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Interactions between radiofrequencies signals and living organisms

Essential problems in the interpretation of epidemiologic evidence for an association between mobile phone use and brain tumours

Difficultés essentielles dans l'Interprétation des preuves épidémiologiques en faveur d'une association entre utilisation du téléphone mobile et tumeur du cerveau

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ABSTRACT

Due to the close proximity of a mobile phone to the head when placing a call, concerns have been raised that exposure from microwaves during mobile phone use may exert adverse health effects and, in particular, may increase the risk of brain tumours. In response to these concerns epidemiological studies have been conducted, most applying the case-control design. While epidemiology can provide decisive evidence for an association between an exposure and a disease fundamental problems arise if exposure is short compared to the natural history of the disease. For brain tumours latencies of decades have been implicated making special considerations about potential effects of exposures necessary that commence during an already growing tumour. It is shown that measures of disease risk like odds ratios and relative risks can under such circumstances not be interpreted as indicators of a long term effect on incidences in the exposed population. Besides this problem, the issues of a suitable exposure metric and the selection of endpoints are unresolved. It is shown that the solution of these problems affords knowledge about the mechanism of action by which exposure increases the risk of manifest disease.

RÉSUMÉ

Du fait de la forte proximité d'un téléphone mobile avec la tête au cours d'un appel, des inquiétudes se sont exprimées quant à la capacité des ondes radiofréquences émises par le téléphone d'induire des effets sur la santé et, tout particulièrement, d'augmenter les risques de cancers du cerveau. Bien que l'épidémiologie permette d'établir des preuves décisives de l'association entre une exposition et une maladie, des problèmes fondamentaux se posent si l'exposition est courte au regard de la durée de « l'histoire naturelle » de la maladie. Pour les cancers du cerveau, les temps de latence sont de l'ordre de la décade, ce qui a amené à considérer l'impact de l'exposition sur une tumeur déjà existante. Nous allons voir que les mesures du risque comme les « *odds ratios* » ou les risques relatifs ne peuvent pas, dans ces circonstances, être interprétées comme des indicateurs de l'incidence d'un effet à long terme sur la population exposée. De plus, les questions de métrique appropriée de l'exposition et de choix des hypothèses ne sont pas résolues. Nous allons montrer que

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la réponse à ces questions nécessite la connaissance du mécanisme d'action par lequel l'exposition augmente le risque de la maladie.

1. Introduction

Epidemiology is under specific circumstances capable of establishing a relationship between an agent and a disease that can be causally interpreted [1]. For cancer as an endpoint, the International Agency for Research on Cancer (IARC) has laid down a pragmatic scheme that is used as a guideline for scientific panels to categorise an agent, mixture or exposure circumstance into one of several groups: group 1, carcinogenic in humans; group 2A, probably carcinogenic in humans; group 2B, possibly carcinogenic in humans; group 3, not classifiable as to its carcinogenicity in humans; group 4, probably not carcinogenic in humans [2]. If a positive relationship between the exposure and cancer has been extracted from epidemiological studies in which chance, bias, and confounding could be ruled out with reasonable confidence, the exposure is classified as a group 1 carcinogen even if there is no animal evidence and also mechanistic understanding is lacking [3,4].

With the global success of mobile telecommunication a technology that previously was restricted to small segments of the population, the debate about long-term low-level effects of radiofrequency and microwave fields (RF-EMF) grew with renewed strength and international panels recommended investigating possible health effects of this technology [5,6]. Since most of the energy absorbed by the human organism when using a mobile phone is restricted to the head area, neoplasms in the head and neck region were considered of primary interest. The WHO EMF program recommended in its research agenda conducting epidemiological studies of mobile phone use with respect to brain tumours and other tumours of the head region. At this time a few such studies were under way [7–11] and one study [12] that had a quite promising design was stopped by court [13] and could not provide meaningful data. It was considered that an international study is required to provide sufficient power to detect also small risks [14].

The epidemiological studies planned and conducted at that time were more driven by public concerns than scientific conjectures [15]. This is not meant as a criticism of the researchers because it is an obligation of science to address public concerns. Only the potential of the planned investigations to resolve the issue may have been overrated because several fundamental issues that need to be addressed before such studies are initiated were neglected or their importance not fully appreciated. Among these issues are: (1) what is the essential component of the exposure possibly associated with the endpoint(s) studied and how can it be measured; (2) what are the endpoint(s) that could be associated with this exposure; (3) what intensity or duration of exposure is required to reliably establish an association?

In the following sections these issues are discussed and then problems in interpreting results of epidemiological studies are summarised.

2. Exposure assessment

At first glance reliable assessment of exposure seems to be the least difficult task. In fact, it is full of unresolved problems. In the case of mobile phone use there are a number of possibilities. We can simply use a dichotomy: use or no use. But even in this most simple case there are essential problems. First we have to define 'use' of a mobile phone. An unambiguous definition would be any use, even if it was only once in a lifetime. But is this reasonable? It depends on the assumed mechanism of action. If we assume stochastic genetic damage in exposed tissues, a single exposure could be sufficient to initiate a malignant transformation. But even in cases where this assumption holds, like exposure to ionising radiation, such a definition may not be practical: it may turn out that there remain virtually no unexposed subjects, or in case of an initially flat dose-response relationship the incidence in those exposed only once could be only marginally increased leading to effect dilution. Therefore, it could be better to define a certain threshold for use of a mobile phone to consider someone exposed. In the Interphone study, for example, regular use was defined as at least an average of one (in- or outgoing) call per week for at least 6 months [16]. Whether such a definition makes sense cannot be decided without knowledge of both, the mechanism of action and the dose-response curve. Both of these are lacking.

However, this is not the only problem. Another essential issue is the time point up to which we must consider exposure as affecting the disease under study. For brain tumours as endpoints as for most neoplastic diseases, typically 10 to 15 years lagged exposure variables are introduced to account for latency (e.g. [17,18]). Hence we disregard all exposures that occurred less than 10 or 15 years before the diagnosis. The reason is that exposures commencing after the disease has been initiated cannot have an effect on malignant transformation. Also in this case we need a theory about the mechanisms by which the exposure affects the disease. There are a multitude of possibilities: exposure may directly affect genetic integrity (this can itself be produced by many different processes); exposure may have an influence on the fate of a deviating cell or cell clone; exposure may interfere with tumour-host interaction; exposure may promote tumour growth; exposure may affect tumour progression; and exposure may have effects on the time course and pattern of tumour dissemination. The etiologically relevant period depends on the nature of the mechanism, the stage(s) during natural history of the disease at which exposure exerts an effect and on their timing in an individual patient. Clearly, for mobile phone use but also for

many other exposures we know little or nothing about the interaction with biological mechanisms to define the etiologically relevant period. For example, if exposure initiates a tumour or affects a tumour initiated spontaneously or by exposures during the initiation phase we must censor exposure about 10 to 15 years before disease manifestation. On the other hand, if mobile phone use has an effect on tumour progression we must disregard early exposure and focus on exposure shortly before diagnosis. If exposure has an effect on tumour growth, all exposures until the last few months, or maybe one year, before diagnosis must be included. Again it is apparent that the duration for which exposure has to be assessed cannot be specified without a theory about the stage of disease development at which exposure has an effect.

Often it is assumed that risk increases with increasing intensity of exposure. This may also be the case for mobile phone use. But how can exposure intensity be defined? Mobile phone use is associated with exposure to microwaves from the uplink signal and with extremely low frequency (ELF) magnetic field exposure from the battery. Microwave energy deposited in the head cannot be directly measured but is either assessed by measurements in phantoms or calculated based on dielectric properties of relevant tissues. The specific absorption rate (SAR) is the rate by which microwave energy is absorbed in a unit of tissue mass. It is proportional to the square of the electric field strength within the tissue. Hence it is the metric that relates use of a mobile phone to the microwave field within a tissue of interest (like the meninges or the cochlear nerve sheath). Unfortunately SAR depends on many variables: on the power of the antenna output that varies by several orders of magnitude, on the type of phone (especially type and location of the antenna), on the way the mobile is held to the head, on the size of the head and on the individual dimensions of the tissue layers. Attempts have been made to reduce this complexity and start with some simplifications [19]. Whether this actually leads to a better representation of actual exposure needs to be shown in future applications.

Aside from the difficulties arising from the complex dependency on the variables mentioned above additional problems are related to the patterns of individual mobile phone use. Other indicators of intensity of use are number of calls, duration of calls, and location (in- or outdoors, in rural or urban areas etc.) of use. Many epidemiological studies, and the Interphone study in particular, have used all or some of these indicators. Whether SAR is used or one of these indicators the problem of constructing a meaningful exposure metric from these data arises. Obviously, aggregation over time is necessary otherwise each subject would have their individual exposure characteristic and no assessment of risk would be possible. It has to be borne in mind that aggregation induces an equivalence relation in the multidimensional space that characterises the individual exposure patterns. Consider, for example, a subject that uses the phone for 5 minutes a week during the first year, then increases use to 15 minutes during the subsequent 5 years and then stops using the phone for one year to start again in the last year with 5 minutes per day. While this is already a gross simplification (the 5 minutes per week may all be consumed in one call, or it may be 10 calls of half a minute etc.) a cumulative measure of duration of calls yields a value of 5980 minutes. The same result would be obtained for a subject that started using the phone for one hour a week during the first year, then reduced use to 20 minutes per week in the next year and to 5 minutes per day in the last year. Are these exposures equivalent with respect to the risk? This is impossible to know without a detailed knowledge of the mechanism of action.

In summary, it is unknown what defines exposure, it is unknown what the etiologically relevant period is for which exposure must be considered, it is unknown how the different patterns of use should be combined into a meaningful exposure metric. Finally, actual internal exposure can only roughly be assessed and it is unknown how and for which periods this exposure should be aggregated.

Another essential problem arises if exposure is assessed retrospectively by interview or questionnaire, as was the case with almost all epidemiological studies of brain tumours conducted so far. How credible and precise are the exposure indicators obtained by these methods? Several validity studies of recall of mobile phone use have been conducted [20–23] that have also been discussed in the recent final publication of the Interphone group on glioma [24]. From these studies it can be concluded that there is fair agreement between self-reports and data from network providers or use determined by software-modified mobile phones that recorded each call. There seems to be a small systematic bias in the sense of an underestimation of the number of calls and an overestimation of the duration of calls. Except for this systematic bias there is considerable random error that will lead to an underestimation of risk. Systematic bias if non-differential (i.e. not different between cases and controls) would also lead to an underestimation of risk. There is little indication of differential bias [25] except for a possible tendency in cases of increasing bias for use more distant in the past. However, this phenomenon was restricted to data from one country only. Much emphasis has been put on the possibility of differential recall bias of laterality (i.e. side of the head the phone is used during calls). Indeed, for low prevalence of use even a small bias could have a strong effect on risk estimates [26]. A validation study in adolescents [27] with software modified phones found 4 of 30 adolescents reporting the opposite side of use as recorded by the phone. Since the recording phone differed substantially from their usual phone it is difficult to interpret this discrepancy. Whether knowledge of the side of the tumour leads to a higher propensity to report the same side for mobile phone use is unknown. However, so far no plausible explanation for such a bias has been proposed.

Considering all these difficulties of exposure assessment it is recommended to proceed by a double strategy: The main focus of assessment and analysis should be the easiest to obtain and maybe also most reliable information on use, that is: overall duration of use or time since first use; on the other hand, because of the lack of knowledge on mechanisms of action all information about patterns of use should be explored and different metrics tested to generate hypotheses about decisive features of exposure that might inform mechanistic considerations. Of course, the latter procedure carries the risk of coming up with chance relationships. It is, therefore, indispensible to independently test such associations either by

splitting the data set into a learning and a test set, or to use data from other investigations to test the robustness of these associations. Furthermore, biological plausibility of such emerging dose-response relationships must be considered and/or tested in experimental trials.

3. Endpoint selection

In many cases the endpoint is determined by conjectures about the processes that lead from exposure to disease. In the case of mobile phones the endpoints, tumours of the head and neck region, are determined solely based on the location of the exposure during calls. However, tumours in this region are no unique entity. The ICD-O differentiates around 100 intracranial tumours, among them more than 50 neuroepithelial tumours, almost 40 meningeal tumours, more than 10 peripheral nerve tumours, and several other tumour types like tumours of the sellar region. These tumours differ in origin, cell types involved, growth pattern, clinical features, and prognosis. If molecular biological features are considered the number of different tumour types is even greater. Which of these different tumours could be affected by mobile phone use? For a few of these malignancies genetic predispositions have been detected. The only firmly established exogenous factors for brain tumours are ionising radiation and certain types of cancer chemotherapy [28]. Although there are some arguments that environmental factors may not contribute to the development of brain tumours it is premature to conclude that such factors do not exist. Among the reasons for failure to establish an association between exogenous factors and brain tumours, the heterogeneity of the disease has been implicated [29]. Indeed, if for example mobile phone use affects certain types of brain tumours only, then including other, unaffected types in epidemiological investigations would dilute an effect. Depending on the fraction of unaffected tumour types and the magnitude of the risk the diluting effect could be strong enough to obscure the risk. Furthermore, if composition of tumour types varies among studies strong heterogeneity of results would occur.

Because of the lack of any a priori reason to select or exclude tumours, great care has to be taken during analysis to explore different types and localisations of growth in order to generate hypotheses for future more focused investigations. It must, however, be stressed that not necessarily the region of highest exposure is also the most likely candidate region for an increased risk. First of all, there is evidence from studies of ionising radiation that tumours are not found in areas of highest exposures but in adjacent regions [30]. Second, the location where the tumour is finally detected may not be the location where it was initiated [31]. Also growth itself may be highly asymmetric with most of the final volume in another area as that of primary growth [32].

As will be shown later, the potential to detect an increased risk after short periods of use depends on the slope of the age–log-incidence function. Therefore, brain tumours with no or decreasing incidence trends for increasing age must be omitted from analysis, at least for short exposure durations. This is the case for oligodendroglioma, pilocytic astrocytoma, mixed glioma, ependymoma and some other morphologies.

4. Impact of exposure duration

Epidemiology has hardly ever been confronted with studying the impact of a technology on neoplastic diseases shortly after it has been introduced. Therefore, few epidemiologists have a clear understanding of the problems that arise from such a situation. Considering brain tumours, average latent periods of 20 to 30 years have been found for glioma [30,33]; 20 to 40 years for meningioma [34]; and for acoustic neuroma about 25 years latency can be delineated from average volume doubling times [35]. Mobile phone use was minimal until the early 1990s when digital phones were marketed. In OECD countries mobile phone penetration rate was 1% in 1990 and rose to 45% in 2000 and to 80% in 2005. Rates were initially highest in Nordic countries with already 5% in 1990, but many European countries made leeway in 2000 with around 50% penetration rate. Consequently epidemiologic investigations started in the late 1990s and accruing data until about 2004 could not enrol subjects that had used a mobile phone for a duration that is compatible with the latent period of brain tumours. While short latencies are not impossible, typical periods are in the order of 10 to 40 years. Average duration of mobile phone use was around 4 years in most studies except those in the Nordic countries where averages were slightly higher (5 to 7 years). Hence it follows that exposure duration in the brain tumour studies was not compatible with the natural history of the disease in the sense that a tumour initiating effect could not have been studied. However, many scientists were of the opinion that mobile phone use may rather exert an effect on tumour growth. "... if RF exposure is assumed to act by promoting the growth of an underlying brain lesion, then the intense recent use, as currently experienced by large numbers in our cohort, might be of more importance than latency or long-term use considerations." [36]. This view is shared by many epidemiologists working in this field; however, it is wrong to assume that such an effect can be found in epidemiological studies if duration of use is short, as will be shown below.

Indeed, if we intend to study the impact of mobile phone use on brain tumours at a time when most persons will have accumulated only a few years of use we must either start from the assumption that such an exposure initiates a tumour with extremely shortened latency (which is a rather remote hypothesis since so far only treatment with growth hormones in combination with therapeutic x-rays led to latencies of less than 10 years [30]), or we assume a growth promoting effect that could be present as long as a mobile phone is regularly used. In the following considerations I will discuss the implications of the latter assumption.

First it is necessary to consider the effect of a growth promoting agent under the condition of an exposure duration that is short compared to the latency period. Since such an agent acts upon an already initiated tumour it will only reduce the latency period due to an increased tumour growth rate. If we consider a population that is exposed to such an agent, how will it differ with respect to tumour incidence from an unexposed population? There will be a slight net increase of the incidence because a fraction will be diagnosed with the brain tumour that otherwise would have died of competing causes. The essential effect is, however, a shift of the age incidence function to the left (to earlier age). If we have a fixed age range, as for example the range 30 to 59 years used in the Interphone study, peculiar observations would be made for some tumours. If the age incidence function has a negative slope, as is for instance the case for pilocytic astrocytoma, then the incidence would be lower in all age groups in the population exposed to the growth promoting agent because the resulting increase from shortened latencies would fall outside the fixed age range. Only if the age incidence function has a positive slope an increase in the incidence can be observed.

The increase of incidence is a function of the magnitude of the shift of the age incidence function and its slope. The shift of the age incidence function can be estimated from considerations about tumour growth. Different patterns of brain tumour growth have been observed including spontaneous involution, constant volumes, and stable growth [35]. In the most extreme case tumour growth is exponential. But whether it is linear or exponential or any strictly monotonous function of time, the shift effected by a growth constant that is increased by a factor f is equal to $(f-1)t_m$, where t_m is the duration of mobile phone use. If, for example, growth is increased by 50% ($f = 1.5$) then the shift of the age incidence function is 50% of the duration of mobile phone use (see Appendix A). Hence for short periods of use the shift is small.

The second problem, the amount by which the incidence could be increased, is related to the shape of the age incidence function. Within the age range of 30 to 59 years the age log-incidence function for malignant brain tumours is almost linear with a slope of 0.05 $\log_e$ units per year (a figure of 0.04 is delineated from [37], more recent data – 2001–2007 – from Austria suggest a slightly higher slope). Consider a case-control study in a population with a rate π of mobile phone users. The odds to find a mobile phone user among controls is therefore $\pi : (1-\pi)$. The odds in brain tumour cases can be found from application of Bayes' theorem (see Appendix B) observing that the incidence function is shifted by a fraction of the duration of mobile phone use and amounts to: $\exp(\gamma \times s) \times \pi : (1-\pi)$. Hence the odds ratio is independent of the fraction of mobile phone users and equal to $\exp(\gamma \times s)$, with γ the slope of the age–log-incidence function and s the shift in years effected by the increased growth rate.

Assuming a large effect on tumour growth with a 50% increase of the growth constant and therefore also a shift of the age incidence function by 50% of the duration of mobile phone use, and taking the average duration of mobile phone use to be 5 years, the expected odds ratio for a case-control study of malignant brain tumours is $\exp(\gamma \times s) = \exp(0.05 \times 2.5) = 1.13$. Such low odds ratios cannot be detected with sufficient power except in very large studies. For a 1:1 matching between 3000 and 7000 cases of brain tumours must be included depending on π, the fraction of mobile phone users in controls, to have 80% power to detect this risk at the 5% level of significance. If we restrict analysis to those with 10 years of mobile phone use, the expected odds ratio under the same scenario is 1.28, a figure that is consistent with the meta-analytical estimate for the odds-ratio for glioma (1.5, 95% CI : 1.2–1.8) [25]. The overall Interphone results [24] for glioma when corrected by a selection odds ratio of 0.8 yields an odds ratio for 10 or more years of mobile phone use of 1.23, almost identical to the above estimate.

Basically, the same procedure can be applied to estimate the impact on population incidence. Let the incidence at age A be $\exp(\beta + \gamma A)$, then the incidence in a fraction π_s with $s = (f-1)t_m$ years shift of the age incidence function from t_m years of mobile phone use is $\exp(\beta + \gamma(A+s))$. It follows that the overall incidence at this age is given by: $\exp(\beta + \gamma A)[1 - \pi + \sum_s \pi_s \exp(\gamma s)]$. For example, Deltour et al. [38] observed an almost unchanged glioma incidence of about 9 per 100,000 in males 40 to 59 years of age in Nordic countries between 1974 and 2003. Applying the formula given above and assuming 20% with 10 years of mobile phone use, 40% with 5 years, and 30% with 2 years and a shift of 50% of the duration of mobile phone use yields an incidence of 10.1 which is within the random Poisson variation of the incidences (annually about 310 cases occur in a population of about 3.4 million, the 95% Poisson confidence interval spans 276 to 347 cases, expressed in incidences per 100,000: 8.1 to 10.2). It follows that for the time being it is unlikely to find an increase at the population level even if mobile phone use would substantially increase tumour growth rate.

5. Problems of interpretation of epidemiologic evidence

As long as there is no doubt that exposure commenced before the disease was initiated odds ratios from case-control studies or relative risks from cohort studies are reliable estimates of the true risk associated with the exposure. If this is not the case, i.e. exposure started after the disease process already begun, the situation is much more difficult. The most severe problem arises if a reversal of cause and effect is possible. For example, clinical features of the developing tumour could lead to reduction or even cessation of mobile phone use. Acoustic neuroma are often associated with hearing problems and tinnitus. A person with such problems is unlikely to be an intensive user of a mobile phone. Patients with malignant brain tumours often have a long history of symptoms including seizures, sensory problems, headaches, and personality changes. Also such symptoms may lead to habit changes concerning mobile phone use. Consider, for example, a subject with an initiated glioblastoma multiforme is starting using a mobile phone and during the first year of use the exposure resulted in a strong growth of the tumour leading to exceptional noise sensitivity and personality disturbances. The patient withdraws from most social contacts and, therefore, virtually stops using the mobile phone. In an epidemiological investigation this

patient will count as a light user, although a strong effect of exposure has occurred that, however, affected both the disease and mobile phone use. Such primary or secondary reversals of cause and effect are the most serious problems because they result in apparent protective effects of exposure. Indications that such effects are actually occurring can be found in early studies of brain tumours [39]. A solution to this problem is to thoroughly investigate earliest signs and symptoms of the growing tumour and to stratify exposure indicators according to the time of onset of these symptoms.

Another problem arising from short exposure duration is due to the inevitable link of the risk estimates to the age incidence function. As mentioned above, for tumours with negative slope and a restricted age range of cases under study leads to an apparent reduction of risk however strong the effect of exposure. But even for diseases with a positive slope of the age incidence function the risk delineated from short exposure durations can never give a true estimate of the impact of unlimited exposure durations. The longer the exposure duration the stronger is the effect of an incidence increase due to overtaking competing causes of death. Therefore, even if studies of comparatively short exposure durations indicate an increased risk – as is the case for mobile phone use and some brain tumours [26] – the magnitude of the risk cannot be inferred.

From the considerations about the relationship between risk estimates and the slope of the age–log-incidence function an interesting prediction can be delineated: brain tumour subtypes with a steeper slope should be associated with higher risks (if all brain tumours are equally affected). For example, glioblastoma should show higher odds ratios especially at younger age than lower grade astrocytoma. Another prediction concerns the age range. As some brain tumours have a steeper increase at younger age, narrowing down the age range (as has been done in the overall Interphone report on glioma [24]) carries the risk of reducing the odds ratios for mobile phone use.

It must be stressed that most of the difficulties discussed above are equally applying to case-control and cohort studies. The opinion that a large cohort study is needed to give decisive answers is questionable. Only if the duration of such a cohort study is approaching the average latency period of the involved diseases, its superior design will take effect. On the other side, the difficulties in exposure assessment and follow up for such a large cohort are unparallelled. That is not meant to say that cohort studies in this area are useless, to the contrary, they are useful for the investigation of a variety of endpoints other than brain tumours. However, it has to be stressed that we cannot hope for answers concerning brain tumour risk until decades.

Appendix A

Assume tumour growth is a strictly monotonous continuous function of time (t) since initiation. Let $y(t)$ be the volume at time t. Then there exists a function $Y(t) = f(y(t))$ such that Y is a linear function of t. In fact, there are indefinitely many such functions. However, all these functions are linearly related and it is irrelevant for the present consideration which of these functions Y is chosen.

Let Y_d be the volume that must be reached until a diagnosis is made. Then t_d for which $Y(t_d) = Y_d$ is the latency from tumour initiation until diagnosis. Let $Y(t) = a + b \times t$, then b is the growth constant of the tumour. If we assume mobile phone use increases tumour growth, this translates into assuming a growth constant $f \times b$ with $f > 1$. Let t_s be the time after tumour initiation when mobile phone use commenced. The tumour volume under these assumptions grows according to:

$$Y(t) = \begin{cases} a + b \cdot t & t \leqslant t_s \\ a + f \cdot b \cdot t - (f-1) b \cdot t_s & t > t_s \end{cases} \tag{A.1}$$

The time t_{dm} until the volume Y_d is reached after onset of mobile phone use ($t > t_s$) is found by equating $a + b \times t_d$ to the term in (A.1) and solving for t. The shift $t_d - t_{dm}$ is obtained by observing that $t_{dm} = t_s + t_m$, where t_m denotes the duration of mobile phone use:

$$\text{Shift} = t_d - t_{dm} = t_m(f-1) \tag{A.2}$$

Appendix B

Let the probability to find a mobile phone user in the target population without brain tumour, denoted $\Pr(E+ \mid D-)$, be π. We assume a linear age–log-incidence function, hence the overall probability to find a brain tumour case at age A in the unexposed population, $\Pr(D+ \mid E-)$, is $\exp(\beta + \gamma A)$. For simplicity we assume that duration of exposure is equal for all age groups within the linear age range. For short exposure durations the assumption of an increase of tumour growth rate during the period t_m of mobile phone use results in a shift of the age–log-incidence function by $(f-1)t_m = s$ years, if f is the factor by which tumour growth is increased above average growth. Hence, the probability of a brain tumour in the exposure population, $\Pr(D+ \mid E+)$, is $\exp(\beta + \gamma(A+s))$.

The expected odds ratio as an estimate of the relative risk in a case control study is given by:

$$\text{OR} = \frac{\Pr(E+ \mid D+)}{\Pr(E- \mid D+)} \frac{\Pr(E- \mid D-)}{\Pr(E+ \mid D-)} \tag{B.1}$$

The probability to find a mobile phone user among patients with a brain tumour is computed by application of Bayes' theorem:

$$\Pr(E+ \mid D+) = \frac{\Pr(D+ \mid E+) \cdot \Pr(E+)}{\Pr(D+ \mid E+) \cdot \Pr(E+) + \Pr(D+ \mid E-) \cdot \Pr(E-)} \tag{B.2}$$

Since the fraction of brain tumour cases in the population is negligibly small $\Pr(E+) = \Pr(E+ \mid D-) = \pi$ and inserting into (B.2) yields:

$$\Pr(E+ \mid D+) = \frac{\exp(\beta + \gamma(A+s)) \cdot \pi}{\exp(\beta + \gamma(A+s)) \cdot \pi + \exp(\beta + \gamma A) \cdot (1-\pi)} = \frac{\exp(\gamma s) \cdot \pi}{\exp(\gamma s) \cdot \pi + 1 - \pi} \tag{B.3}$$

Observing that $\Pr(E- \mid D+) = 1 - \Pr(E+ \mid D+)$ inserting (B.3) into (B.1) we find:

$$\mathrm{OR} = \exp(\gamma s) \tag{B.4}$$

This completes the proof of the assertion in the text.

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