Abstract. Two Swedish epidemiological studies have shown an association between the use of mobile telephones, mainly of the analogue type, and brain tumours. These findings have been corroborated in a Finnish study. Supportive evidence has also come from studies in USA, but these investigations, as well as a Danish study, are inconclusive due to, e.g., few exposed subjects, short latency periods and methodological shortcomings. The Swedish Radiation Protection Authority (SSI) engaged two epidemiologists from a private company to conduct a review of the literature. They claimed that use of mobile telephones is not associated with increased risk for brain tumours. Their conclusion was, however, based on an unbalanced view of current literature in favour of studies showing no association. These circumstances are further explored in this communication.

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1. Introduction

The Swedish Radiation Protection Authority (SSI) recently engaged two US epidemiologists to review published epidemiological studies on the relationship between the use of mobile telephones and cancer risk. They were Drs John D. Boice Jr and Joseph K. McLaughlin from the private company International Epidemiology Institute (IEI). In their review [(1), here referred to as the SSI report], they claimed that no consistent evidence was observed for increased risk of brain cancer, meningioma, acoustic neuroma, ocular melanoma, or salivary gland cancer due to mobile phone use.

However, these two epidemiologists were co-authors of the Danish cohort study by Johansen et al (2), which is among the reviewed studies. The Danish Cancer Fund, two Danish mobile phone net operators and IEI financed this study. Boice and McLaughlin were also co-authors of the Danish melanoma study by Johansen et al (3). Additionally, one of the US studies (4) that was classified as well designed in the SSI report was preceded by a publication on study design (5). In this publication John Boice was co-author. Inskip et al (4) referred regarding material and methods to that particular article about study design: ‘the study methods have been described in detail previously’ (5). Thus, the very positive words by Boice and McLaughlin about these studies should be viewed with this as background. John Boice and Joseph McLaughlin did not declare if they had any conflict of interest.

The letter from the SSI to Dr Boice asking for ‘evaluation of epidemiological studies on cellular telephones and cancer risks’ was dated 15th May, 2002. The letter stated that ‘the report should be ready within 2 to 4 weeks after the publication of the new Swedish data’. In fact the Swedish studies constituted two of the reviewed 10 epidemiological studies, but of the 14 pages discussing all studies, 7 pages were devoted to the two Swedish studies alone.

The aim of the SSI report was to give a balanced presentation of the evidence, which in our opinion was not achieved. A balanced presentation should view the evidence from all sides. Starting from the hypothesis of no association, what are the strengths of the studies showing no effect and what are the weaknesses of those showing an effect. But the review should also look the other way: if actually there is an association, what are the strengths of the studies showing an effect and what are the weaknesses of those that do not? In the present case the discussion is highly unbalanced in favour of those studies that did not show biological effects of exposure to emissions from mobile phones.
The Swedish studies by Hardell et al (6–8), which demonstrated an association between the use of cellular phones and cancer, and a few studies that addressed this concern in the United States are considered ‘non-informative’ by Boice and McLaughlin, either because the follow-up was too short or numbers of cancers too small (USA) or because of ‘methodological limitations’ (Sweden).

According to the authors, there are five well-designed epidemiological studies, conducted in three countries and using different designs: three hospital-based case-control studies in the United States (4,9,10), a registry-based case-control study in Finland (11), and a registry-based cohort study of over 400,000 cellular phone users in Denmark (2). Boice and McLaughlin find a consistent picture from these studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date.

Furthermore, they say that the emerging results of experimental studies have failed to confirm earlier reports of possible adverse outcomes from radiofrequency exposure, and that there is no biologically plausible mechanism known today supporting a carcinogenic effect of non-ionising radiofrequency fields.

This report caused the SSI to send out a press release about the possible risks associated with the use of cellular phones stating: ‘the current state of the science is reassuring’. But is the knowledge such that we can say it is reassuring? We shall here look closer at the so-called well-designed studies and give our views on why we do not consider them to support this view.

2. Epidemiological studies

Johansen et al (2) performed a population based cohort study comprising all mobile phone users in Denmark from 1982 up to 1995, a total of over 700,000. Those with a company paid phone were discarded, about 200,000. The duration of use was given only for digital (GSM) subscribers, of whom 93% had less than 3 years of mobile phone use. A non-significant risk given only for digital (GSM) subscribers, of whom 93% had phone were discarded, about 200,000. The duration of use was to 1995, a total of over 700,000. Those with a company paid

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2. Epidemiological studies

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Considering the methods of the study, one has to ask whether this study could have found an elevated brain cancer risk if there was one. The most important prerequisite for the study of non-ionising radiation induced brain tumours is to allow for reasonable latencies. Although there is broad agreement that microwaves cannot directly induce malignancy, a contribution of exposure during the initiation phase or during tumour growth cannot be ruled out. These hypotheses have to be considered separately. Concerning contribution during the initiation phase, there is convincing evidence for average latencies of more than 5 years for brain tumours. In the cohort there were only about 8% that could be used for such an analysis. The expected annual number of brain and nervous system tumours in this sub-cohort is about 1-2 cases. The analysis for latency in the article by Johansen et al (2), given in their Table III, has apparently accumulated these cases over the total period of phone use without allowing for a reasonable latency period (e.g. disregarding all cases earlier than 5 years after first use of a mobile phone).

Overall the power of the study of Johansen et al (2) to detect a 50% increase of brain tumour incidence in long-term mobile phone users under the given latency constraints is negligibly small. If on the other side we consider the hypothesis of a contribution of mobile phone use on brain tumour growth we have to differentiate the types of brain tumours. There are gross differences in growth rates between different types of tumours, ranging from weeks between first clinical signs and diagnosis to decades. It is difficult to detect an influence of mobile phone use on growth rate of fast-growing tumours, like glioblastoma, in such a cohort study. Hence, considering influence on growth rate, all glioma brain tumours of grades III and IV should be analysed separately. If mobile phone use increases growth rate of slowly growing brain tumours, what is the consequence with respect to cumulative incidence? Depending on the ratio of observation to manifestation duration an increase of incidence can be expected. However, the observation period (in this study an average of 3.1 years after first use of a mobile phone) was too short to detect such an effect, as also the authors conceded: ‘latency may be too brief to detect an early-stage effect or an effect on the more slowly growing brain tumours’. Hence the study cannot contribute to the assessment of a possible role of mobile phone use on brain tumours. This evaluation also holds, mutatis mutandur, for malignant diseases of the haematopoietic and lymphatic tissue.

The authors refer to an American study (12) that showed that 48% were not the only users of the phone. They also write about the limitations in their study: ‘our study may currently have too few heavy users to exclude with confidence a carcinogenic effect on brain tissue following intense, prolonged use of cellular phones’. Although this reservation is quite weakly expressed, considering that they had no data on intensity of use, and in over 40% not even data on duration of use, even this statement seems to have been forgotten by Boice and McLaughlin as as well the SSI when drawing their conclusions about the current knowledge.

Muscat et al (9) studied malignant brain tumours in patients from five different hospitals in the US. Data from 469 cases and 422 controls matched for sex, age, race, hospital and month of admission were available. Controls were hospital patients, but except for two hospitals not cancer patients. In contrast to the Swedish studies (6-8) interviewers of patients were not blinded to case status, and time of interview differed substantially between cases and controls. Both points might have biased results towards the null hypothesis, especially the second one. It is definitely wrong that recall bias usually results in spurious positive findings, as the authors argued. The effect of recall bias on the odds ratio depends on the height
and sign of the correlation between bias and case status. In the present study by Muscat et al (9) most case patients were interviewed within two days after surgery. Thus, if there were recall bias it would have been positively correlated with brain tumour diagnosis and hence would have reduced a possible association!

Out of the 469 cases included in the study only 66 had been using mobile phones, and the corresponding number among the controls was 76 out of 422. The exposure in mobile phone users was such that 86% of the cases and 85% of the controls had been using an extended antenna during the calls. Of all the phones, 88% were analogue and 50% of one brand. The duration of use was on average 2.8 years for the cases and 2.7 years for the controls. The mean usage time per month was 2.5 and 2.2 h for cases and controls, respectively. The study population is thus very small and with extended antenna the exposure to microwaves in the brain becomes low and area of exposure is shifted to parietal and occipital locations. Together with the short time of usage this study is not very informative.

However, it should be mentioned that of the 41 cases in the study with information about laterality, 26 had been using the phone on the ipsilateral and 15 on the contralateral side. Overall the odds ratio (OR) associated with use of a handheld cellular telephone was 0.8. The highest histology-specific risk estimate was found for neuroepitheliomatous cancers with an OR of 2.1. However, it seems that diagnosis was not unequivocal in all cases. Comparison with the distribution of histological types between users of handheld cellular telephones and non-users reveals a highly significant difference (p<0.001), due to an increased frequency of neuroepitheliomatous cancers (21% vs. 5%) and a reduced frequency of glioblastoma (44% vs. 53%) and astrocytoma (11% vs. 19%). One of the most severe methodological problems of the study is the predominance of glioblastoma, comprising more than half of the cases. Glioblastoma are of highest malignancy (grade IV) and have a very high growth rate with weeks to at most months from first disease signs to diagnosis.

If emissions from mobile phones were considered as a factor influencing any stage of the malignant process, tumour locations at the irradiated area have to be chosen; otherwise the chance to detect an association would be substantially reduced.

Concerning the significant difference in morphological types of brain tumours between users and non-users of mobile telephones there are at least two explanations. First, exposure to emissions from mobile telephones increases growth rate of already initiated brain tumours; this would have an noticeable effect only on slowly growing tumours, because e.g. a latency decrease of glioblastoma from 2 months to 1 month would have no effect on annual incidence, while in low-grade astrocytoma a decrease from 2 years to 1 year would increase incidence. Another explanation would be that patients that develop high-grade brain tumours avoid using mobile telephones. However, this explanation is unsatisfactory because these patients often have no early clinical signs while those developing low-grade tumours may experience years of various symptoms that are more likely to result in avoidance of mobile telephones. It is also possible that the effect is due to confounding by age, because older patients might have less history of cellular telephone use and at the same time more often experience high-grade tumours. However, the effect on histological type seems to be too strong to be solely due to age. In fact, it can be shown that even considering age as a confounder, the data are compatible with an increased growth rate in mobile phone users.

Muscat, the principle author of this study (9), participated in a meeting in Paris, where he reported on the study but giving an OR of 2.2 [95% confidence interval (CI) = 1.0-4.7] for neuroepithelioma (13). There is still another publication from this study (14), and now the OR is 2.6 (95% CI = 1.2-5.4). We have no explanation for this discrepancy. The publication gives no account of the procedure to assess histological types. Neuroepithelioma can unambiguously be diagnosed only by immunohistological methods. In the absence of data on immunostaining there is always a possibility to shift cases between ganglioglioma and mixed types. We do not know, however, whether or not such allocation problems occurred.

In summary, the study of Muscat et al (9) has a number of methodological deficiencies, most important the short latency, the predominance of glioblastoma, and the too small number of tumours that can possibly be considered in a study of localised exposure. Note that already in 1948 several conditions for irradiation induced tumours have been established, among these: exposure must precede diagnosis by at least 5 years and localisation of tumour must be at the irradiated site (15). It is worth mentioning that in the Paris report (13) Muscat writes: ‘although the current study shows no effect with short-term exposure to analogue cell phones, further studies are needed to account for longer induction periods and for the possible effects of GSM phones’.

The exposure to mobile phones is also of short duration in the study by Inskip et al (4). They also did a hospital based case control study comprising 782 cases collected during 1994-1998. They enrolled 489 patients with primary malignant brain tumours (glioma or neuroepitheliomatous tumours) but also 197 patients with intracranial meningioma, and 96 patients with acoustic neuroma. Overall 799 hospital based control patients were frequency matched by sex, age, ethnic group, and proximity of residence to hospital. No increased risk was observed either for primary malignancies or for meningioma or acoustic neuroma. Also no association was found with the side of the head the telephone was typically used when phoning. Difference in distribution of histological types between users and non-users was highly significant (p<0.0001) as in the study by Muscat et al (9). This difference was due to a pronounced reduction of the frequency of glioblastoma (57% in non-users vs. 27% in users) and an increase in astrocytoma (12% vs. 21%), oligodendroglioma (15% vs. 27%) and other glioma (6% vs. 11%). Also neuroepitheliomatous tumours were more frequent in users, however, the difference was less pronounced as in the study of Muscat et al (9), possibly reflecting differences in diagnostic procedures. The difference, however, that is consistent between both studies, is that between high-grade and low-grade tumours, fast and slowly growing ones. In both studies the frequency of low grade, slowly growing tumours was substantially higher in mobile phone users as compared to non-users. Also in the study of Inskip et al (4) the authors did not note this important effect. Because of this important and yet unexplained difference, further investigation should put emphasis on the determination of growth rate.
However, only 2.6% of the cases and 3.3% of the controls had used phones regularly for more than 5 years (4). The authors did not state anything about use with extended antenna but since the study was done at about the same time as Muscat et al did their study (9) it can be assumed that the same is valid here and thus the majority may have been using the phone with extended antenna. Thus, also here the study population is small and the exposure is low, something that the authors also point out: ‘potential risks associated with digital phones or higher operating frequencies could not be addressed’. Furthermore they say: ‘they are not sufficient to evaluate the risks among long-term, heavy users and for potentially long induction periods’. A small increased risk for anaplastic astrocytoma was seen with OR = 1.8 (95% CI = 0.7-5.1), but Boice and McLaughlin chose to disregard this in their review. Also for acoustic neuroma a risk increase with OR = 1.9 (95% CI = 0.6-5.9) was found among those who had used a mobile phone ≥5 years.

A second report by Muscat et al (10) about mobile phones and acoustic neuroma contains strong evidence for a reversal of cause and effect: they found a higher incidence of acoustic neuroma at the contralateral side (with respect to predominant mobile phone use), which is consistent with the assumption that cases tended to change the side of phone use because of hearing problems caused by the growth of the tumour. This is totally according to expectation but points to the insufficient latency because it indicates that mobile phone use followed and not preceded the development of the disease. The side of the phone could also have been misclassified if information on the used ear was not assessed for the whole period of use.

Auvinen et al (11) studied brain tumours among 398 cases diagnosed during 1996. Also in this study the total number of users was low, only 13% of the cases had ever had a mobile phone subscription. The inclusion time was very short, for analogue (NMT) users 2-3 years and for digital (GSM) less than one year. They reported an increased risk for gloma, OR = 2.1 (95% CI = 1.3-3.4) for NMT users whereas for GSM the OR was 1.0. When the duration of use of analogue phones was analysed as a continuous variable a significant risk increase with 20% per year was seen for glioma, OR = 1.2 (95% CI = 1.1-1.5). Boice and McLaughlin did not discuss this finding. Auvinen et al (11) concluded that further studies with a larger number of cases and a better exposure assessment and longer exposure duration are necessary for a meaningful risk assessment.

The five studies (2,4,9-11) mentioned in the SSI report (1) as corroborating the hypothesis of no association, have in common that they covered very few cancer cases with mobile phone use and they also had very short duration of use. None of the studies can in principle say anything about SAR were possible to obtain.

Let us also review some of the statements indicating lack of epidemiological accuracy. Some results in the Boice and McLaughlin report are given without stating the number of individuals involved. Some of the confidence intervals will become wide because of the low number of long-term users. The discussion about risk with regard to laterality is strange. They avoid mentioning that the significant results were found for ipsilateral phone use, while no increased risk was seen for contralateral use. They also carry out an unscientific discussion about dose-response depending on the type of phone used by the person. The only thing that can be said in this respect is that the number of hours of use for the different phones, but also here the knowledge is imprecise because no data about SAR were available.

Boice and McLaughlin make a rather remarkable statement about the inclusion criteria in the Hardell et al (6-8) studies that only included patients alive at the time of the investigation ‘study results based only on survivors are likely to be distorted since the surviving cases represent a highly selected group’. Since a significantly increased risk was found in the overall material for analogue phones, OR = 1.3 (95% CI = 1.02-1.6) and a particularly high risk for acoustic neuroma, OR = 3.5 (95% CI = 1.8-6.8) their statement means that mobile phone use should have a preventive effect for development of brain tumour among persons dying shortly after their operation, thus particularly for the malignant tumours. To get a total risk of 1.0 a decreased risk is needed among the deceased. That is not biologically plausible. Furthermore, it is not clear how their statement can be valid for acoustic neuroma, which has a good prognosis.

Let us close this by some remarks about study design. Both the Hardell et al (6-8) and the three US studies (4,9,10) were case-control studies and standard methodology was used. In general the Swedish studies can be considered to be the
better ones from a methodological point of view by their access to different registers. The US studies were using hospital patients as controls, which is a selected group and cannot be considered representing the general population. All studies used questionnaires to assess exposure. In the Muscat et al study (9) the interviews were done with the patients at bedside within a few days after a brain tumour surgery. Also in the Inskip et al study interviews were done at hospitals (4). It can be discussed how valid the answers may be with regard to the situation with a recent operation with anaesthesia, ongoing drug therapy and the trauma the diagnose itself means. In the Swedish studies the interviews were done in a quiet stage a few months after surgery and in the home of the patients. This is an advantage compared to the other procedures.

Boice and McLaughlin bring forward no factual reasons for the statements about the Swedish studies being non-informative. They complain about the detailed presentation of the results and state that this may mean that the results are found by ‘chance’ without discussing the biological plausibility of the results. Detail reporting is more scientifically valid than just selecting some of the results. Let us quote the study by Auvinen et al (11): ‘in conclusion, information obtained directly from subjects on mobile phone use seems preferable to a register-based approach, which has insufficient level of information’. This should have been something for Boice and McLaughlin to consider in their review of the studies they themselves participated in.

4. Experimental studies

Concerning experimental studies it is concluded in the SSI report that the only positive report on an association between exposure to mobile phone type signals and cancer (17), now can be refuted since another study with the same type of transgenic mice did not find any effect (18). However, these two studies are very different in design and it is not possible to draw that conclusion. Repacholi et al (17) exposed the mice 30 min before light on at 06:00 and another 30 min 12 h later before light off for 18 months. Utteridge et al (18) exposed the animals for 60 min during daytime, 5 days per week, for 24 months. What influence has these different timings of exposure, both the intermittence and the time of the day? Can it be said that 2x30 min is equal to 1x60 min? Today we do not have an answer to this. In radiation therapy fractionated doses are used, i.e. two treatments per day, to reduce the repair time of the cell damage.

Another difference between the two studies is that in the first one the animals were free to move in their cages during exposure while in the second one they were restrained in tubes. The latter is better from a dosimetrical point of view but instead a stress reaction cannot be ruled out. To what extent this would influence the cancer development is not precisely known. It should, however, be noted that immobilisation stress might obscure an effect of exposure (19).

The allusion to the study of Utteridge et al (18) should suffice as an example how the evidence has been distorted: ‘thus it can be concluded that the Repacholi et al (17) study has been refuted, which is of importance because this was the only experimental evidence suggesting a carcinogenic effect from RF exposure in the animal literature’. Even a beginner in science knows that only the hypothesis of no effect can be refuted, while a positive finding cannot be balanced by a negative result. The chance to erroneously accept the hypothesis of no effect is in most cases considerably higher as the chance to erroneously reject the hypothesis of no effect! But there are many other reasons, material ones, why the result by Utteridge et al (18) is doubtful; however, the SSI report takes it for granted.

5. Interaction mechanisms

The mechanistic understanding of how low intensity microwaves affect living tissue is unfortunately almost non-existent. Interestingly enough, findings from several experimental systems, i.e. cells, worms and chick embryos (20-22) show that the exposure affects the expression of stress proteins (heat shock proteins, hsp). It is still not established if these changes only are of positive character or if they can lead to detrimental effects.

French et al (23) have in a review article proposed the hypotheses that radiofrequency fields can cause chronically increased levels of a specific protein, hsp70. A short increase is a normal and powerful defence mechanism, but according to French et al (23) long-term increased levels may cause an increased risk of tumour formation. The area is, however, to a large extent unexplored.

6. Concluding remarks

With this as a background we find it remarkable that the authors of the SSI report can put forward the cohort studies and the hospital-based case control studies in the way they are doing without considering the shortcomings in these studies, and the limited possibility they offer for making a statement about long-term heavy use of cellular phones, especially of the digital type. They conclude: ‘in our view, a consistent picture has emerged from these studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date’. In the hands of other authors of reviews that would take into account all the existing data as well as the shortcomings that appear in the studies, both the epidemiological ones and the experimental work, the conclusion may very well have been the complete opposite: ‘in our view, a consistent picture is emerging from these studies that a causal association between use of cellular phones and brain tumours cannot be ruled out’.

The current state of knowledge is thus not reassuring and further research is needed to find an answer to the question whether there are health risks associated with the use of mobile phones based on scientific findings. Regarding the recent Swedish study more results have been published that further refute the critique by Boice and McLaughlin (24,25).

References