 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 most exposed to RF-EMF emitted by the device (62). However, no such pattern was found, and the mean distance between tumour midpoint and the phone axis at the ear was similar among regular MP users and never or non-regular 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 non-differential 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 mobile-phone use among people with tumours in highly exposed areas of the brain were compared with the corresponding characteristics in patients with tumours located in other parts of the brain (16). This study found some indications that people with gliomas in the most exposed brain areas are more likely to be long-term MP users based on eleven exposed cases. 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 (112). In another analysis of 792 gliomas from the Interphone study a statistically significant association between the intracranial distribution of gliomas and the self-reported location of the phone was observed (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, 19 case-control studies and 2 cohort studies on meningioma have been conducted (see online supplementary 1). In the meta-analysis of nine unique, non-overlapping studies with a total of 2,686 exposed cases (2, 7, 11, 17, 22, 33, 45, 49, 50) ever use of MP was inversely associated with meningioma risk (mRR=0.91; 95% CI 0.84-0.98) (eFigure 1) and not associated with long-term use of >10 years (mRR=1.03, 0.90-1.17) based on 558 exposed cases, with no heterogeneity between studies in both meta-analyses (Figure 1). In a French study (22) cumulative duration of >896 hours resulted in an OR of 2.57 (1.02 to 6.44) and in a Swedish study >1,486 h of cumulative mobile phone use yielded an OR of 1.3 (1.1-1.6). In Interphone meningioma risk for >1640 hours 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 increase 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).

***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 online supplementary 1). 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) (eFigure 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 cumulative duration of MP use, four studies found increased risk estimates for the highest usage category although not always statistical significant (eFigure 3): >680 hours (OR=1.46, 0.98-2.17), >1001 hours (OR=3.1, 1.5-6.4), >1487 hours (OR=2.6, 1.5-4.4) in three Swedish studies (40, 43, 82) and >1640 hours (OR=1.32, 0.88-1. 97) in Interphone (51). Like for glioma, no upward trend of OR with increasing cut-offs was seen.

Sparse data available on trends of acoustic neuroma incidence does not indicate an increase since MP use became widespread (61, 73). A case-case analysis of 787 acoustic neuroma cases from Japan found some indication of increased risk for ipsilateral use (95), in particular among heavy users (>20 min/day). Interestingly, cases with ipsilateral frequent use were found to have tumours with smaller diameters. This may suggest a detection bias since hearing capacity is decreasing with progressing disease. Thus, people using the ear with the tumour may realize earlier that they might have a unilateral hearing loss. Such detection bias would explain the seemingly association between side of MP use and occurrence of the tumour. Also a Swedish case-control study indicated that laterality analysis for this specific type of tumour could be biased (82).

***Pituitary tumours***

Only 5 case-control studies (11, 44, 98, 104, 108) and one cohort study (11) addressed the risk of pituitary tumour from MP use, contributing 375 exposed cases to the meta-analysis. Overall, ever use of MP was not associated with pituitary tumour risk (mRR=0.86; 95% CI 0.56-1.31), although between-study heterogeneity was high (eFigure 1). Risk for long-term use was 1.07 (0.65-1.77) based on three studies with 42 exposed cases (Figure 1).

***Salivary gland tumours***

Eleven case-control studies and one cohort study addressed the risk of salivary gland tumours. Based on 657 exposed benign or malignant salivary gland tumour cases, no risk increase (mRR=0.92, 0.80-1.06) among ever MP users was observed (eFigure 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 tumours was observed in Swedish and Nordic adults between 1970-2009 (105).

***Childhood brain tumours***

So far, results on the association between wireless phone use and childhood brain tumours in children and adolescents are available from only one case-control study. Participants were aged 7 to 19 years and diagnosed with a brain tumour 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 since the brain tumour 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 on-going (94).

Notable increases in astrocytoma risk among persons who started to use wireless phones before age 20 years (5-fold for MP, and a 4-fold for cordless phones) were observed in a Swedish case-

control study (37). Nowadays, a large majority of young adults has started MP use before the age of 20 and therefore risks of such a magnitude are not compatible with incident time trends in Sweden or other countries for this age group (26, 64). Other case-control studies have not found increased risks in the youngest age-group (59).

A time trend study of brain tumour 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 (97) and for 5 to 19 years old between 1990 and 2008 (106), in England among people aged 10–20 years between 1998 and 2007 (25), in Australia for 0-19 years old individuals between 2000 and 2008 (29) and in the United States for the age group 0 to 19 years between 1977–2006 (48) and for 5-19 years old persons between 1990 and 2007 (13).

## DISCUSSION AND CONCLUSION

In 2011 the IARC (International Agency for Research on Cancer) classified RF-EMF as "possibly carcinogenic based on limited evidence in humans and in experimental animals" (6, 46). The epidemiology Working Group based their evaluation mainly on findings from the Interphone and Swedish-Örebro case–control studies of glioma and acoustic neuroma, and stated (p. 410): "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." Since then several new studies or study-updates have been conducted (see cumulative meta-analysis in eFigure 4). In our meta-analysis of long-term MP users no indication for an increased risk of meningioma, pituitary and salivary gland tumours emerged, whereas meta-estimates of glioma and acoustic neuroma risk were slightly above one with confidence intervals including the null effect (Figure 1) and considerable across-study heterogeneity. A sensitivity analysis using different datasets of unique and non-overlapping studies shows that our findings

are robust to the choice of dataset as long as they are not overlapping (eFigure 5). The observed absence of risk is in line with earlier meta-analyses (58, 89), while some recent meta-analyses reported significantly increased brain tumour risk from long-term MP use (14, 86, 117). However, they paid less attention to avoid multiple counting of the same individual data or combined different disease entities.

In the 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 due to non-differential exposure misclassification, in particular by the cohort studies lacking detailed exposure information and relying on subscriber status before a given time point (33), or few basic questions on how often (daily *vs* less often), and how long a MP had been used (11). This is expected to dilute any exposure-response relation if there is a true association. The on-going COSMOS study is collecting operator data prospectively and will not suffer from this type of bias (100). In case-control studies also, bias to null from substantial non-differential exposure misclassification may over-compensate some recall bias (71, 114). Thus, it is theoretically conceivable that a real risk went undetected.

On the other hand, the mRR of glioma and acoustic neuroma in long-term users were mainly driven by the pooled Örebro studies with average ORs for all MP latency categories >10 years of 1.69 (1.40-2.03) for glioma (39) and of 2.49 (1.74-3.56) for acoustic neuroma (43). Simple calculations out of the pocket 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 regularly using MPs, and a 50% penetration rate was achieved in Europe in 2000. Nowadays in Sweden substantially more than 50% of the population is a long-term MP user, and an excess glioma risk in the order of 60-70% would yield an increase of at least 30% in glioma incidence

rates that has not been observed in Swedish people aged less than 70 years (eFigure 6). An observed excess risk of about 150% for acoustic neuroma would produce an even stronger increase in incidence rates. Published time trends analyses do not indicate any noticeable increase in brain tumour incidence since the introduction of MP. 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 non-ionizing radiation as observed for ionizing radiation, one would expect that any relevant risk should already have started to emerge by now (26, 64, 69, 96).

These inconsistencies should encourage re-visiting those case-control studies with large excess risk to investigate what design or conduct feature has led to this over-estimation 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 (87). 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 (111).

Recall bias is also a likely explanation for the increased risk for ipsilateral use observed in some studies as this was at least partly compensated by a decreased risk for contralateral use, which is biologically implausible (99). For acoustic neuroma, this type of analysis is particularly vulnerable to bias due 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 tumours 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 year), rare brain tumour 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.

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FIGURE CAPTIONS

**Figure 1:** Figure 1: Meta-analyses of tumours of the head and *long-term (>10 years)* mobile phone use.

Figure 1: Meta-analyses of tumours of the head and *long-term (>10 years)* mobile phone use. Note odds ratios for Hardell 2015 (glioma) and Hardell, 2013 (neuroma) have been derived by pooling their odds ratios of all latency categories >10 years for mobile phone use.