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Michael Kundi

doi: 10.1289/ehp.11902 (available at http://dx.doi.org/)
Online 26 September 2008

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National Institute of Environmental Health Sciences

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U.S. Department of Health and Human Services

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Michael Kundi

Institute of Environmental Health

Medical University of Vienna, Austria

Correspondence to:

Prof.Dr.Michael Kundi

Institute of Environmental Health

Medical University of Vienna

Kinderspitalgasse 15

1095 Vienna, Austria

Tel: +43-1-4277-64726

Fax: +43-1-4277-9647

Email: michael.kundi@meduniwien.ac.at

Running Title: Mobile Phones and Cancer

Key Words: acoustic neuroma; brain tumors; causation; epidemiology; glioma; meningioma; mobile phones; risk assessment

Abbreviations:

AM	Amplitude modulation
CAPI	Computer Assisted Personal Interview
EGFR	Epidermal Growth Factor Receptor
EMF	Electromagnetic Fields
GSM	Global System for Mobile Telecommunication
ITU	International Telecommunication Union
MP	Mobile Phone
NMT	Nordic Mobile Telecommunication
SAR	Specific Absorption Rate
SES	Socio Economic Status
UMTS	Universal Mobile Telecommunication System
WHO	World Health Organization

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Abstract

OBJECTIVE: During the last decade mobile phone use increased to almost hundred percent prevalence in many countries of the world. Evidence for potential health hazards accumulated in parallel by epidemiological investigations has raised controversies about the appropriate interpretation and the degree of bias and confounding responsible for reduced or increased risk estimates.

DATA SOURCES: Overall 33 epidemiological studies were identified in the peer reviewed literature most of which (25) were about brain tumors. Two groups of studies have collected data for 10 or more years of mobile phone use: the Hardell group from Sweden and the Interphone group, an international consortium from 13 countries coordinated by the International Agency for Research on Cancer.

DATA SYNTHESIS: Combined odds ratios from these studies for glioma, acoustic neuroma, and meningioma were 1.5 [95% CI: 1.2-1.8], 1.3 [0.95-1.9], and 1.1 [0.8-1.4], respectively.

CONCLUSIONS: Methodological considerations reveal that three important conditions for epidemiological studies to pick up an increased risk are not met: (1) no evidence based exposure metric is available; (2) the observed duration of mobile phone use is generally still too low; (3) no evidence based selection of endpoints among the grossly different types of neoplasias is possible due to lack of etiological hypotheses. Concerning risk estimates selection bias, misclassification bias, and effects of the disease on mobile phone use could have reduced estimates, recall bias may have led to spuriously increased risks. The overall evidence speaks in favor of an increased risk, but its magnitude cannot be assessed at present due to insufficient information on long-term use.

Introduction

Due to the enormous increase in mobile phone use starting in the mid 1990s and reaching almost 100% prevalence in many countries worldwide by now, concerns have been raised that even small risks to develop chronic diseases such as cancer from mobile phone use may have substantial impact on public health. In fact, never before in history any device of comparative prevalent use was associated with such high exposure to high-frequency electromagnetic fields (EMFs). (In addition, there is exposure to extremely low-frequency magnetic fields from battery discharge.) Although from the perspective of the thermal-effects paradigm the rate of energy deposition in tissues of the mobile phone user is below levels that are considered harmful, there is a debate since the 1930s that tissue heating may not be the only relevant effect elicited by exposure to high-frequency EMFs and hence there may be a relevant risk that has not been established yet due to the scarcity of exposure conditions that are comparable across a significant proportion of the population. Note that for all the diverse high-frequency exposures occurring in environmental and occupational settings ranging from long-waves (a type of AM broadcasting with carrier frequencies between 153 and 280 kHz) to radar waves only few long-term observational studies have been published (for an overview see Ahlbom et al. 2004; Krewski et al. 2001; Kundi et al. 2004). Similarly scarce are long-term animal studies of low-level exposures in the pre-mobile-phone era. Hence there were insufficient data to decide about health risks from low-level exposures at the time mobile phones were introduced, but the prevailing opinion that at exposures below guideline levels no relevant health effects occur led to the expectation that mobile phones are safe. However, the exponential growth of mobile phone use came as a surprise to the industry as well as to scientists involved in EMF risk assessment and therefore it was proposed that the existing gaps in knowledge should be addressed in both experimental as well as epidemiological investigations focusing on exposures occurring in mobile telecommunications.

Starting from the mid 1990s many epidemiological studies of mobile phone use have been conducted world-wide most of them focusing on tumors of the head region. But despite the growing database the concerns have not been settled and there still exists a controversy about possible adverse health effects. While some may be inclined to attribute the ongoing debate to the enormous economic impact

modern telecommunication has obtained during the past decade, it is also mirroring fundamental difficulties and a permissible range of interpretation under circumstances of insufficient knowledge. Despite this state of affairs, not all arguments that have been put forward in this controversy are valid. In the following sections I will concentrate on epidemiological findings and their interpretation although experimental work deserves similar critical appraisal.

I will first give a brief overview of the results of epidemiological investigations of mobile phone use and tumors of the head region. I will then address methodological problems associated with these studies and, by application of the pragmatic approach proposed earlier (Kundi 2006), discuss whether epidemiological evidence supports a causal interpretation of an association between mobile phone use and brain tumors.

Overview of epidemiological studies

Table 1 presents an overview of results of epidemiological studies on the association between brain tumors and mobile phone use. Other endpoints include salivary gland tumors (Hardell et al. 2004; Lönn et al. 2006; Sadetzki et al. 2008), uveal melanoma (Stang et al. 2001), non-Hodgkin lymphoma (Hardell et al. 2005c; Linet et al. 2006), facial nerve tumors (Warren et al. 2003) and testicular cancer (Hardell et al. 2007), but for these diseases the database is insufficient to date.

Except for the early cohort study from the US (Dreyer et al. 1999) that was stopped by court after one year of follow up and the Danish retrospective cohort study (Johansen et al. 2001; Schüz et al. 2006b) all investigations were case-control studies.

Inspection of the overall results column in table 1 from 25 epidemiological studies may be summarized as demonstrating lack of support for an increased risk. Only few risk estimates are significantly elevated and there are even some that are significantly reduced. Risk estimates for longer duration of use are on average higher than overall estimates and, where available, estimates for ipsilateral mobile phone use (i.e. use of the mobile phone on the same side where the tumor occurred) tend to be even higher. Implications of these findings are discussed in the next sections.

Methodological problems

Although there are a number of established study designs in epidemiology that have been successfully applied in thousands of investigations in the past fifty years, maybe few epidemiologists are fully aware of the conditions that are necessary to detect an existing risk by application of these methodologies. Analytical epidemiology intends to estimate the risk as a function of exposure to an agent by application of one of three classical study types: the cross-sectional, the case-control, or the cohort study design. Theoretically, all three types are capable to detect an existing risk under ideal conditions, but differ in their sensitivity to effects of extraneous and confounding factors.

For all study designs it has to be assumed that exposure to the agent can be assessed with a certain sensitivity and specificity. In the case of mobile phone use it is unknown what the exposure metric should be. Absorption of electromagnetic energy in the body of the user depends on technical features of the phone and the network as well as on anatomical features and habits of use. This situation seems at first glance to be not much different from, say, an exposure to an air pollutant that also varies in time and space and which internal dose will depend on physiological conditions. The problem with mobile telephones is much more profound. What aspect of the complex exposure condition described by ‘mobile phone use’ could be responsible for an effect? It is obvious that given a certain indicator of mobile phone use such as years of regular use, cumulative number of calls, cumulative hours of use, or cumulative absorption of electromagnetic energy in a certain area of the body there are indefinitely many exposure conditions that are equivalent under the chosen metric and hence induce an equivalence relation in the space of exposure patterns that cannot be assessed as to its suitability with respect to any outcome measure without a sound mechanistic theory.

Another essential problem is related to the long induction periods and latencies of tumors in the head and neck region. It is not to be expected that mobile phone use that was insignificant before the mid 1990s could be studied with respect to its influence during induction period, because in almost all users malignant transformation has likely occurred long before exposure to mobile phones commenced. While an influence during initiation phase cannot be ruled out, many authors have expressed the opinion that, if there is an effect at all, it is an effect on tumor promotion or progression

(Johansen et al. 2001; Muscat et al. 2000; Stang et al. 2001). If this is actually the case, several scenarios have to be considered. For example, acoustic neuroma were summarized by Mohyuddin et al. (2003) to exhibit tumor growth in 48-70% of patients, stable tumor volumes in 27-50% and involution in 2-10%. If mobile phone use has an influence on growth rate this might result in either restart of growth in stable tumors, an increase of growth rate in growing tumors, or an inhibition of involution. The net result would be an earlier onset of symptoms and an earlier diagnosis. If there is an effect of the specified type, the age incidence function in exposed would be shifted compared to the unexposed population by a fraction of the exposure duration as long as duration of use is short compared to the natural history of the disease. Given the age incidence function has a positive slope this shift is equivalent to an increased incidence in the exposed population for any given age. For simplicity assume the exposed segment of the population has an age incidence function shifted by two years. Taking the slope for the age incidence function for brain tumors as 0.04 (on the log incidence scale, Wrensch et al. 2002) the expected odds ratio can be computed. Assuming the exposed fraction of the population as 5% the expected odds in controls for exposure would be 5:95. By application of Bayes' theorem it follows that the expected odds for mobile phone exposure in cases would be 5*exp(2*0.04):95 and hence the odds ratio is exp(2*0.04)=1.08. Note that the result is independent of the exposure prevalence and depends only on the shift of the age-incidence function and its slope. Given the lower number of mobile phone users at older age, the expected odds ratios from studies with short exposure durations (and hence small shifts in the age incidence function) are too small to be detected with acceptable power.

The third fundamental problem is related to the vast diversity of tumor types to be considered. WHO differentiates about 50 types of brain tumors; there are more than a dozen different histological salivary gland tumors and so forth. Furthermore, in recent years molecular histopathology revealed many differences within certain types of tumors. For example, there are at least two clusters of glioblastoma multiforme, the most frequent malignant brain tumor in adults, one that expresses loss of heterozygosity on chromosome 17p with mutation of the p53 tumor suppressor gene, while the other cluster is characterized by an amplification of the EGFR oncogene. Is it possible that all these diverse

types of tumors respond uniformly to mobile phone radiation? We cannot hope to extract sensitive types by epidemiological investigations because of the small numbers for each distinct type.

In summary, the three most important conditions for epidemiology to arrive at a conclusion concerning a potential risk of an agent are:

- It must be possible to measure (at least by a surrogate marker) the component of the agent that is related to the risk
- For agents that promote the disease in question, duration of exposure must be a substantial fraction of the history of the disease
- There must be good a priori reason to select specific types of diseases that are sufficiently homogenous to support the assumption of more or less uniform etiology.

None of these preconditions are met in the study of mobile phone use and cancer. As a consequence even substantially increased risks might go undetected and evidence will tend to be not unequivocal.

Do mobile phones cause brain tumors?

In order to assess a possible causal relationship between an agent and cancer a pragmatic dialog approach was delineated (Kundi 2006). According to this procedure epidemiologic evidence has to be assessed concerning the four aspects: temporal relation, association, environmental and population equivalence. If there are no valid counter arguments against the evidence for an association, this suffices for a verdict of causation. If evidence from epidemiology is insufficient, other evidence that increases or decreases confidence in a causal relationship could be included to come to a conclusion.

Temporal relation

Assessment of temporal relation is not a trivial problem. It is impossible for any case of a brain tumor to define the point in time when the disease started. Before a tumor can be diagnosed, which in case of brain tumors either occurs by coincidence if it is detected by imaging techniques applied for other reasons, or due to symptoms produced by the growing cell mass, it was likely present for many years

or even decades. For meningioma average induction periods of about 20 to 40 years have been calculated in adults based on observations of patients exposed to ionizing radiation (Umansky et al. 2008). For acoustic neuroma slow growth with average volume doubling times of about 1.7 years suggest similar induction periods (Mohyuddin et al. 2003). For glioma, case reports (Kranzinger et al. 2001) and long-term follow up after childhood radiation therapy of tinea capitis (Sadetzki et al. 2005) also suggest induction periods of decades. Considering temporal relation between exposure and the diverse steps of brain tumor development the following four phases may be differentiated: 1) exposure commenced before the first step of malignant transformation; 2) it started during induction phase (that could itself last for several years); 3) onset of exposure occurred during non-invasive growth phase; 4) exposure started during final (autonomous) growth. In cases 1 and 2, exposure might influence malignant transformation itself and cause de novo occurrence of a brain tumor. In case 3, exposure might influence fate of the deviating clone and could decrease latency or probability of spontaneous involution and therefore either increase incidence due to a shift of latency or because a tumor that would otherwise remain obscure during lifetime manifests itself clinically. In case 4, no contribution of exposure is possible. Unfortunately little is known about the duration of these phases. Furthermore, there are likely gross differences between tumor types concerning absolute and relative length of these steps during natural history of the disease. While slowly growing tumors like most meningioma and schwannoma may have unchanged growth rates during prolonged periods of time, other brain tumors like glioblastoma show an explosive final growth after possibly long periods of more stable behavior. For radiation induced tumors already in 1948 it was proposed to allow for at least five years induction periods (Cahan et al. 1948). Concerning an influence on growth rate it was shown above that also for an effect during latent growth to be detected in epidemiological studies exposure must have been during a substantial proportion of growth phase. Therefore, for both, an influence during induction phase and on tumor growth rate, at least five years latency or duration of exposure, respectively, must be allowed for to fulfill the criterion of temporal relation. Because for virtually all carcinogens, repetitive or prolonged exposures are necessary to bring about an increased cancer incidence, it is necessary to consider not only time since first exposure but also duration of exposure. Number of calls and average duration of calls seem to be too difficult to remember for periods far in the past, but

during which periods a mobile phone was regularly used is more easily recalled and therefore could be the best choice for exposure determination (it even may, in principle, be validated by network provider data). Years of regular mobile or cordless phone use up to five years before diagnosis would possibly be the appropriate exposure meter for most slowly growing tumors. Because such evaluations were not performed, instead exposure duration or latency of 10 years or more, as available, was assessed and included in table 1. In these subjects at least half of the exposure duration falls within an etiologically relevant period.

Association

Concerning association, I computed a meta-analytical estimate of the risk for the different brain tumor types based on all independent studies reporting odds ratios for 10 or more years of mobile phone use. For glioma three studies can be included (Hardell et al. 2006c; Lahkola et al. 2007; Schüz et al. 2006a) reporting data on overall 233 exposed cases and 330 exposed controls among 2792 glioma patients and 6195 control subjects studied. No heterogeneity across studies was found and the combined odds ratio is 1.5 [95% confidence interval – CI: 1.2 – 1.8]. For acoustic neuroma two independent pooled analyses (Hardell et al. 2006b; Schoemaker et al. 2005) give an overall odds ratio of 1.3 [95% CI: 0.95 – 1.9], based on 67 exposed cases and 311 exposed controls among 912 and 5715 cases of acoustic neuroma and controls, respectively. Risk for meningioma from mobile phone use of 10 or more years was reported in two individual studies (Hardell et al. 2006b; Schüz et al. 2006a) and one pooled study (Lahkola et al. 2008). Overall odds ratio is 1.1 [95% CI: 0.8 – 1.4] evaluated from 116 exposed cases and 320 controls among a total of 2506 meningioma patients and 6223 control subjects. Hence there is an increased risk for all these endpoints from mobile phone use that was statistically significant for glioma. In these analyses it is assumed that mobile phone use induces the neoplasia. If mobile phone use has additionally or exclusively an effect on tumor growth this analysis is not entirely appropriate because an effect on the growing tumor can only be exerted by exposure on the same side of the head where the tumor is located. Combined estimates for ipsilateral mobile phone use of 10 or more years give the following results: odds ratio 1.9 [95% CI: 1.4 – 2.4] for glioma, 1.6 [95% CI: 1.1 – 2.5] for

acoustic neuroma, and 1.3 [95% CI: 0.9 – 1.9] for meningioma. Hence there are clear indications of increased risks for all three endpoints.

According to the dialogue approach, association must be assessed whether or not there are valid counterarguments. Valid counterarguments are in the first place those that are based on considerations about the impact of possible biases.

Potential biases

As apparent from table 1, ever (regular) use of a mobile phone rarely revealed increased risks for any type of brain tumor. Except for the Finish study of Auvinen et al. (2002) only the Swedish group of Hardell and coworkers reported significantly elevated estimates of relative risks.

Most studies summarized in table 1 were done based on the Interphone protocol (Cardis et al. 2007) that defined regular use as at least one outgoing or incoming call per week for at least 6 months, with ever regular use starting one year before reference date. While reference date was defined as date of diagnosis in cases and the same date of the matched control, in not individually matched studies (e.g. Hepworth et al. 2006) there are problems in defining reference date due to the interview lag time. Because of the fast increase in mobile phone use during and before the study period the methods applied to compute the reference date for controls could be a source of bias. Information provided in the study reports is insufficient to decide whether or not adjustments were biased. In some reports (Hepworth et al. 2006; Schoemaker et al. 2005) controls were allocated into categories of interview lag time at random without consideration of age and gender of the cases within these categories, while in others (Lönn et al. 2004a) average lag between diagnosis and identification in a matched set was subtracted from date of control identification. The first method will introduce bias if distribution of age and gender within categories of lag times differs, the second if date of identification differs between cases and controls. These possible biases have to my knowledge not been considered previously. In the Interphone study data were collected during end of 2000 thru beginning of 2004 (with some differences between countries). During this period mobile phone penetration rate increased from about 60% to about 90% in the European Union according to ITU. Insufficient adjustment for differences in interview date would result in underestimation of risk.

In the studies by the Hardell group from Sweden, mobile and cordless phone use within the last year before reference date was disregarded. Any use of a mobile or cordless phone was counted except if hands-free devices or external car antennas were used. Reference date for controls was set to the date of diagnosis of the matched case. In some reports of pooled data sets, individual matching was disregarded and controls from different studies were included. Insufficient adjustment of reference date could have led to bias also in this case.

The Hardell group defined the unexposed as those that have not used a mobile or cordless phone for longer than one year prior to diagnosis (or reference date in controls). The Interphone group disregarded cordless phones in analyses of mobile phone use (and vice versa). It has been argued (Cardis et al. 2007; Takebayashi et al. 2006) that cordless phone use is associated with much lower exposure to microwaves and therefore cannot be counted in exposure assessments. This view is not correct. Average power levels are not much different between cordless phones (average levels of 10 mW) and mobile phones (median average output power 6 to 16 mW in urban areas, Lönn et al. 2004b). Considering the typically longer duration of daily use of cordless phones as compared to mobile phones it is not a rational procedure to exclude them from total exposure. The fraction of cordless phone users among cases and controls not using mobile phones ranged from about 22% in Hardell et al. (2006b) to almost 40% in the German Interphone study (Schüz et al. 2006a). If we assign, sensitivity of exposure determination in the Interphone study from neglecting cordless phone use a value of 74% in cases and 78% in controls (according to the data of Hardell et al. 2006b) a true odds ratio of 1.5 is reduced to 1.2. Still greater reductions of the odds ratio result if the differences in cordless phone use were actually greater.

In the Interphone studies data acquisition concerning exposure was predominantly done by computer-assisted personal interviews (CAPI). In about 95% of glioma cases and controls, exposure assessment was based on CAPI (Cardis et al. 2007). Reports from five Nordic countries (Lahkola et al. 2007) reveal a fraction of more than 40% of cases that were interviewed in the hospital. But this fraction ranges from almost 100% in Finland to 3% in the UK. Data acquisition was completely different in the studies of the Hardell group: A questionnaire was sent to home addresses of cases and controls and

upon return, questionnaires were evaluated for errors, omissions and discrepancies. If necessary, additional information was sought by telephone interviews blinded to case status.

Method of data acquisition could be important in several respects: 1) interviews not blinded to case status may introduce a bias from the expectations of the interviewer; 2) the interaction between interviewee and interviewer as such can lead to bias (Rosenthal effects); 3) answering a questionnaire at home is less demanding (especially considering the conditions after surgery) than personal interviews; 4) at home it is possible to check telephone bills or to inspect contracts with network providers in order to verify data. For these reasons the questionnaire method seems to be superior to the interview technique. However, there are also advantages of the CAPI method: data can be immediately checked for errors and discrepancies; the interviewer can explain points that are not clear and may help in recalling inquired items. Validation studies (Berg et al. 2005; Vrijheid et al. 2006a; Vrijheid et al. 2006b) within the Interphone study showed only a moderate correlation between self reported intensity of mobile phone use and traffic data from network operators but confirmed usage data as valid proxy for microwave exposure. For the (not very important) recent mobile phone use, self reports seem to be fairly accurate, but for earlier use no data on reliability are available. Considering results from Christensen et al. (2005) memory performance is decreased especially in patients with high grade glioma. Exposure assessment in these patients could be particularly biased if done by interviews as compared to the questionnaire method. Direction of bias is rather underreporting of mobile phone use, since it is more likely that a patient forgot once using a phone years ago as falsely stating mobile phone use.

In the Interphone studies overall participation was 65% for glioma cases, 78% for meningioma, and 82% for acoustic neurinoma (Cardis et al. 2007). For controls participation was 53% but showed large variation across centers, ranging from 35% to 74%. The Hardell group, applying postal questionnaires, reported participation rates of 88% to 91% in cases and 84% to 92% in controls (Hardell et al. 2006d). Participation rate in cases was computed based on eligible cases that received a questionnaire, defined as those with ascertained primary brain tumors alive at the time of identification and whose participation was not denied by their physician. If the definition of eligible cases of the Interphone

studies were applied participation rate would amount to about 65 to 85% in the different studies. In the Interphone studies on average 13% (range 2% to 44%) of case interviews were performed as proxy interviews. As shown by the Interphone group (Vrijheid et al. 2006a) response bias due to differential selection of groups of the population with higher prevalence of mobile phone use has possibly the highest impact even outweighing recall bias. Lönn et al. (2005) showed that non-participating cases had almost the same proportion of mobile phone users (50% as compared to 52% in participants), but non-participating controls differed markedly from participants (34% as compared to 59%). Effect of this selection bias might be even greater if long-term use is considered. Consequence of selection bias can easily be determined because the biased odds ratio is equal to the product of the true odds ratio and the selection odds ratio. Given the non-response analysis of Lönn et al. (2005), the selection odds ratio is computed as 0.65 if overall participation rates of the Interphone studies are considered. All 46 odds ratios in the report of Lönn et al. (2005) except one in the overall analysis of glioma and meningioma were below 1. Assuming the selection odds ratio is 0.7 as computed based on the non-participation interviews almost all these odds ratios would increase above one and none would be significantly less than 1 (as was the case for 7 of the 46 odds ratios). For example, the odds ratio for more than 10 years of mobile phone use for glioma reported as 0.9 would increase to 1.3.

As has been pointed out previously (Kundi 2004; Kundi et al. 2004; Schoemaker et al. 2005) early symptoms of a developing brain tumor may have influenced behavior regarding mobile phone use. In particular growing acoustic neuroma are frequently associated with hearing problems and tinnitus. Such symptoms may lead to a restriction of use, change of the side of the head the phone is held during calls, and even to discontinuing mobile phone use. Lönn et al. (2004a), in their study of acoustic neuroma, assessed impact of hearing loss and tinnitus 5 years before reference date and reported no differences in risk estimates for patients with and without hearing loss. Whether this is an indication that such symptoms have no impact on mobile phone use and therefore do not bias risk estimates is difficult to assess because no data were reported. In Schoemaker et al. (2005) 59% of regular phone users among controls reported predominantly right-sided use, 33% left-sided use and 8% use on both sides. Authors argue that if mobile phones cause acoustic neuromas, one might expect a higher proportion of tumors on the right than on the left side of the head among regular phone users.

This expectation is, however, completely unfounded. In contrast, tumor growth may cause behavioral changes as indicated by the distribution of mobile phone use in cases, with only 49% right-sided, 40% left-sided users, and 11% that used the phone on both sides.

While response bias, misclassification bias and insufficient correction of interview lag time between cases and controls will reduce risk estimates towards or even below unity, there are biases that could lead to a spuriously increased risk. Especially one point has been raised frequently: increased risk estimates of ipsilateral mobile phone use (table 1) could be due to recall bias. If mobile phone use affects tumor development and growth it is important to consider side of the head the phone is held during calls. It has been shown that 97% to 99% of the total electromagnetic energy deposited in the brain is absorbed at the side of the head the phone is held during calls (Cardis et al. 2008). Due to this asymmetry an effect at the site of the growing tumor is expected only or mainly for ipsilateral use. There is no objective method to retrospectively assess side of the head the phone has been used. Asking a person about this aspect of use could result in bias. A person may be inclined to suspect mobile phone use as a causal factor and may therefore tend to report using it at the same side as the tumor has occurred. On the other hand, also the reverse may be claimed, that a person wants to dismiss the possibility that using the phone has anything to do with the disease and is therefore falsely reporting the opposite side of use. But even if a patient is not intentionally distorting the answer, recent surgery may cause memory deficiencies leading to recall bias. It has been argued (Hepworth et al. 2006) that the reduced risk on the contralateral side indicates such recall bias. However, this risk reduction was due to an artifact of the method applied. Estimate of risk for contralateral mobile phone use was done based on non-regular and ipsilateral phone users as reference. It follows that whenever the risk of ipsilateral phone use is above 1, the risk of contralateral use must be below 1 (the expected value of the odds ratio in this case is $(\pi_o+\pi_i)/(\pi_o+\psi\pi_i)$, where π_o is the proportion in the population of non-users and π_I of ipsilateral users and Ψ is the odds ratio for ipsilateral use). All meta-analytical odds ratios for ipsilateral mobile phone use are above 1 and those for glioma and acoustic neuroma are statistically significant. If there was no misclassification bias in controls and perfect sensitivity, then a small recall bias in the direction of a preference for reporting mobile phone use at the side of the tumor of about 3% would reduce these enhanced odds ratios for long-term (> or ≥ 10 years) use to 1.

However, considering overall results for ipsilateral use, recall bias must reduce specificity in cases by 30% to 40% to remove the observed enhanced risk. The specificity that reduces an observed increased odds-ratio to 1 is given by $[1+(\Psi^*-1)\pi]^{-1}$ (where Ψ^* is the observed odds ratio and π is the exposure prevalence in the population) given that sensitivity in both cases and controls and specificity in controls are 1. For example, taking the study of Hardell et al. (2005a) with an overall odds ratio for ipsilateral mobile and cordless phone use of approximately 3.0 for acoustic neuroma and a prevalence of about 23% of ipsilateral mobile or cordless phone use the specificity must be as low as 68% to remove the observed effect. That is, 32% of those not exposed at all or not on the side of the tumor must have falsely stated they have been exposed. In other words, more than half of mobile phone users among cases and none among controls must have given the wrong side of the head for their predominant use to remove the observed increased risk. It should be noted that also the case-only approach of Takebayashi et al. 2008 cannot solve the problem of recall bias.

As can be seen in table 1 several Interphone groups (Christensen et al. 2005; Klaeboe et al. 2007; Lahkola et al. 2007; Lahkola et al. 2008; Lönn et al. 2005) reported odds ratios that were significantly less than one, implying a protective effect of mobile phone use for brain tumors. Although there is a remote possibility that mobile phone use may enhance apoptosis or activate DNA repair such processes will hardly affect tumor development at an advanced stage and is therefore no valid explanation for these reduced risk estimates that rather suggest systematic bias. Selection bias, as delineated above, could explain some of these results. However, there are likely additional biases that contributed to the overall effect. Let us consider this aspect from the perspective of the ceteris paribus condition and in particular from the condition of population equivalence. Mobile phone use is not randomly distributed within the population but usage patterns will be associated with certain attributes such as occupation, gender, SES and age. Some of these attributes can be accounted for by matching or during analysis, but there could be an association with the disease that cannot be removed by these procedures. Exploration of prior symptoms in brain tumor cases often reveals that there were indications of the disease process many years in the past: epileptic seizures, personality changes, a variety of cognitive and perception problems etc.. It is not unlikely that some of these symptoms will reduce the probability that a person chooses to use a mobile phone - or a telephone in general. Such

habit changes would have the greatest impact on measures of cumulative duration and intensity of use. If aspects of the disease influence mobile phone use the ceteris paribus condition is violated from the very beginning. It is evident that this implies also a violation of the condition of temporal relation, because a reversal of cause and effect may occur. These difficulties are related to the generally short duration of mobile phone use. A solution could be inclusion of case history information and formation of distinct subgroups differing in duration of symptoms related to the developing disease. Obviously, influence of symptoms on mobile phone use will predominantly reduce risk estimates because the odds for mobile phone use in cases will be lowered.

Due to the mentioned biases that could operate in case-control studies, one may be inclined to put some weight on the only cohort study (Johansen et al. 2001; Schüz et al. 2006b) presently available. However, this investigation is severely flawed and cannot contribute to risk assessment (see also Hardell et al. 2008).

Confounding

Environmental equivalence seems to be sufficient in all investigations and confounding an unlikely cause of bias because there are only few known risk factors for brain tumors. Therapeutic and to a lesser degree diagnostic x-rays to the head region increase the risk for several types of brain tumors. In some studies this was considered as a possible confounder but without effect on the risk estimates indicating that there is no correlation between such irradiation and mobile phone use. Other possible confounders include neurofibromatosis and tuberous sclerosis, family history of brain tumors, and medical treatment with growth factors all of which are very rare conditions without reason to assume a relationship with mobile phone use. Age and sex are the most important confounders that have been considered in all studies either by matching or during analysis. Also socio-economic status (SES) has been indicated as possible confounder and was included in most analyses. However, including SES in the analysis will not remove selection bias that seems to be related to SES in some Interphone investigations.

Assessment

Overall, arguments in favor or against an association between mobile phone use and brain tumors are not equally strong. There is evidence for selection bias, exposure misclassification from excluding cordless phone use, reversal of cause and effect from neglecting early symptoms of the disease and short exposure duration. All these factors lead to reduction of the observed risk estimates. The only strong argument against an association is the possible impact of recall bias. There is maybe underreporting especially of early mobile phone use due to memory deficits after surgery, but most concerns have been raised for a potential distortion in reporting side of the head the phone is held during calls. Handedness correlates not very high with side of the head the phone is used (concordances of only about 60% have been determined, Hepworth et al. 2006) and there are no other methods at hand to validate these data. There are, however, some arguments that speak against a decisive influence of recall bias: Most participants of the Interphone and Hardell studies were enrolled during 1997 to 2003, at a time when mobile phone use was not widely discussed as a potential risk factor for brain tumors. In Hardell et al. (2002a) among 232 brain tumor cases that expressed their view about potential causes of their disease, only two named mobile phones. Lönn (2004) asked 70 brain tumor cases and controls whether they consider mobile phones as a risk factor for brain tumors and found no difference between both groups. Even if patients consider mobile phones as a factor contributing to their disease, what would they gain if they give the wrong side of use? As most people are using the mobile on their own free decision it would be assuming they want to blame themselves. In several studies mobile phone use was only one of different risk factors investigated. Bias from patients' attribution would likely extend also to these other factors and spuriously increased risks should have been observed in some of them. While reporting bias of this type may explain an increased risk for long-term ipsilateral use it is hardly an explanation for the increased overall risk of ipsilateral use revealed in several investigations (Hardell et al. 2002a; Hardell et al. 2005a; Hardell et al. 2006a; Hepworth et al. 2006).

When considering the discussion above, the conditions for a causal interpretation of the observed association between mobile phone use and brain tumors are not fully met. However, discussion of the

potential violation of the conditions of temporal relation, as well as population and environmental equivalence revealed that it must in all likelihood have reduced the observed association. Only for the important result on ipsilateral mobile phone use a spuriously increased risk due to recall bias cannot be completely dismissed. In such a situation evidence from other sources may increase or decrease confidence in a causal relation between mobile phone use and cancer.

Additional evidence

Since the 1930s there is a scientific controversy about other than thermal effects of high-frequency EMF. Absorption of electromagnetic energy is now well understood and poses no principal difficulty of integration into Maxwell's theory of electromagnetism. It can be shown that the rate of absorption of electromagnetic energy in a homogenous volume of biological tissue is proportional to the temperature increase within this volume. Therefore, at high levels of EMF exposure significant heating occurs that can be dangerous to health. Exposure standards have been issued that limit exposure to thermally save levels. However, telecommunication and broadcasting applications of high-frequency EMF are not only radiating energy but also information. This is done by modulation of the high-frequency carrier. It has been proposed that the modulation frequencies could be of biological significance and invoke non-thermal effects. In addition, also the high-frequency signal itself could cause effects at low levels in combination with the simultaneous presence of the earth magnetic field (Chiabrera et al. 2000). In principle, interactions between EMF and matter are subject to two descriptions, classical or quantum electrodynamics. In a living cell many important processes occur by electron transfer across membrane structures in a well organized manner, ions are crossing selective channels, proteins get activated and deactivated by cascades of precisely regulated enzymes, processes that are occurring on a quantum scale. Recently (for an overview see Vanderstraeten and Verschaeve 2008), by application of 'omics' research, it has been shown that cells may respond with activation of proteins and genes at non-thermal levels of exposure which was also observed in vivo (Karinen et al. 2008). But still, due to the lack of a mechanistic model, these results are uncertain as to their interpretation with respect to long-term health relevant effects. Since long it has been speculated (Lai and Singh 1997; Phelan et al. 1992) that free radical formation is involved in EMF induced health

effects. Although there is some evidence of formation of free radicals at non-thermal levels of EMF (see Simkó et al. 2006), there are many difficulties with this approach. It would be much too simplistic to assume that free radicals are directly produced by the interaction with the EMF. Rather these radicals are produced by the cell itself as an intermediate step of the response to sensing the field (Friedman et al. 2007).

Concerning prior epidemiological evidence of a relationship between high-frequency EMF other than those used in mobile telecommunication and brain tumors, despite some reports of increased risk (Berg et al. 2006; Grayson 1996; Szmigielski 1996; Thomas et al. 1987), the evidence is inconclusive to date.

Results of epidemiological studies of mobile phone use summarized above indicate an association that is of moderate strength and in the range delineated for passive smoking and lung cancer. There is no meaningful indicator of exposure 'dose' available, but longer latencies are associated with higher risk estimates and there are indications that risk is higher in rural areas where phones typically radiate at higher intensities (Hardell et al. 2005b). These aspects do increase confidence in a causal relationship.

In the case that epidemiology faces problems due to short exposure durations life-time animal bioassays gain importance in establishing a carcinogenic risk. Unfortunately standard procedures cannot be applied for exposure to microwaves from mobile phones. In hundreds of animal carcinogenicity assays it has been shown that even for DNA reactive agents exposure during most of the life-span of the animals at the Maximum Tolerated Dose is necessary to significantly increase incidence. Such high exposures are impossible for high-frequency EMF due to interference with heating. Hence levels much too low for an increased incidence to be expected have to be applied. Some solutions to this problem have been proposed: (1) co-exposure or prior exposure to a known carcinogen; (2) implantation of tumor cells; (3) use of animal strains with a habitually increased tumor incidence. Because of the unknown mechanism of action none of these attempts can be evaluated according to their suitability. More than 30 long and medium term animal assays have been published in the past decade most of which do not comply with basic criteria (Kundi 2003). Concerning brain tumors there is no suitable model for the human disease. Application of ethylnitrosourea during

gestation results in an increased incidence of brain tumors but increases many other tumor incidences as well. A further problem is the much smaller size of laboratory rodents resulting in a completely different exposure pattern at telecommunication frequencies. In contrast to humans using a mobile phone with a localized exposure at the side of the head the phone is held, animal exposure is a whole body exposure. Although devices have been constructed that result in a predominant head irradiation (Adey et al. 2000), still pattern and distribution within the brain will be completely different from human exposures. It is not surprising then that up to now only few animal experiments have found some indication of an increased cancer risk (e.g. Hruby et al. 2008; Repacholi et al. 1997; Tillmann et al. 2007).

Interpretation of epidemiological findings would be much easier if genotoxicity of mobile telecommunication signals could firmly be established. In vitro experiments have brought about diverse results that at present provide only equivocal evidence for genotoxic effects. But also in the case of genotoxicity assays procedures widely used for assessing environmental and nutritional toxicants may not be ideally suited for the study of EMF. For example if, as suggested by Lai and Singh (2004), exposure induced effects imply activation of the Fenton reaction, cells rich in free iron would be responsive while others would be not. Hence overall evidence without considering mechanistic hypotheses is of limited value. Nevertheless, about one quarter of published genotoxicity studies found an effect of low-level exposures (Vijayalaxmi and Obe 2004; Vijayalaxmi and Prihoda 2008).

Overall, animal and in vitro experiments do not reduce confidence in a causal relationship but do not provide unequivocal support either. The main problem identified is the lack of a coherent research strategy that unifies strengths of different disciplines to unravel the intriguing problem of low-level EMF health effects from a biophysical perspective.

Conclusions

Epidemiologic evidence compiled in the past 10 years starts to indicate an increased risk, in particular for brain tumors (glioma, meningioma, acoustic neuroma), from mobile phone use. Considering biases

that may have been operating in most studies the risk estimates are rather too low although recall bias could have increased risk estimates. The net result, when considering the different errors and their impact, is still rather an elevated risk. The magnitude of the brain tumor risk is moderate but it has to be borne in mind that estimates are still from short durations of exposure. While from the perspective of public health an increase of brain tumors incidence of 50% or more poses substantial problems of neurosurgical care, the individual perspective is less dramatic: in industrial countries the life-time brain tumor risk is 4-8 per 1000. Should mobile phone use increase these figures to 6-12 per 1000, the individual risk is still low.

While at present evidence for a causal relationship between mobile phone use and brain tumors relies predominantly on epidemiology, and in particular on the large studies of the Swedish group of Hardell, there are no valid counter arguments and no strong evidence decreasing confidence in a causal relationship. Weak evidence in favor of a causal relationship is provided by some animal and in vitro studies, but overall, genotoxicity assays, both in vivo and in vitro, are in themselves inconclusive to date.

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Table 1: Overview of results (odds ratios or standardized incidence ratios and 95% confidence intervals) from epidemiological studies of mobile phone use and brain tumors

Study	Type	Cohort size/ #Cases and controls	Average duration of MP use	Overall results	Results for longer duration of MP use	Result for ipsilateral MP use
Dreyer et al. 1999	Cohort	133423 hand-held MP 152138 portable bag	~2 y	2 (brain tumor 4 deaths)	--	--
Hardell et al. 1999; Hardell et al. 2000; Hardell et al. 2001	Case-control	209 Brain tumor cases 425 Controls	~6 y	0.98 [0.69-1.41]	>10y 1.20 [0.56-2.59]	2.42 [0.97-6.05] 2.62 [1.02-6.71] (multiv.)
Muscat et al. 2000	Case-control	469 Malignant brain tumor cases 422 Controls	~3 y	0.85 [0.6 – 1.2]	≥ 4y 0.7 [0.3 – 1.4]	2.01 [0.92-5.89]
Inskip et al. 2001	Case-control	489 Glioma 197 Meningioma 96 Acoustic neuroma 799 Controls	~3 y	1.0 [0.7 – 1.4] 0.8 [0.5 – 1.2] 0.8 [0.5 – 1.4]	≥ 5y 0.6 [0.3 – 1.4] 0.9 [0.3 – 2.7] 1.9 [0.6 – 5.9]	0.86 [0.65-1.35] (overall)
Johansen et al. 2001 Schüz et al. 2006b	Retrospective cohort	420095 subscribers	2001 ~3 y 2006 ~8 y	1.0 [0.8 – 1.1] 1.0 [0.9 – 1.1]	≥ 3y 1.2 [0.6 – 2.3] ≥10y 0.66 [0.44 – 0.95]	--

Study	Type	Cohort size/ #Cases and controls	Average duration of MP use	Overall results	Results for longer duration of MP use	Result for ipsilateral MP use
Auvinen et al. 2002	Case-control	398 Brain tumor cases	~2.5 y Analogue	1.6 [1.1 – 2.3]	>2 y 1.6 [0.9 – 2.8]	--
		1986 Controls	~ 1 y Digital	0.9 [0.5 – 1.5]	0.6 [0.1 – 4.5]	
Muscat et al. 2002	Case-control	90 Acoustic neuroma	~3 y	0.68 [0.34-1.38]	≥3 y 1.7 [0.5 – 5.1]	0.55 [0.50 – 1.05]
		86 Controls				
Hardell et al. 2002a	Case-control	1303 Brain tumor cases	~7 y Analogue	1.3 [1.02-1.6]	>10y 1.8 [1.1 – 2.9]	1.8 [1.3 – 2.5]
			~4 y Digital	1.0 [0.8 – 1.2]	--	1.3 [0.99-1.8]
			~6 y Cordless	1.0 [0.8 – 1.2]	2.0 [0.5 – 8.0]	1.3 [1.01-1.8]
		611 Meningioma	~7 y Analogue	1.1 [0.7-1.5]	>10y 1.0 [0.1 – 16.0]	--
			~4 y Digital	0.8 [0.6-1.03]	--	
			~6 y Cordless	0.9 [0.6 – 1.1]	--	
		159 Acoustic neuroma	~7 y Analogue	3.5 [1.8-6.8]	>10y 3.5 [0.7-16.8]	--
			~4 y Digital	1.2 [0.7 – 2.2]	--	
		1303 Controls	~6 y Cordless	1.0 [0.6 – 1.7]	2.0 [0.2 – 22.0]	
Hardell et al. 2002b[a]	Case-control	588 Malignant brain	~7 y Analogue	1.13 [0.82-1.57]	>6 y 1.17 [0.75-1.81]	1.80 [0.96 – 3.38] >6 y
		tumor cases	~4 y Digital	1.13 [0.86-1.48]	1.71 [0.67-4.34]	2.29 [0.59 – 8.93]
		581 Controls	~5 y Cordless	1.13 [0.85-1.50]	1.56 [0.92-2.63]	1.16 [0.55 – 2.46]

Study	Type	Cohort size/ #Cases and controls	Average duration of MP use	Overall results	Results for longer duration of MP use	Result for ipsilateral MP use
Christensen et al. 2004	Case-control	106 Acoustic neuroma	~4 y	0.90 [0.51-1.57]	≥10y 0.22 [0.04-1.11]	0.68 [0.58 – 0.90]
		212 Controls				
Lönn et al. 2004a	Case-control	148 Acoustic neuroma	~5 y	1.0 [0.6 – 1.5]	≥10y 1.9 [0.9 – 4.1]	3.9 [1.6 – 9.5] ≥10 y
		604 Controls				
Christensen et al. 2005	Case-control	175 Meningioma	~5 y	0.83 [0.54-1.28]	≥10y 1.02 [0.32-3.24]	
		81 Glioma I-II		1.08 [0.58-2.00]	1.64 [0.44-6.12]	
		171 Glioma III-IV		0.58 [0.37-0.90]	0.48 [0.19-1.26]	
		822 Controls				
Hardell et al. 2006a	Case-control	317 Malignant brain	~10 y Analogue	2.6 [1.5-4.3]	>10y 3.5 [2.0 – 6.4]	3.1 [1.6 – 6.2]
		tumor cases	~6 y Digital	1.9 [1.3-2.7]	3.6 [1.7 – 7.5]	2.6 [1.6 – 4.1]
		692 Controls	~6 y Cordless	2.1 [1.4-3.0]	2.9 [1.6 – 5.2]	2.9 [1.8 – 4.7]
Hardell et al. 2005a	Case-control	305 Menigioma	~9 y Analogue	1.7 [0.97-3.0]	>10y 2.1 [1.1-4.3]	1.6 [0.7-3.9]
			~5 y Digital	1.3 [0.9-1.9]	1.5 [0.6-3.9]	1.5 [0.9-2.5]
			~5 y Cordless	1.3 [0.9-1.9]	1.9 [0.97-3.6]	1.6 [0.97-2.6]
		84 Acoustic neuroma	~9 y Analogue	4.2 [1.8-10]	>10y 2.6 [0.9-8]	5.1 [1.9-14]
			~5 y Digital	2.0 [1.05-2.8]	0.8 [0.1-6.7]	2.9 [1.4-6.1]
		692 Controls	~5 y Cordless	1.5 [0.8-2.9]	0.3 [0.03-2.2]	2.4 [1.1-5.1]

Study	Type	Cohort size/ #Cases and controls	Average duration of MP use	Overall results	Results for longer duration of MP use	Result for ipsilateral MP use
Lönn et al. 2005	Case-control	371 Glioma	~9 y Analogue	0.8 [0.5 – 1.2]	≥10y 0.8 [0.5 – 1.5]	1.6 [0.8 – 3.4] ≥10y
			~3 y Digital	0.8 [0.6 – 1.0]	≥5y 0.8 [0.6 – 1.2]	
		273 Meningioma	~9 y Analogue	0.7 [0.4 – 1.3]	≥10y 0.9 [0.5 – 2.0]	1.3 [0.5 – 3.9] ≥10y
		674 Controls	~3 y Digital	0.6 [0.5 – 0.9]	≥5y 0.8 [0.5 – 1.2]	
Schoemaker et al. 2005[b]	Case-control	678 Acoustic neuroma	~8 y Analogue	0.9 [0.7 – 1.2]	≥10y 1.1 [0.7 – 1.7]	1.8 [1.1 – 3.1] ≥10y
		3553 Controls	~4 y Digital	0.9 [0.7 – 1.1]	0.7 [0.2 – 3.5]	
Hepworth et al. 2006	Case-control	966 Glioma	~5 y	0.94 [0.78-1.13]	≥10y 1.14 [0.74-1.73]	1.24 [1.02-1.52]
		1716 Controls				
Schüz et al. 2006a	Case-control	366 Glioma	~4 y	0.98 [0.74-1.29]	≥10y 2.20 [0.94-5.11]	
		381 Meningioma		0.84 [0.62-1.13]	1.09 [0.35-3.37]	
		1494 Controls				
Klaeboe et al. 2007	Case-control	289 Glioma	~4 y	0.6 [0.4 – 0.9]	≥6y 0.8 [0.5 – 1.2]	1.2 [0.7 – 1.2] ≥6y
		207 Meningioma		0.8 [0.5 – 1.1]	1.0 [0.6 – 1.8]	1.4 [0.7 – 2.9]
		45 Acoustic neuroma		0.5 [0.2 – 1.0]	0.5 [0.2 – 1.5]	0.7 [0.2 – 2.5]
		358 Controls				
Takebayashi et al. 2006	Case-control	101 Acoustic neuroma	~4 y	0.73 [0.43-1.23]	≥8y 0.79 [0.24-2.65]	0.90 [0.50-1.62]
		339 Controls				

Study	Type	Cohort size/ #Cases and controls	Average duration of MP use	Overall results	Results for longer duration of MP use	Result for ipsilateral MP use
Lahkola et al. 2007[c]	Case-control	1521 Glioma 3301 Controls	~6 y	0.78 [0.68-0.91]	≥10y 0.95 [0.74-1.23]	1.39 [1.01-1.92] ≥10y
Schlehofer et al. 2007	Case-control	97 Acoustic neuroma 194 Controls	~4 y	0.67 [0.38-1.19]		
Hours et al. 2007	Case-control	96 Glioma 96 Controls		1.15 [0.65-2.05]	>4y 1.96 [0.74-5.20]	
		109 Acoustic neuroma 214 Controls		0.92 [0.53-1.59]	>4y 0.66 [0.28-1.57]	
Takebayashi et al. 2008	Case-control	88 Glioma 132 Meningioma 392 Controls	~4 y	1.22 [0.63-2.37] 0.70 [0.42-1.16]	>6.5y 0.60 [0.20-1.78] >5.2y 1.05 [0.52-2.11]	1.24 [0.67-2.29] 1.14 [0.65-2.01]
Lahkola et al. 2008[d]	Case-control	1209 Meningioma 3299 Controls	5.5 y	0.76 [0.65-0.89]	≥10y 0.85 [0.57-1.26]	0.99 [0.57-1.73] ≥10y

MP…mobile phone, X y…X years

[a] Data are a subset from Hardell et al. 2002a

[b] Includes data from Christensen et al. 2004 and Lönn et al. 2004a

[c] Includes data from Lönn et al. 2005, Christensen et al. 2005, Hepworth et al. 2006 and Klaeboe et al. 2007

[d] Includes data from Lönn et al. 2005, Christensen et al. 2005 and Klaeboe et al. 2007