MOBILE TELEPHONES AND CANCER—A REVIEW OF EPIDEMIOLOGICAL EVIDENCE

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There is considerable public concern about possible long-term adverse health effects of mobile phones. While there is scientific controversy about long-term health effects of high-frequency electromagnetic fields lasting for at least 50 yr, the rise and success of mobile telecommunication made it necessary to investigate the problem more comprehensively and assess the possible risk cautiously because never before in history has a substantial proportion of the population been exposed to microwaves in the near field and at comparably high levels. Because the mostly localized exposure target region is the head, most epidemiological studies focus on brain tumors. Overall nine epidemiological studies have been published, four from the United States, two from Sweden, and one each from Denmark, Finland, and Germany. Seven studies were mainly on brain tumors, with one investigating in addition to brain tumors salivary gland cancer and another cancer of the hemato-poietic and lymphatic tissues, and one examining intraocular melanoma. All studies have some methodological deficiencies: (1) too short duration of mobile phone use to be helpful in risk assessment, (2) exposure was not rigorously determined, and (3) there is a possibility of recall and response error in some studies. Nevertheless, all studies approaching reasonable latencies found an increased cancer risk associated with mobile phone use. Estimates of relative risk in these studies vary between 1.3 and 4.6 with highest overall risk for acoustic neuroma (3.5) and uveal melanoma (4.2), and there is evidence for enhanced cancer risk with increasing latency and duration of mobile phone use.

Several reviews on the issue of possible adverse health effects of mobile phones have been published (Moulder et al., 1999; Royal Society of Canada, 1999; IEGMP, 2000; Rothman, 2000; Krewski et al., 2001a, 2001b; Health Council of the Netherlands, 2002). Most of these reviews stated that evidence for a relationship between the use of cellular telephones and cancer is weak to nonexistent. The most recent one (Boice & McLaughlin, 2002) published by the Swedish Radiation Protection Institute (SSI) even claimed that "a consistent picture has emerged from these [epidemio-logical] studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date." (p. 2).

The issue of a possible relationship between mobile phone use and cancer is of considerable importance with respect to public health because there has never been a comparable situation in which hundreds of millions of people are exposed in the near field to comparatively high levels of micro-waves. Except for special applications of wireless technology, mobile telecommunication emerged about 20 yr ago, but a substantial population began to use this technology only in the last decade following the development of digital systems. In the near future, already the third generation of mobile telephones will be marketed on a greater scale and it is possible and even likely that the issue of a relationship between mobile phone use and cancer will still not have been resolved by then. The rate of technological change makes epidemiological studies of effects of these products extremely difficult if not impossible. This is due to the long induction periods and latencies. At present the differences between the first-generation analogue telephones and digital telephones, let alone the differences within these groups, make an overall assessment difficult. In the future this will be aggravated by the introduction of new generation telephones. These differences are considerable

and crucial: Some older analogue system phones operated at higher power but had often extensible antennas, leading to a completely different exposure pattern as compared to digital telephones. There is no agreement on whether or not type of modulation of carrier waves plays an important role. If it does, then also differences between frequency and pulse modulated systems have to be considered. In addition, type and location of the antenna vary considerably, leading again to substantial differences in exposed regions of the body. Furthermore, there is evidence for great variation in absorption rate in different subjects. Hence the fact that someone is a user of a mobile telephone is only a very crude approximation for actual exposure. It has to be stressed that due to the fact that it is almost impossible at present to evaluate actual exposure at the site of interest (e.g., bone marrow, brain tissue, choroid), every epidemiological finding based only on the surrogates, type of phone and duration and intensity of use, will be biased toward the null hypothesis. The bias will be greater the cruder the estimate.

Despite great progress in dosimetry, calculation of internal exposure and measurements in phantoms are still only rough approximations. Note that the volume of averaging is 1 or 10 g of "tissue" that, in reality, is dielectrically not homogeneous. Within such a volume there are typically 10^8 to 10^{10} cells that may be exposed to quite different field strengths depending on the structure of the tissue. Although average temperature increases within the volumes of interest may be negligibly small, this does not preclude a response of the cells to the internal field based on a local change in ion–ligand binding or other processes that may interfere with cellular function (Adey, 1997). However, understanding of mechanisms other than those based on heating is still poor.

From these considerations it follows that even if there is sufficient information on exposure at the individual level, still no quantitative index of that aspect of the exposure that is crucial for an effect to occur can be derived.

Many discussions about a possible relation between mobile phone use and cancer start from the argument that the photon energy of microwave radiation is far too low to induce breaking of molecular bonds and thus exposure cannot directly affect DNA integrity. While this is obviously true, it seems to imply that because this is the case such exposures cannot be mutagenic. It must be emphasized that for low-level exposure to ionizing radiation only about 35% of DNA damage is produced by such direct effects, while the higher proportion is due to radical formation (Reuvers et al., 1973). In tissues or confluent cell suspensions in addition the bystander effect must be considered. Besides the fact that not even for ionizing radiation-induced carcinogenesis is a direct effect on DNA a necessary condition, malignant processes can be affected at a multitude of stages and thereby increase the risk of disease. Roughly, the process can be subdivided into the following stages: initiation (occurrence of a mutation, either induced or spontaneous), fixation (cells have to undergo divisions in order that the mutation will be fixed within the genome), survival (deviant cells or their daughter cells have to survive the life span of the organism), promotion (the clone has to grow to reach the neoplastic stage), progression (increase of malignancy, invasive growth, angiogenesis, metastases, etc.). At the initiation stage, processes acting at the level of the genome and epigenetic processes have to be discriminated. There are factors that increase mutation rate by damage of DNA and factors that reduce DNA repair capability and/or efficiency. The net result is the same: an irreversible state of DNA deviation that may lead to a malignancy. A necessary condition, however, is the fixation of genetic deviation by cell division and block of apoptosis. Hence, factors that promote cell division or reduce apoptosis will be efficient also at initiation stage. Similar conditions apply to progression, because it typically involves genetic events. Additionally, there are factors that influence tumor–host interaction. Such factors may reduce or increase host defense mechanisms, and others may reduce or increase efficiency of the transformed cells. At this level small changes may have great effects, due to the resultant imbalance between tumor growth and tumor attack by hosts defense mechanisms.

It is a very simplistic view to look at a possible carcinogenetic effect of microwave exposure only with respect to induction of malignant transformation. Some of the reports on epidemiological studies contain statements about possible mechanisms of action:

"Because RF [radio frequency] signals are unlikely to cause gene mutations, the biologic process underlying a possible association between exposure to cellular telephones and the risk of cancer

has been proposed to be a thermal or nonthermal mechanism that promotes tumor growth" (Johansen et al., 2001, p. 206).

"If RF energy from cellular telephones is tumorigenic, it might act as a promoter or in the progression phase of cancer" (Muscat et al., 2000b, p. 3007).

"A hypothesized mode of action is that RFR [radio frequency radiation] might promote (that is, speed up) the development of cancer that has been caused by other agents . . . if RFR decreased the amount of ocular melatonin, it would promote the development of uveal melanoma" (Stang et al., 2001, p. 11).

"It is generally agreed that the heating of brain tissue by cellular telephones is negligible, and that any carcinogenic effect would have to be mediated through a nonthermal mechanism, the nature of which remain a matter of speculation. Direct genotoxic effects are unlikely" (Inskip et al., 2001, p. 79).

Epidemiological studies have not been specifically designed to test a promoting effect or an influence at the progression stage. All studies published so far were designed to estimate relative risk (the ratio of incidences in exposed to not exposed) either applying the case-control paradigm or a cohort study methodology. However, if an agent acts as a promoter or at the progression stage this effect is grossly underestimated by relative risk, which is efficient to estimate risk of initiation. This can easily be shown by application of multistage models. In the future, emphasis should be put on the time of first use and intensity of use of mobile phones. These data may be modeled along the lines of a multistage model (following, e.g., Moolgavkar & Luebeck, 1990). Furthermore, especially for brain tumors it is of utmost importance to assess the time point of first clinical signs of the disease and to analyze the duration between these first signs and diagnosis as a surrogate for growth rate.

There is a debate going on for decades concerning indications from epidemiological studies supporting a causal hypothesis. This debate has been triggered mainly by the tobacco controversy. The issue has not been resolved yet; however, a number of important distinctions have been made that are widely accepted by the scientific community and that go back to the Hill criteria (Hill, 1965). Among these criteria there is one that is necessary and several that are supportive but neither necessary nor sufficient for a decision on the causative role of the agent. It is significant that in the context of electromagnetic field (EMF) research and its evaluation the supportive criteria have been discussed (Repacholi & Cardis, 1997; Repacholi & Stolwijk, 1991), while the only one that is necessary has not even been mentioned. It is no surprise then that most epidemiological studies of a possible association between EMFs and cancer are insufficient with respect to this criterion, and this is especially true for the studies of mobile telephones. The only necessary criterion of a causation is that there is a reasonable latency between onset of exposure and diagnosis. The latency has to conform with what is known about the dynamics of the disease. Concerning brain tumors, ocular melanoma, and leukemia, diseases of main interest in this context, little is known about induction period and latencies. Information concerning latency stems from x-ray therapy of tinea capitis, childhood leukemia, and ankylosing spondylitis, from atomic bomb survivors and studies of occupational exposures. From these sources a minimum latency of 5 yr can be derived. Concerning acute leukemia, shorter latencies are possible due to the early differentiation stage of the deviant cell population. However, for brain tumors, exposures more recent than 5 yr before diagnosis should be discarded in the analysis, at least if the study is designed to estimate relative risk with respect to incidence. Studies investigating influences on promotion or progression are not restricted by latency considerations but have to be designed and analyzed differently (discussed earlier).

For evaluation of epidemiological evidence the scheme outlined in Table 1 has been used. The criteria for classification presented are only the most important ones; other considerations and criteria specific for the various designs were supplemented.

EPIDEMIOLOGICAL STUDIES

Overall, nine epidemiological studies (see Table 2) on mobile phones and cancer have been published so far: four studies in the United States, two in Sweden, and one each in Finland, Germany, and Denmark. All except two were case-control studies.

TABLE 1. Criteria for the Classification of Epidemiological Studies

Classification	*Description* and criteria
Evidence of association	*Study provides conclusive evidence for an association between exposure to the agent and the outcome of interest* Exposure history, including measurements, provided on an individual basis Relevant confounders considered Latency consistent with etiology of the disease No heterogeneity of risk across relevant strata Clear indication of increase of risk with increase in meaningful exposure meta-meter
Weak evidence of association	*Study provides some evidence for an association between exposure to the agent and the outcome of interest* Exposure history on an individual basis with some supportive measurements Relevant confounders considered Latency approaching meaningful values consistent with aetiology of the disease No heterogeneity of risk across relevant strata Some indication of increase of risk with increase in meaningful exposure meta-meter
Limited evidence of association	*Study provides limited evidence for an association between exposure to the agent and the outcome of interest* Only surrogates of exposure history available Relevant confounders considered Latency approaching meaningful values consistent with aetiology of the disease Some heterogeneity of risk across relevant strata or no indication of increase of risk with increase in meaningful exposure meta-meter or no meaningful exposure meta-meter available
Very limited evidence of association	*Study provides only very limited evidence for an association between exposure to the agent and the outcome of interest* Only surrogates of exposure history available Latency not sufficient in a relevant proportion of cases Not all relevant confounders considered or some heterogeneity of risk across relevant strata or no indication of increase of risk with increase in meaningful exposure meta-meter or no meaningful exposure meta-meter available
Inconclusive	*Study is inconclusive with respect to an association between exposure to the agent and the outcome of interest* Assessment of exposure history insufficient or latency too short in the majority of cases or relevant confounders not considered or gross heterogeneity of risk across relevant strata
Non-informative	*Study is noninformative with respect to an association between exposure to the agent and the outcome of interest* Too small number of relevant cases (power 50% or less to detect a moderately elevated risk) Too short duration of follow-up No information on exposure
Evidence of no association	*Study provides evidence for lack of association between exposure to the agent and the outcome of interest* Study has high (~ 90%) power to detect a relevant risk Latency is sufficient to detect an effect at all stages of the disease No association with the relevant endpoint but association with known confounders Several meaningful exposure meta-meters do not change the overall lack of association (e.g., duration, intensity of exposure, peak and average exposures)

Rothman et al. (1996b) and Dreyer et al. (1999)

Design   The first study published was a cohort mortality study among cellular telephone customers in the metropolitan areas of Boston, Chicago, Dallas, and Washington, DC (Rothman et al., 1996b). The study has not been completed due to legal problems, and only results of overall mortality during 1 yr of follow-up have been reported and some additional analyses on cause specific mortality (Dreyer et al., 1999). The design was based on a sound idea, that in order to assess a possible brain tumor risk associated with mobile phone use it would be best to compare customers

using cellular telephones with the antenna in the handpiece to those using transportable bag phones with the antenna separated from the head piece. Telecommunication companies provided data files of customers, in total 770,390 records, from which 256,284 records with an ascertained social security number could be matched to the Death Master File.

Results   In total, 604 deaths occurred during 1994, considerably less than expected from the total population, which can be attributed to a healthy group effect, because subjects were selected with active accounts on 1, January 1994 and few had accounts for longer than two years. There was no statistically significant difference in mortality rates between users of the two types of telephones. Unfortunately telephone type was unknown for 58%, 19% had a mobile telephone with the antenna in the handpiece, and 23% used a portable bag or car telephone.

Discussion   The study cannot be evaluated as it is because of the insufficient follow-up, small number of deaths, and high number of customers with unknown telephone type. It can be seen as a feasibility study, especially if the additional information in Rothman et al. (1996a) and Funch et al. (1996) is used. In contrast to the evaluation by some reviewers, including those of the Swedish Radiation Protection Institute (Boice & McLaughlin, 2002), the results of these studies demonstrate that usage of subscriber lists is an insufficient means to conduct cohort or case-control studies (a conclusion that was also drawn by Auvinen et al., 2002). It provides no reliable data on individual telephone use. Funch et al. (1996) showed that only 48% of subscribers were the only users of the mobile telephone; furthermore, only a correlation of .74 was found between billing records and reported cellular telephone use. Altogether these data demonstrate that records from providers as the only basis are insufficient and will result in substantial exposure misclassification. It is interesting to note that the original idea of the study, the comparison of two types of mobile phones with different locations of the antenna, cannot be pursued anymore because bag telephones are out of use. This points again to the problems epidemiology is facing due to the fast technological changes.

Hardell et al. (1999, 2000, 2001)

Design   A registry-based case-control study has been reported by Hardell et al. (1999, 2000, 2001). Originally the study was designed to analyze cases of primary brain cancer in the Uppsala–Oerebro region that were registered during 1994–1996, and in the Stockholm region during 1995–1996. Later, on request of the WHO International EMF project that was conducting a feasibility study, cases of benign brain tumors were also included, but only for the Stockholm region and only for the year 1996, to fulfil the time criteria for the WHO study. This caused a controversy, because the authors were accused of not including all eligible cases (Ahlbom & Feychting, 1999). From 270 cases fulfilling the inclusion criteria, 37 were excluded because their attending physician judged them as unable to participate. Two controls were matched by gender, age, and study region to each of the 233 cases using the Swedish Population Register. A questionnaire was sent to cases and controls containing questions about various topics: medical x-ray examination, occupational exposure to chemicals, drinking habits (low-energy drinks), and cellular telephone use. When answers were missing or unclear, a trained nurse (blinded to case status) supplemented the information by telephone interviews. By this method a high response rate was reached amounting to 93% in cases and 94% in controls. A further eight cases (and their controls) had to be omitted after analysis of their medical records because of recurrent disease or misdiagnosis. Thus the study encompasses 209 cases and 425 controls and for analyses of tumor location 197 cases with available histopathologic reports.

Results   Overall there was no difference between cases and controls concerning percentage of users of mobile phones (37% vs. 38%) and median number of hours a mobile telephone was used (in total 136 h); hence the overall odds ratio (OR) was close to 1: OR=0.98 (95% confidence interval CI 0.69, 1.41). Within the overall analysis a latency of 1 yr was considered (all exposures within 1 yr prior to diagnosis were disregarded). From 78 exposed cases lateral tumor locations were observed in 75 (53 malignant and 22 benign). Some of the odds ratios of ipsilateral use (reported predominant mobile phone use at the side the tumor was located) were elevated, especially for temporal locations (OR=3.03 for right side and OR=1.55 for left side). A further analysis (Hardell et al., 2000, 2001) gave a combined odds ratio of 2.42 for ipsilateral use and temporal, occipital, and temporo-parietal locations, which increased to a significant value of 2.62 (CI: 1.02, 6.71) in the

multivariate analysis. However, these figures are only based on small numbers of exposed cases and must be interpreted with caution.

Discussion   From the viewpoint of a possible association between brain tumors and mobile phone use these results have to be interpreted as underestimations of the true risk. If exposure acts as a promoter or during progression stage, estimates of relative risks underestimate this effect considerably. Furthermore, although the study had a higher proportion of subjects with long-term use as compared to the other investigations, there are too few cases of relevant brain tumor types that can be considered in a latency analysis. Brain tumors comprise a heterogeneous class differing in origin, malignancy, and other features (Black, 1991); hence it is conceivable that not all of them are affected equally by exposure to EMFs, so that combining them in an overall estimate will dilute the effect.

On the other hand, if there is actually no association between mobile phone use and brain tumors, is there an alternative explanation for the results? Various arguments have been put forward that should throw doubt on the validity of the findings. One of these arguments refers to the fact that the investigation was prevalence based (Boice & McLaughlin, 2002). However, this is a completely irrelevant argument against positive findings. Studies of cancer with high fatality rates that leave out deceased cases may have a considerably reduced power to detect an existing risk. Furthermore, an ambiguity may arise if a factor is not related to the disease but only to lethality. The assumption that the positive association between ipsilateral use of a mobile phone and brain tumors is due to leaving out deceased cases is only consistent with the assumption that the use of a mobile phone is protective against early death from brain tumor, or, equivalently, beneficial for high-grade tumors. This is a very remote possibility, although a "hormesis" effect of exposure to EMFs is discussed, but it is hard to believe that it is restricted to tumors of high malignancy.

Another argument must be taken more seriously. It is the possibility of recall error in cases and controls concerning mobile phone use and especially concerning side of the head where the telephone was held during conversations. Recall bias is an important source of error in case-control studies. But it is not possible to make a general statement about the magnitude and direction this bias may have on risk estimates. This is due to the fact that the consequences of recall bias depend on six parameters (and multiples thereof if they vary across strata): the recalled rates of mobile phone usage in cases and controls, the false exposure rates in cases and controls, and the false nonexposure rates in cases and controls. With all other parameters held constant, the effect of recall bias may lead to spurious positive results if the false exposure rates are higher in cases than in controls. In the extreme case that there is no recall bias in controls and only a recall bias in cases reporting mobile phone use but not in those reporting no use, the bias (ratio of estimated to true odds ratio) is given by the simple formula $[1 - (1-f)e]/[(1-f)(1-e)]$, where f is the rate of falsely stated exposure to mobile phones in a proportion e of cases reporting such use. Considering that the rate of stated mobile phone use was approximately 37%, in order to reduce the observed odds ratio of 2.6 to 1.0, inserting into the formula reveals that the recall bias f must be 0.5; hence 50% of those stating use of the mobile phone on the side of the head where the tumor was located must have been wrong while all other answers were correct. It is hardly conceivable that this was the case. In contrast to what has been stated in some comments (e.g., Health Council of the Netherlands, 2002), the habit of holding the phone preferentially to one side of the head is stable, not unlike being right- or left-handed, and there can almost be no error of memory. If there is a bias, it must have other sources as simple problems of recall. There might be a tendency to blame the mobile phone as a causal factor of the disease. However, at the time of the study, in 1997, there was almost no public discussion yet about this issue and mobile phone use was not the only factor investigated, and hence a similar bias has to be expected for other exposures investigated, but there is no indication that this happened. Overall, recall bias is a very unlikely explanation for the reported association. Note that the other recall biases, the false exposure rate in controls, and the false nonexposure rate in cases lead to an underestimation of the true risk.

Exposure to emissions from mobile phones during calls is restricted to the side of the head where the antenna is located. Exposure at the contralateral side is at least a factor of 10 lower (Dimbylow & Mann, 1999). Hence if tumors are considered that originate and grow locally, estimating the incidence ratio based on all tumors amounts to case misclassification, and to base it on

all mobile phone users amounts to exposure misclassification. In analogy to irradiation-induced brain tumors, only those can be considered that manifest themselves at or around the exposed region. Due to different types of mobile phones and different habits of use these regions vary. Highest exposures occur in the temporal, temporo-parietal, parieto-occipital, and occipital regions. Older types of mobile phones, especially those with extensible antennas, may have a pattern of exposure shifted more to the parietal and occipital region. Only tumors at these locations and the regional cranial nerves and meninges can be considered in a study of localized exposure. Furthermore, a case can only be considered exposed if exposure occurred at the ipsilateral side (predominant side of use). As with many other functions, telephone use is strictly lateralized and very few subjects (around 10%) demonstrate no preference for one side. There are different ways to deal with this problem: Exposure can be stratified into four categories: (1) no use of a mobile telephone, (2) contralateral use, (3) use at both sides, and (4) ipsilateral use. However, no such stratification is possible in controls because ipsilaterality cannot be defined, and hence all matched controls in each subset that use a mobile phone have to be considered exposed. Another method has been proposed by Inskip et al. (2001); it estimates relative risk based on the odds ratio of ipsilateral relative to contralateral use. However, in this case information from controls is neglected, and besides the possibility of confounding, the power is substantially reduced. The first method has been used by Hardell et al. (1999). It has been stated (Health Council of the Netherlands, 2002) that "Research on this so-called laterality can better be conducted in a cohort study." Concerns have been raised that subjects might give biased answers if the object of the research were known. However, this was not the case in the study of Hardell et al. (1999, 2000, 2001). Further, biased coding and interviewer bias are very unlikely because interviewers and personnel checking and coding the data were blinded to the case status. It is a triviality that it would be better to conduct a cohort study, but besides the long duration of such a study and the enormous sample size necessary, there are other shortcomings that make them difficult if not impossible (e.g., prospective exposure surveillance).

It seems that there are no valid or strong arguments against the reported association between ipsilateral use of mobile phones and brain tumors. However, the strongest arguments have consistently been given by the authors themselves: In their first paper (Hardell et al., 1999) and both subsequent publications (Hardell et al., 2000, 2001) they stated that results were based on low numbers and must be interpreted with caution. From a purely statistical point of view, a significant result in a small sample is a stronger indication of an effect than in a large sample. The problem is that the ordinary theory of random samples cannot be applied to case-control studies of this type because all cases within a certain region and during a certain period of time that fulfill the inclusion criteria are intentionally included and only controls are randomly sampled. This may cause a dependency on features of the population of cases that are related to the region or time period. The only possibility to overcome this problem is a (random) selection of a variety of other regions and to investigate the robustness of the association across these regions. The number of relevant cases was too small to make an internal robustness analysis. Therefore, the advice by the authors to apply caution in interpreting the association is well founded.

Muscat et al. (2000b)

Design   Muscat et al. (2000b) studied malignant brain tumors in patients from five different hospitals in the United States accrued between 1994 and 1998. Data from 469 cases and 422 controls matched for gender, age, race, hospital, and month of admission were available. Controls were hospital patients. In two hospitals controls were predominantly cancer patients. Information on mobile phone use was obtained by structured interviews with patients, and in the first year also with proxies (in total 49). According to a presentation at a meeting (Muscat et al., 2000a), most case patients were interviewed within 24 to 48 h after surgery. Control patients were interviewed on average 5 mo later than case patients. From eligible cases, 132 (23%) were excluded due to death or illness.

Results   Only 66 cases (14%) had been using mobile phones, and the corresponding number among the controls was 76 (18%). Eighty-six percent of cases and 85% of controls had been using an extended antenna during calls. Overall 88% were using analogue phones and more than 50% of one brand only. The mean duration of use was 2.8 yr for cases and 2.7 yr for controls. Only 17 cases

(4%) and 22 controls (5%) had been using the mobile phone 4 yr or longer. The average usage time per month was 2.5 h and 2.2 h for cases and controls (that is, about 4 to 5 min/d), respectively. Overall the OR associated with use of a handheld cellular telephone was 0.8 (CI: 0.6, 1.2). The highest histological-specific risk estimate was found for neuroepitheliomatous cancers with an OR of 2.1 (CI: 0.9, 4.7); however, it seems that diagnosis was not unequivocal in all cases. Brain tumors occurred more frequently on the ipsilateral side (the side where the telephone was predominantly used) than on the contralateral side (26 vs. 15 cases).

Discussion   The study has a number of severe methodological deficiencies. If, as has been done by Hardell et al. (1999), the last year preceding diagnosis is omitted from evaluation of exposure, the number of cases and controls using a mobile phone would be reduced to 45 and 46, respectively, numbers too low to provide a meaningful basis for analysis. Note that already in 1948 several conditions for irradiation-induced brain tumors had been established, among them that exposure must precede diagnosis by at least 5 yr and localization of tumor must be at the irradiated site (Cahan et al., 1948). If these conditions had been observed it seems that not more than about five cases would remain for analysis. It seems that authors were aware of these problems. They stated, "Further studies are needed to account for longer induction periods, especially for slow-growing tumors" (Muscat et al., 2000b, p. 3007).

Furthermore, as cited earlier, they tend to assume that if exposure from mobile phones is tumorigenic, it might act as a promoter or at the progression stage. If this is the case then the predominance of glioblastoma, accounting for more than half of their cases, might obscure an effect at these stages. This is due to the high malignancy of these tumors, with only weeks to at most months between first clinical signs and diagnosis. The tumor grows so rapidly that endothelial walls of tumor-supplying vessels are often deficient and hypoxia of brain tissue occurs, leading to necrosis. It is impossible to detect an effect on growth of glioblastoma using a traditional case-control design. Very little is known about induction period of these tumors; it is possible that initial transformation already occurs during embryogenesis, but there is definitely a possibility that environmental conditions such as exposure to emissions from mobile phones promote differentiation into the malignant phenotype.

Up to now no environmental or occupational factor has been firmly established to be associated with the development of glioblastoma, while there is sufficient evidence of x-ray-induced meningioma and meningeal sarcoma (Karlsson et al., 1998; Daentzer & Boker, 1999; Strojan et al., 2000). If an agent is effective during the latent phase of tumorigenesis, many years and maybe decades must expire before overt disease occurs. Hence the study is deficient both for rapid- as well as for slow-growing tumors, since duration of mobile phone use was too short for an effect on the latent stage and effects during the growth phase cannot be studied by this case-control approach.

From the viewpoint that there is an association between mobile phone use and brain cancer the study is inconclusive because there are almost no relevant data on this issue. Some support, however, may be seen in the effect on laterality. From 41 evaluable tumors, 26 occurred at the side predominantly used during calls and only 15 on the contralateral side. However, Muscat et al. (2000b) argued that frequency of tumors in the temporal lobe was somewhat higher on the contralateral side. In the recent review of the SSI (Boice & McLaughlin, 2002) it was stated that this is the region of highest exposure. However, the review neglected the fact that 86% used an extension antenna, which results in a shift of the exposure pattern to the parietal and occipital region (depending on the angle at which the phone is held during calls). Omitting temporal tumors would result in a highly significant laterality of 21 versus 6 cases. However, it was not reported how many of the remaining tumors were in the frontal lobe, which receives also only low amounts of irradiation and must also be omitted. A reasonable method to assess laterality would be to calculate the specific energy absorption rate (SAR) for the brands of mobile phones used by each subject (including the information on extending the antenna) scaled by the anatomical features of the head of the patient and to select the regions of exposure based on this information.

Another aspect should be mentioned that was not discussed by Muscat et al. (2000b): There was a highly significant difference in the distributions of histological types between users of handheld cellular telephones and nonusers, 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%). There are different explanations for this finding: If there is an effect of mobile phone use on tumor growth rate, it would result in a relative shift from fast-growing to slow-growing tumors; on the other hand, the difference could be due to age and gender, because histological types vary with age and gender, as is the case for mobile phone prevalence. Another explanation would be that patients who develop high-grade brain tumors avoid using mobile telephones; however, this explanation is unsatisfactory because these patients often have no early clinical signs while those developing low-grade tumors may experience years of various symptoms that are more likely to result in avoidance of mobile telephones.

Strictly speaking, there is no support for the hypothesis of no association between cellular telephone use and brain cancer from this study due to the methodological problems mentioned. Considering marked effects at an advanced stage of the malignant process, the study seems to rule out a contribution of mobile phone use because neither an association with years of use nor an association with intensity of use was found. However, some caveats are necessary. The study has been attributed as an incidence study, but besides the fact that a hospital-based study of brain cancer can never be an incidence study (patients dying prior to hospital admission are excluded), also almost a quarter of all eligible cases have been omitted due to their state of illness. Furthermore, subjects were interviewed by personnel not blinded to case status and only shortly after surgery that may have resulted in interviewer as well as recall bias. Muscat et al. (2001) have argued that recall bias usually results in spurious positive results, which is wrong (see earlier discussion). Finally, due to the predominance of high-grade tumors, even significant effects at an advanced stage could have remained unnoticed.

Inskip et al. (2001)

Design   A similar case-control study that also included benign brain tumors was reported by Inskip et al. (2001). The study, comprising 782 cases diagnosed during 1994–1998, was also hospital based. It enrolled 489 patients with primary malignant brain tumors but also 197 patients with intracranial meningioma and 96 patients with acoustic neuroma. Overall 799 hospital-based control patients were frequency matched by gender, age, ethnic group, and proximity of residence to hospital. Interviews were done by a research nurse and were audiotaped. Because of illness or death of the patient, 97 (12%) proxy interviews were conducted in cases and 24 (3%) in controls.

Results   Regular use of a hand-held cellular telephone was reported in 18% of cases and in 22% of controls. No data were shown about extensible antennas; however, since the study was conducted during the same time period as that of Muscat et al. (2000b), a similarly high proportion can be assumed. Only 22 cases (3% of all cases; 16% of regular users) and 31 controls (4% of all controls; 18% of regular users) used a mobile telephone regularly for 5 yr or longer. Average daily use was not stated, but according to the distribution given it must have been similarly low as that reported by Muscat et al. (2000b). Further, no data on type of telephone were given, but considering the study period a predominance of analogue telephones can be assumed (as is also presumed by the authors). Overall 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 where the telephone was typically used. Highest relative risk with respect to affected lobe was found for the parietal lobe (1.1; CI: 0.6, 2.1). An increased risk of 1.9 was reported for acoustic neuromas in subjects using a mobile phone for 5 yr or longer, but this estimate was based on 5 cases only and was statistically not significant.

Discussion   Many of the same deficiencies as already noted for the study of Muscat et al. (2000b) are apparent in this investigation. The main problem is the low number of relevant cases. The authors concede that their "findings should be seen as an estimate of the risk at an early stage of the use of this technology" (Inskip et al., 2001, p. 85). However, it is questionable whether the results can contribute to risk assessment even under this limitation. As stated earlier, too little is known about the early stages of the malignant process and about location of its origin. For some types demonstrating a clear pattern of predilection and for tumors originating from neural tissue, growth at the location of malignant transformation can be assumed; however, how long it takes to reach a stage of autonomous growth is a matter of speculation in malignant tumors.

In benign tumors, growth rate is typically slow and time of diagnosis depends on chance and the location of growth, when the tumor causes atrophy of surrounding tissues. A causative role for exposure is possible (as has been indicated for x-ray exposure) but will afford study that covers decades of latency. There is a slight indication of rising risks for increasing years of use in meningioma: 0.5 for less than 0.5 yr, 0.8 for up to 3 yr, and 1.1 for 3 yr or more (0.9 for 5 yr or more but based on 6 cases only). In addition, effects might rather be on growth rate and be underestimated in this type of study. It is even possible that due to early symptoms of tumor growth, patients reduce or discontinue the use of mobile phones. Hence a negative association between daily use and risk might be observed for recent times while a positive one may occur for earlier periods.

In primary malignant brain tumors, growth rate depends on cell type and degree of malignancy. For slow-growing tumors the same arguments as for benign ones apply. For fast-growing tumors exposure effects on growth rate cannot be detected by the approach chosen. Hence the predominance of high-grade tumors comprising 45% of all malignant tumors in this study and 52% in the study of Muscat et al. (2000b) is a severe deficit.

Similar to the study of Muscat et al. (2000b), the difference in distribution of histological types between users and nonusers of mobile phones was highly significant. This difference is due to a pronounced reduction in the frequency of glioblastoma (57% in nonusers vs. 27% in users) and an increase in astrocytoma (12 vs. 21%), oligodendroglioma (15 vs. 27%), and other glioma (6 vs. 11%). Again neuroepithelomatous tumors were more frequent in users; however, the difference was less pronounced than in the study of Muscat et al. (2000b), possibly reflecting differences in diagnostic procedures. The difference, however, that is consistent between both studies is that between high-grade and low-grade tumors, fast- and slow-growing ones. In both studies the frequency of low-grade, slow-growing tumors was substantially higher in mobile phone users as compared to nonusers. A calculation of possible confounding by age reveals that the results are compatible with a doubling of growth rate even considering the higher age of subjects with glioblastoma and their lower prevalence of mobile phone use. It has to be emphasized that this does not prove that actually an influence on growth rate occurred, it should, however, alert the scientific community to apply designs that can be used to estimate not only incidence ratios but also effects on tumor growth.

Finally it should be mentioned that proxy interviews might be insufficient to assess laterality. It is doubtful whether even very close relatives have a correct recollection of what side of the head was used by the patient for placing the phone during calls.

The study supports neither the assumption of a brain tumor risk associated with mobile phone use nor the assumption of no risk. Authors conclude that their results "do not support the view that exposure to low-power microwave radiation from hand-held, analogue cellular telephones causes malignant or benign tumors of the brain or nervous system" (Inskip et al., 2001, p. 85), but they have not tested this assumption and therefore this conclusion is not correct. What they have tested is that exposure at an advanced stage of the disease has no influence on incidence. This can be answered in the affirmative, but whether this is a relevant hypothesis is doubtful.

Johansen et al. (2001)

Design   Johansen et al. (2001) performed a population-based cohort study by using subscription files from both Danish operating companies. Between 1982 (the year operation started) until the end of 1995, 723,421 subscribers were identified. During this period three types of mobile phone systems were operating: the NMT 450 and the NMT 900 (analogue systems operating in the 450- and 900-MHz frequency bands respectively) and the digital GSM 900 system. These systems were introduced into the market in the sequence stated. From the total of 723,421 subscribers, 303,326 were omitted for different reasons; the greatest part were corporate subscribers (200,507 subscriptions). The remaining 420,095 cellular telephone subscribers (58% of all subscribers) were matched with the Danish Cancer Registry for any entry until end of 1996. Year of first subscription was earlier than 1991 in 7.9%; hence for 92.1%, duration of observation cannot have been longer than 5 yr. Duration of subscription could only be computed for GSM subscribers, it was less than 3 yr in 92.9 %.

Results   During the follow-up period 3391 cancers were registered, equivalent to an incidence of about 300×10^{-5} cases per year. This is a quite low incidence, reflecting the low average age of the population of subscribers (median age in males was 37 and in females 38 yr). Standardized incidence ratio (SIR) with respect to the Danish population for all cancers was 0.86 in men and 1.03 in women. This low incidence in men is mainly due to less frequent cancers of the lung, pharynx, esophagus, and stomach. This points to a confounding effect of social class, besides a typical healthy group effect. This effect was not observed in women. No changes in SIRs in women were reported for cancers of pharynx, esophagus, rectum, larynx, breast, uterus, ovaries, kidney, and bladder and for lymphoma. Highest SIR in males was computed for testicular cancer (SIR=1.1; CI:1.0, 1.3).

Brain and nervous-system tumors and leukemia were of special interest and analyzed more comprehensively. Overall, 154 tumors of the brain and nervous system occurred, but only 24 were available for latency analysis. Concerning morphological types an increased SIR was observed for a heterogeneous group of tumors ("others and unspecified": SIR=1.3; CI: 1.0, 1.7), comprising roughly one-third of all brain and nervous-system tumors. Glioma (all types combined) incidence was not increased. Highest incidence was observed for occipital lobe location (SIR=1.8; CI: 0.6, 4.2), while temporal and parietal locations were less frequently observed than expected.

For leukemia the same subgroups as for brain tumors showed highest SIRs (analogue and digital phone users and digital phone users with a subscription duration of 3 yr or more); however, number of cases was small, 10 and 6 cases, respectively.

Discussion   This study has also a number of methodological deficiencies. First of all the number of subjects followed for a reasonable period of time to account for latency is too small and the subscribers are too young to provide a basis for estimating a possible cancer risk due to mobile telephone use. As stated earlier, subscription files are not reliable databases to be used as the sole bases for epidemiological studies. Johansen et al. (2001) could only obtain the date of first subscription for all types of telephone systems, but neither duration of subscription nor a surrogate for intensity of use (like average or cumulative monthly bills) could be supplied by the network companies. Hence individuals who canceled their subscription 1 mo after entry date are included in the same way as subjects who used the mobile phone until the end of follow-up. Furthermore, considerable exposure misclassification can be expected from the fact that a substantial proportion of subscribers might not be the sole users and may not be users at all. The very low number of subscriptions in women (less than 15%) points to this allocation problem.

In the study, NMT 450 subscribers were also included that were likely using bag or car telephones, which produce no relevant exposure to the user. The most severe problem, however, was created by leaving out corporate subscribers. These are likely to be not only the heavy users, but also those with the longest duration and earliest onset of use. Furthermore, it is not clear whether corporate subscriptions were for single or multiple users (extension number systems).

The consequence of these misclassifications is a substantial underestimation of risk. To estimate the magnitude of this bias some assumptions are necessary: From Funch et al. (1996) we estimate that 48% of subscribers were not the sole users; furthermore, it was assumed that 10% of subscribers were not users at all—the roughly 200,000 corporate subscribers were assumed to be those with earliest onset and hence would accumulate at least as many person-years as individual subscribers included into the study. Under this assumption a true incidence ratio of 2 is underestimated by about 30%, a true incidence ratio of 4 by about 50%.

Obviously, due to the enormous increase of mobile phone use, such studies are not possible anymore because the total population can no longer serve as a reference. It should be emphasized that this study was not altogether faulty. It is legitimate to explore a cohort design of this type. However, given the limitations of such a study, results have to be interpreted cautiously. Such caution has not always been observed by Johansen et al. (2001). As an example, the discussion of brain tumor incidence may be illustrative. They point to the hypothesis of a promoting effect of mobile phone use on tumor growth and then state, "Such a mechanism implies that current use of cellular phones might be of particular importance, although our data show an absence of a brain cancer excess in recent calendar years when phone use dramatically increased" (Johansen et al., 2001,

p. 206). That such an implication is altogether wrong has already been stated. There is no promoting mechanism that is compatible with pathogenesis of brain tumors that would result as yet in a noticeable effect on incidence. The authors continue by stating, "Furthermore, tumors located in the temporal, parietal, or occipital lobes or in the meninges were also not found to be in excess. If it is assumed that tumor promotion occurs close to the site of exposure, this finding provides additional evidence against an association between cellular telephone use and brain cancer." This interpretation again goes far beyond what can be concluded from their study. Besides the risk-diluting effect inherent in their study design, there are additional aspects that need to be considered. First of all, location of tumor was only assessed for glioma. Typically about half of them are of highest malignancy where tumor growth is too fast to be noticeably influenced by external factors. Furthermore, given the evidence of Funch et al. (1996), Hardell et al. (1999), and Muscat et al. (2000b), about 90% predominantly use the mobile phone at one side of the head; hence, according to the argument of Johansen et al. (2001) about irradiation site, only those cases in the specified lobes that occurred on the side of predominant phone use can be considered. Because no information was available on laterality, risk estimates by SIR are further diluted by combining glioma occurring on the contralateral side (with the same incidence as in the unexposed population) with those on the ipsilateral side that could be increased in incidence. If the relative risk of mobile phone use is R, then the risk dilution factor (assuming an equal incidence in left and right lobes) is $2R/(R+1)$. Altogether, 21 gliomas in these lobes occurred. Assuming about half of them are grade III–IV, there are about 10 cases remaining for analysis. It is a little premature to speculate about the implications of such small numbers of tumors. Given the arguments proposed so far and considering the healthy group effect, a reasonable estimate of the dilution factor would be in the range of about 3; hence the correct figures of risk associated with ipsilateral mobile phone use may be about 1.5 to 5.3. Johansen et al. (2001) stated:

> Conceivably, the latency may be too brief to detect an early-stage effect or an effect on the more slowly growing brain tumors. Moreover, our study may currently have too few heavy users to exclude with confidence a carcinogenic effect on brain tissue following intensive, prolonged use of cellular telephones. (p. 206)

Considering the fact that they have no data on duration of use for 42% of their cohort and no data at all on intensity of use, these expressed reservations are weakly formulated.

Starting from the assumption of an association between mobile phone use and cancer, some interesting results can be underlined. Given the predominance of short follow-up periods, no increase in incidence can be expected in the overall analysis. However, both for brain tumors and for leukemia, highest SIRs were observed in those subgroups that had longest duration of follow-up. Unfortunately, the population of subscribers with sufficiently long duration of follow-up was too small to detect elevated risks. Assuming no relationship between use of cellular telephones and cancer, the study, although consistent with this assumption, cannot substantially contribute to the evidence due to its methodological limitations.

Stang et al. (2001)

Design   A combined hospital- and population-based case-control study of uveal melanoma was reported by Stang et al. (2001). Within an international study on occupational risk factors for rare cancers, the authors supplemented an investigation of occupational exposure to high-frequency EMF. All incident cases of uveal melanoma diagnosed between 1995 and 1997 reported by clinical and pathological departments and by the Cancer Registry in Hamburg in the regions of Bremen, Essen, Hamburg, Saarbrücken, and Saarland were eligible in the population-based study. During the study period, 44 cases were reported and 37 (84%) were interviewed. Controls were randomly selected from the residence registry matched for gender, age, and region applying a matching ratio of up to 10 (depending on the stratum-specific incidence of any of the rare cancers investigated). Overall, 327 (participation rate was 48%) controls were included in the population-based uveal melanoma study. Additionally a hospital-based study at the Division of Ophthalmology of the University of Essen was conducted. During the study period, from December 1996 to March

1998, 92 patients residing in North Rhine Westphalia were admitted to the hospital and 81 (88%) could be included in the study. Two control patients with newly diagnosed benign diseases of the posterior eye segment matched by gender, age, and region were selected for each case. Participation rate in hospital controls was 79%. Cases and controls were interviewed face to face or by telephone by trained interviewers about medical history, lifestyle factors, details of occupational history, and occupational exposure to EMFs. Among these aspects, usage of radio sets (older telecommunication devices known as walkie-talkies) and mobile phones was determined. If such devices were used for several hours a day, date of start and end of exposure and the way the device was carried by the subject were asked for.

Results From all sources of exposure to EMFs at the workplace only usage of radio sets and mobile phones had consistently elevated odds ratios. Exposure to mobile phones was classified by two independent raters as possible, probable, or certain. The combined result for these categories were OR=3.2 (CI: 0.6, 17.0) in the hospital-based study, OR=2.3 (CI: 0.2, 14.2) in the population-based study, and OR=2.8 (CI: 1.0, 7.9) for the pooled analysis. These figures increased if a latency of 5 yr was considered. Adjustment for socioeconomic status did not alter the results, nor did iris or hair color.

Discussion Several methodological deficiencies are also apparent in this study. First, assessment of exposure to devices that may induce exposure of the eye to high-frequency EMF was insufficient. Because of combining mobile phones and radio sets in one question, exposure to one or the other had to be assessed by raters based on answers to additional questions. The limitation to heavy use is a reasonable starting point; however, it would have been better to determine the intensity of use. Additionally, patients should have been asked about predominant side where the device was used. Low response rates in controls of the population-based study might have resulted in a bias, if response was associated with usage of mobile phones; however, direction of bias will depend on the sign of the correlation between participation and mobile phone use and there is no empirical basis for a preference of a positive or negative correlation. The study has also been criticized that it did not investigate confounding by exposure to ultraviolet (UV) light (Inskip, 2001). Admittedly, the study would have gained credibility if the few possible occupational and environmental risk factors like UV, arc welding, and intense (accidental) heating of the eye had been included. On the other hand, it has to be stressed that in order for one of these exposures to be a confounding factor of the association between mobile phone use and uveal melanoma, it not only has to be a risk factor but it must also be correlated with mobile phone use, for which there is no indication.

However, besides these weaknesses the study has some very important strengths. First, it combines two study types that could lend credibility to the findings in case of consistency. This was actually the case. Both the hospital-based study and the population-based study had consistently increased odds ratios for occupational use of radio sets as well as mobile phones. Another important point is latency. Overall, 25% were starting to use mobile phones before 1990, thus already accruing at least 5 yr of use at the start of the study period. Allowing for a latency of at least 5 yr resulted in an increase of odds ratios, a further indication of a true association.

It has been speculated (Inskip, 2001; Johansen et al., 2002) that if mobile phone use increases relative risk by a factor of 4 (as indicated by the results of Stang et al. [2001] for probable/certain exposure), this should be observable by an elevated incidence in the population paralleling prevalence of mobile phone use. However, this assumption is flawed: The German study was about occupational and heavy use of mobile phones and cannot be simply related to the marked increase in subscribers; greater heavy occupational use might have been not as significant as that in overall subscribers. Furthermore, latency has to be considered; hence if there is a rise due to mobile phone use, it must be lagged behind increase in subscribers; assuming an incidence of uveal melanoma of about 8×10^{-6} cases per year, and under the assumption that about 5% of mobile phone users belong to the group of heavy users, and assuming further that 80% of the population are mobile phone subscribers, a 4-fold increase of risk in heavy users would result after some years of time lag in an increase to 9×10^{-6} cases per year. Such a small increase cannot be detected based on a Poisson-type variation of the number of cases per year without accumulating cases for a considerable period of time (note that the nominal 95% CI for an incidence of 8×10^{-6} cases per year is 6 to 11×10^{-6} cases

per year for a country like Denmark for which Johansen et al. [2001] made their calculations). Even assuming a continuous elevation of risk from 1 in rare users to 4 in heavy users, the increase in population incidence would remain within the given limits of Poisson variation. A hypothesis about an enhanced incidence may be tested in another 5–10 years time, assuming that digital mobile phones carry the same risk as the older analogue types that must be prevailing in the study of Stang et al. (2001).

The most forceful argument for the claim of no association between mobile phone use and risk of uveal melanoma is the low number of exposed cases. The assumption of an existing risk is supported by the results of Stang et al. (2001) with the consistency of elevated odds ratios and their increase if latency and duration of exposure are considered. The authors gave a mechanistic explanation for their result. They refer to the possible promotion of melanoma development by suppression of intraocular melatonin. While there is experimental evidence for the antiproliferative effect of melatonin, reduction of ocular melatonin levels is only conceivable by two mechanisms: by a response to an irradiation during the secretion phase or by disregulation or functional damage of secreting cells in the retina and ciliary body. The first mechanism affords exposure in the night or at least late evening, which is unlikely in occupational settings but may be a special feature of occupations that had early and intensively used mobile phones. At present there is some indication that the second mechanism may be invoked by exposure to extremely low frequency EMFs (Ishido et al., 2001), but no data are presently available for exposure to EMFs from mobile phones or radio sets.

Response bias is unlikely because the study investigated a variety of occupational conditions that have had a prominent role within the working day. Interviewer bias is also unlikely because interviewers were not aware of study hypotheses and had to assess a great number of different items. Furthermore, interviewers were supervised during the whole study period to ensure consistent quality. The mentioned deficiencies of interview material, however, do not invalidate the conclusions drawn because increased risks have been observed both for mobile phones and radio sets. Even if there is some misclassification, only one can be exchanged by the other and hence would not lead to substantial changes in risk estimates.

Muscat et al. (2002)

Design Muscat et al. (2002) presented results of a hospital-based case-control study of mobile phones and acoustic neuroma. From 1997 to 1999, 90 patients with acoustic neuroma admitted to one of two hospitals in New York were included (it is not stated whether or not these were all eligible patients). Eighty-six control patients with a variety of nonmalignant conditions were frequency matched by gender, age, race, and hospital to cases. All patients were interviewed in person (except for one patient).

Results Overall 20% of patients with acoustic neuroma and 27% of controls regularly used a mobile phone. This difference is mainly due to salespersons, which were more frequently found among controls and had the highest rate of mobile phone use (73%). Cases used a mobile telephone on average for 4.1 yr, while controls had an average usage duration of only 2.2 yr. Controls, however, reported an average monthly use of 6.6 h, compared to 4.6 h in cases. An elevated risk was reported for a duration of use of 3 yr or longer (OR = 1.7; CI: 0.5, 5.1). Investigation of laterality revealed a reduction of risk.

Discussion This study uncovers a number of flaws that may have had an impact also in other investigations. Authors argued that despite the increased risk for duration of usage, cumulative use showed no change in risk due to the fact that case patients were less frequent users. However, relying on subjects' recall of their history of mobile phone use carries the risk of a recency bias, since they will tend to report intensity of use as well as monthly bills conforming to their recent experience. Given the fact that acoustic neuroma is often associated with unilateral hearing loss, tinnitus, vertigo, and later brainstem symptoms, it is likely that due to these symptoms frequency and intensity of mobile phone use were reduced in patients. Not only is the analysis of risk with respect to intensity and cumulative use affected by this bias, but there is also an indication of a reversal of cause and effect: Analysis of laterality revealed evidence for a less frequent occurrence of acoustic

neuroma on the side of the head where subjects reported using the phone. Muscat et al. (2002) mentioned, and this is admittedly a straightforward interpretation, that patients may have switched hands due to hearing problems at the side of the tumor. The situation can be summarized as follows: There could be an increased risk to develop acoustic neuroma, such that a stage of clinical manifestation is reached earlier, due to the use of mobile phones (inferred from the almost twofold longer duration of use in patients compared to controls); however, during progression of the disease use of mobile phones is discontinued or frequency of use is reduced and side of usage is switched, leading to reduced risk as estimated from reports on recent use. These problems could be avoided if sufficient periods of latency are allowed for.

Muscat et al. (2002) concluded that their study "did not support the hypothesis that use of handheld cellular telephones causes acoustic neuroma" (p. 1306). It must again be stressed that this was not the hypothesis tested. To test a hypothesis of causation the causal factor must precede the disease. However, this was not the case. Rather, the following hypothesis was tested: "Does the development of acoustic neuroma change mobile phone use?" Schwannoma develops slowly and remains covert for a long time, and even after first clinical signs occur it may last years until diagnosis. Authors were aware of these facts and indicated that the results were inconclusive and provide no basis for the statement cited earlier.

Auvinen et al. (2002)

Design A register-based case-control study of brain tumors and salivary gland cancer was reported by Auvinen et al. (2002). All brain tumors and salivary-gland cancers diagnosed in patients between 20 and 69 yr of age in Finland in the year 1996 were included. Overall 398 brain-tumor cases and 34 salivary-gland cancer cases were identified. For each case, five age- and gender-matched controls were selected from population register. Subscription files of the two cellular network providers operating in 1996 were scanned to identify cases and controls that held a private subscription at or before diagnosis of the case. By this procedure 13% of brain-tumor cases, 12% of salivary-gland cancer cases, and 11% of controls were found to have had a personal subscription to a cellular telephone network. Among brain-tumor cases 40 (10%) had an analogue phone subscription and 16 (4%) a digital phone (some had both). Average duration of subscription was 2–3 yr for the analogue system and less than 1 yr for digital phones. Therefore, only results from analogue phone subscribers are discussed here.

Results Odds ratio for ever having had a subscription was significantly elevated (OR = 1.6; CI: 1.1, 2.3) for brain tumors but not for salivary-gland cancer. There was a tendency for an increase of risk by increasing duration of subscription (OR = 1.2 per year; CI: 1.0, 1.3) for brain tumors. Increase of brain-tumor risk was mainly due to glioma (OR = 2.1; CI: 1.3, 3.4). Comparison of histological subtypes of brain tumors in 32 users and an equal number of nonusers based on gender- and age-matched groups revealed a reduction of glioblastoma (31% in users and 44% in nonusers).

Discussion The study is an interesting contribution to the question of study methodology. It was totally based on registry information and no contact to the subjects was therefore necessary. However, it allows only very limited conclusions, because a number of deficiencies of the method may lead to an attenuation of a possible association between risk and mobile phone use. First of all, digital phone use cannot be considered due to insufficient latency and also analogue phone subscription was only for an average of 2–3 yr; hence only less than half approached reasonable latencies. Second, authors stated that before 1996 there were more subjects using mobile phones based on a corporate subscription (that was not assessed in this study) than private subscriptions. Exposure misclassification of this type (underreporting) leads to a reduction of risk estimates. Authors claim that the attenuation effect was about 10%. However, this holds only for an equal underreporting in cases and controls. Finally, laterality, which might be of crucial importance, cannot be analyzed applying this methodology.

Overall, the study of Auvinen et al. (2002) is consistent with an elevated risk of brain tumors associated with mobile phone use. Small number of relevant cases, however, prohibit far-reaching conclusions. On the other hand, it does not lend support to the assumption of no risk because it apparently has no bias that would lead to spurious positive results.

Hardell et al. (2002a, 2002b)

Design   A further, larger case-control study of brain tumors was reported by Hardell et al. (2002a, 2002b). Overall results were reported in Hardell et al. (2002a) and a more comprehensive analysis of malignant brain tumors in Hardell et al. (2002b).The study design was similar to that of the previous study (Hardell et al., 1999) discussed earlier. In addition to the exposures addressed, in the questionnaire of the first study cordless telephones were included, and in addition to use of car telephones with an outside antenna, use of hands-free sets was assessed. Furthermore, the study region was extended to cover Uppsala–Örebro, Stockholm, Linköping, and Göteborg medical regions. From 1997 to 30 June 2000, 2561 cases were reported from regional oncology centers. Inclusion criteria were met by 1713 cases. Main reasons for exclusion were death (540 cases) and other than primary brain tumors (232 cases). From 1713 eligible cases, 96 were excluded because of incapacity to participate or denial of treating physician or unknown address. Of the remaining 1617 cases, 88% answered the questionnaire. One age-, gender-, and region-matched control was selected from the population register for each case. Ninety-one percent of controls answered the questionnaire.

Results   Use of analogue telephones was reported by 17.3% of cases and 14.8% of controls, digital telephones by 29.6% of cases and 29.5% of controls, and cordless phones by 28.1% of cases and 26.9% of controls. Median time of use until 1 yr preceding diagnosis was 7 yr for analogue phones, 3 yr for digital phones, and 5 yr for cordless phones. For analogue phones an increased risk was found (OR = 1.3; CI 1.02,1.6) that rose to an OR of 1.8 (CI 1.1, 2.9) for latency periods exceeding 10 yr. Odds ratio for ipsilateral use of an analogue phone was 1.8 (CI 1.3, 2.5) and, especially for temporal locations, 2.5 (CI 1.3, 4.9). For malignant brain tumors and ipsilateral use an OR of 1.9 (CI 1.2, 3.0) was found. Results for digital phones were: overall OR = 1.0 (CI 0.8, 1.2), for ipsilateral use OR = 1.3 (CI 0.99, 1.8), and ipsilateral use and temporal location OR = 1.1 (CI 0.6, 1.9); malignant brain tumors and ipsilateral use were associated with an OR of 1.6 (CI 1.05, 2.4). For use of cordless phones an overall OR of 1.0 (CI 0.8, 1.2) was reported, and ipsilateral use was associated with an OR of 1.3 (CI 1.01, 1.8). Highest odds ratios for histopathology types were calculated for acoustic neurinoma (OR = 3.5; CI 1.8, 6.8) and analogue phone use.

Discussion   This is the first study that, at least for analogue phones, reached latencies that are conclusive and diagnostically accepted in studying brain tumors. For digital phones duration of use may still be to short, while for cordless phones median time of use seems to be borderline. Results for analogue phones met the criterion established by Rothman (2000): "Were a study to find an increase in overall risk for brain tumour that was limited to tumours on the same side of the head that the telephone was used, that would be a much more compelling finding" (p. 1839). However, in our opinion the problem is still more complicated. First, the argument has to be rejected that an association with the side of the head on which the telephone was predominantly used requires, conditional on no overall increase of brain tumor risk, the implausible inference that telephone use does not affect the risk of whether a brain tumor will occur but only its location. If telephone use is associated with a faster tumor growth, an effect on incidence will likely remain unnoticed unless a substantial proportion of cases are included that have had long-term exposure. Still, due to the long latencies of brain tumors, an effect on the initiation stage and hence on the risk of developing a brain tumor may not be found. Rather, the results of Hardell et al. (1999, 2000, 2001, 2002a, 2002b) point to an effect on later stages of the process, and because in this case the OR underestimates the risk it must be substantial, especially for benign tumors. Furthermore, as stated earlier, due to symptoms experienced by some of the cases change of habits might occur, possibly resulting in switching the side of the head on which the telephone is used. If recent exposures (or in some types of brain tumors even longer periods of several years) are included this may reduce the OR for ipsilateral use. If, due to symptoms, mobile phone use is discontinued, not allowing for long enough latencies will also reduce risk estimates for the contralateral side. Indications of such effects can be found especially for cordless phones (see Hardell et al., 2002a, Table 4).

As was the case with the earlier study (Hardell et al., 1999), this report has also been criticized for its exclusion of a considerable proportion specifically of malignant brain-tumor cases due to their terminal illness or being already deceased. The arguments against this criticism need not be replicated here. It was also stated that the results for cordless phones are further evidence of distorting bias. This argument is based on the assumption that power of cordless phones is 25 to 100 times lower than for cellular phones. First, it should be emphasized that GSM cellular phones have a power regulation as well as a DTX mode that together lead to average exposure levels not much higher than for cordless phones. Second, the average duration of calls is several times longer for cordless phones as compared to mobile cellular phones. Furthermore, the argument is based on the speculation that if there is a risk it must be a function of cumulative power. However, there are a number of serious problems with such an assumption: Emission is, across individuals, only weakly correlated to internal field strengths (due to differences in position of the phone, shape and size of the head and dielectric properties of tissues); it is unknown when the decisive event or events have happened and therefore the duration for accumulation of exposures is unknown (it makes no sense to sum up exposures that occurred after these events); it should be further emphasized that to rely solely on an argument of equivalent energy may miss decisive aspects of exposure. It was already stated in 1981 about SAR that "it may not be the only factor, e.g. frequency and/or modulation of the radiation field may strongly affect biological effects. Consequently, the nature of the radiation fields should always be considered in addition to the SAR" (UNEP/WHO/IRPA, 1981, p. 45).

The way laterality was assessed by Hardell et al. (2002a, 2002b) was also criticized: "Other investigators use more standard approaches such as within case comparisons and find no association with tumor location and ear most frequently used during phone conversations (Inskip et al., 2001; Muscat et al., 2000, 2002; Auvinen et al., 2002)" (Boice & McLaughlin, 2002, p. 21). It is incorrect that these authors use "more standard approaches." In fact, Inskip et al. (2001) especially developed a method for this purpose (that was subsequently also used by Muscat et al. [2002] but not by the other cited authors). The approach is simply based on the OR of a coincidence of a tumor and the side where the phone was used in cases disregarding controls, thereby losing control over confounders, and hence faulty. Furthermore, Auvinen et al. (2002) did not investigate laterality at all because the study was registry based.

From the view of no association between mobile phone use and brain tumors the only possible bias that is not refutable is related to social stratum. A comprehensive recent review (Wrensch et al., 2002) concluded that there are only a few proven causes (inherited genetic syndromes, therapeutic exposure of the head to ionizing radiation, and, for brain lymphoma, immunosuppression) that account only for a small proportion of cases. Still unexplained are ethnic and gender differences. Some studies also found indications of higher risks for subjects of higher economic status (that, however, could be confounded by ethnic differences). Grayson (1996), in a study of 230 brain tumor cases in U.S. Air Force personnel, found higher brain-tumor risk with increasing rank, but also an elevated risk of exposure to radiofrequency and microwave (RF/MW) fields that was independent of rank. Another indication that socioeconomic status has probably not been a confounder is the result of Auvinen et al. (2002) that showed no differences in this respect between cases and gender- and age-matched controls drawn from the population register.

In contrast, the assumption of a relationship between mobile phone use and brain tumors is supported by the results of Hardell et al. (2002a, 2002b). Two aspects are of great importance: the increase of risk with greater latency, and the consistent relationship between the side of the head where the phone was reported to be used during calls and the location of the tumor.

BRIEF OVERVIEW OF EPIDEMIOLOGICAL INVESTIGATIONS ON HIGH-FREQUENCY EMF AND CANCER

Table 3 gives an overview of epidemiological studies of cancer that have been published since 1990 and that underline the problems associated with the study of high-frequency electromagnetic fields (EMFs). There is a broad spectrum of sources of high-frequency fields, and for specific types there are at most a few studies that can be considered. Furthermore, due to the predominant retrospective

TABLE 2. Synopsis of Epidemiological Studies on Mobile Phone Use and Cancer

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Rothman et al. (1996a)	Cohort, mortality (overall 1994)	Private subscribers to car or bag phones (23%), hand-held phones (19%) or unknown types (58%) in metropolitan area of Boston, Chicago, Dallas, and Washington, DC (total 256,284)	Subscribers alive 1.1.1994 Linkage to death records	No difference in overall mortality between car/bag phone users and hand-held phone users	Follow-up only 1 yr, small number of deaths, no cause specific deaths, exposure not ascertained. Noninformative
Dreyer et al. (1999)	Cohort, cause-specific mortality during 1994	Expansion of Rothman et al. (1996a)	Subscribers alive 1.1.1994 Linkage to death records		Follow-up only 1 yr, investigation stopped by legal problems Noninformative
Hardell et al. (1999, 2000, 2001)	Registry-based case-control, prevalent brain-tumor cases 1994–1996	209 Brain-tumor cases and 425 matched controls in the Uppsala–Örebro and Stockholm region	Questionnaire and interviews Histopathological records etc. examined	Overall no increased risk for mobile phone use (OR 0.98) Association with the side of head where the phone was used (OR 2.42), significant in multivariate analysis (OR 2.62)	Small number of relevant cases, short duration of use, indication of a "laterality" effect important. Limited evidence for association
Muscat et al. (2000b)	Hospital-based case-control, prevalent brain-cancer cases 1994–1998	469 Brain cancer cases and 422 frequency-matched controls from hospitals in New York, Providence, and Boston	Personal interviews Pathological records and MR images examined	Overall no increased risk for mobile phone use (OR 0.85), highest risk found for neuro-epitheliomatous type (OR 2.1); indication of an association with side of predominant use (p = .06)	Short duration of use (only 14 cases ≥4 yr), predominance of glioblastoma (no effect on growth rate detectable, for induction too short latency), effect of laterality possible Inconclusive

TABLE 2. Synopsis of Epidemiological Studies on Mobile Phone Use and Cancer (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Inskip et al. (2001)	Hospital-based case-control, incident hospital brain-tumor cases 1994–1998	782 Brain-tumor cases (489 malignant) and 799 frequency-matched controls from hospitals in Phoenix, Boston, and Pittsburgh	Personal or proxy interviews Histopathology etc. examined	Overall no increased risk for mobile phone use (OR 1.0), OR 0.9 for glioma, 0.7 for meningioma, and 1.4 for acoustic neuroma (OR 1.9 for 5 yr or longer use); no association with side of predominant use	Short duration of use (only 22 cases ≥5 yr), predominance of glioblastoma, too small number of relevant cases, laterality assessed by faulty method Inconclusive
Stang et al. (2001)	Registry- and hospital-based case-control, primary incident uveal melanoma cases 1995–1997 registry, and 1996–1998 hospital	37 Registry and 81 hospital cases of uveal melanoma and 475 matched controls from Bremen, Essen, Hamburg, Saarbrücken, Saarland, North Rhine Westphalia	Personal interviews Diagnosis reviewed by pathologist	Increased risk for occupational heavy use of mobile phones (OR 4.2), increase to OR 4.9 for 5 yr latency, consistent trends in both study groups	Not optimal assessment of exposure, no determination of side of use, private use not inquired, confounding by UV exposure unlikely but not determined, long-term and heavy users but small numbers Very limited evidence of association
Johansen et al. (2001)	Retrospective cohort, cancer incidence 1982–1996	420,095 Private subscribers (58% of all subscriptions) in Denmark 3391 Cancer cases (154 brain tumors, 84 leukemia cases) occurred	Subscription records (duration of subscription only available for GSM, 57% of study group) Diagnosis from cancer registry	Significantly reduced SIR for males (SIR 0.86) and no difference in females (SIR 1.03) for all cancers; for brain tumors and leukemia highest (but insignificant) SIRs for longest duration of use	Great proportion of subscribers (and possibly the heavy users) excluded, insufficient duration of follow-up (92% GSM users less than 3 yr of use), for 43% no duration of use determined, no information on side of use, allocation bias likely Inconclusive

TABLE 2. Synopsis of Epidemiological Studies on Mobile Phone Use and Cancer (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Auvinen et al. (2002)	Registry-based case-control, incident brain-tumor and salivary-gland cancer cases 1996	398 Brain-tumor cases (198 malignant) and 34 salivary-gland cancers and 2156 matched controls from Finland	Registered cases and controls (drawn from population register) linked to subscription records Diagnosis from cancer registry	Significantly increased risk for brain tumors and analogue phone use (OR 1.6) and increasing trend for years of use (1.2 per year); no significantly elevated risk for salivary-gland cancer	Omission of corporate subscriptions, bias by use of subscription records possible, short duration of use, small number of relevant cases, side of use cannot be analyzed, important trend for years of use Very limited evidence of association
Muscat et al. (2002)	Hospital-based case-control, incident (?) hospital cases of acoustic neuroma 1997–1999	90 Cases of acoustic neuroma and 86 frequency-matched controls from two hospitals in New York	Personal interviews Pathology records and MRI examined	Insignificantly elevated risk for >2 yr of mobile phone use (OR 1.7) Tendency for reversal of laterality (RR 0.65; p=.07)	Too short duration of use, indication for change of predominant side of use due to symptoms Inconclusive
Hardell et al. (2002a, 2002b)	Registry-based case-control, prevalent brain-tumor cases 1997–2000	1429 Brain-tumor cases and 1470 matched controls (1303 complete pairs) from the Uppsala–Örebro, Stockholm, Linköping, and Göteborg region	Questionnaire and interviews Histopathological verification	Significantly elevated risk for analogue phones (OR 1.3), increased risk with increasing latency, highest overall risk for acoustic neuroma (OR 3.5); significantly elevated risk for ipsilateral use overall and for malignant tumors	Study approaches reasonable latencies in analogue phone users, still too few cases for differentiation on histopathological types and location; important association with side of predominant use Limited evidence of association

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Hayes et al. (1990)	Hospital-based case-control, prevalent cases of testicular cancer 1976–1981	271 Cases of testicular cancer and 259 controls (other cancers) from three hospitals in Washington, DC (two military hospitals)	Telephone or personal interviews with cases and controls and their mothers, classification by industrial hygienist of MW/RF exposure Histopathological records inspected	Significantly elevated risk for self-reported MW/RF exposure (OR 3.1), no association for classification based on job title	Small number of exposed cases. Most controls (75%) were lymphoma, leukemia, melanoma, or brain-tumor cases for which an association with MW/RF exposure is possible, therefore risk dilution may have occurred; lack of correlation between job-title assessment and self-reported exposure Very limited evidence for association
Muhm (1992)	Occupational retrospective cohort, mortality in workers from Boeing employed within the EM pulse test program from mid 1960 through 1986	304 Male workers from Boeing (USA) that took part in the health surveillance program between 1970 and 1986	Employment within the EM pulse test program from company records Review of death certificates	Indication of healthy worker effect from significantly reduced overall mortality (SMR 0.56); insignificantly elevated mortality from haematopoietic cancers (SMR 3.31)	Only one case of leukemia and one lymphoma case occurred (0.1 and 0.2 expected, respectively) The study missed living patients Exposed personnel not formally part of Boeing crew were also not included Noninformative
Selvin et al. (1992)	Ecological, childhood incidence of cancer of hematopoietic and lymphatic tissues and brain cancer 1973–1988	51 Cases of leukemia, 37 cases of lymphatic cancer, and 35 brain-cancer cases in the city of San Francisco in individuals less than 21 yr old	Distance to a microwave tower (Sutro Tower) Diagnosis from cancer registry	Insignificantly elevated risk for brain tumors (RR 1.16) and lymphomas (RR 1.17) and insignificantly reduced risk for leukemia (RR 0.73)	Analysis is based on the (false) assumption of a monotonous relationship between distance from point source and exposure Inconclusive

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TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Tynes et al. (1992)	Registry-based occupational cohort, cancer incidence (especially leukemia and brain tumors), 1961–1985.	37,945 Male electrical workers from Norway identified in 1960s census followed through 1985	Classification of exposure by job title Linkage to cancer registry	Significantly increased leukemia incidence (SIR 2.85) and insignificantly reduced brain-tumor incidence (SIR 0.61) in workers possibly exposed to RF	Small number of relevant cases (9 leukemia, 3 brain tumors); exposure misclassification reducing risk estimate possible Limited evidence of association
Davies and Mostofi (1993)	Cluster cohort, testicular cancer 1979–1991	In 340 police officers (north-central United States) 6 cases of testicular cancer occurred	Personal interviews Pathological records examined	Significantly elevated risk (SIR 6.9)	Only common exposure was to hand-held radar; no confounders detected Very limited evidence of association
Armstrong et al. (1994)	Occupational nested case-control, cancer incidence 1970–1988 (1978–1988 France)	2679 Cases of cancer and 4026 matched controls nested within a cohort of electrical utility workers (approx. 190,000 workers) in Quebec and France	Job-exposure matrix and personal measurements of exposure to pulsed EMF	Significantly elevated risk for all cancers (OR 1.39) in ≥90th percentile exposure group Insignificantly elevated risk for Hodgkin's (OR 1.33) and non-Hodgkin's lymphoma (OR 1.80) but not for all hematologic cancers; insignificantly elevated brain cancer risk (OR 1.90), highly significant increase of lung cancer risk (OR 3.11), and significant dose response	Lung cancer risk was elevated despite consideration of relevant confounders (smoking, exposure to chemicals, ionizing radiation) but largely confined to Quebec Limitations are lack of precision of personal dosimeters and insufficient follow-up for cohort in France (only to end of employment) Limited evidence of association

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Maskarinec et al. (1994)	Ecological and case-control, acute childhood leukemia 1979–1990	12 Cases of childhood leukemia and 48 matched controls from Waianae (Hawaii) selected from files of local health care centers	Telephone interviews with parents; distance from a radio tower (within or outside 2.6 km) Diagnosis from Hawaii tumor registry	Significantly elevated incidence for district surrounding radio tower (SIR 2.09) Insignificantly elevated risk in case-control study (OR 2.0) Unusual cluster of nonlymphocytic leukemia	Power of case-control study very low (only ~ 50% for an OR of 5) Only insufficient data on exposure available Cluster of ANLL unexplained Very limited evidence of association
Cantor et al. (1995)	Registry case-control, female breast cancer mortality 1984–1989	33,509 Breast-cancer cases and 117,794 matched controls (noncancer deaths) selected from records of 24 U.S. states	Job-exposure matrix of 31 workplace exposures Cause of death from registry	Significantly elevated risk for highest exposure category of RF EMF exposure in white women (OR 1.14) and black women (OR 1.34) if adjusted for socioeconomic status	Strong effect of socioeconomic status indicates interaction with factors unaccounted for in analysis (mainly fertility pattern, breast-feeding, and hormone substitution therapy) No clear dose-response relationship. Inconclusive
Holly et al. (1996)	Case-control, hospital cases of uveal melanoma 1978–1987	221 Male white cases from the Ocular Oncology Unit at the UCSF and 447 matched controls collected by random digit dial method (western United States)	Telephone interviews about occupations and occupational and leisure time exposures Histopathologically confirmed diagnosis	Significantly increased adjusted odds ratio for MW/radar exposure (OR 2.1)	Study was explorative Possible confounding by other exposures not assessed Very limited evidence of association

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Tynes et al. (1996)	Occupational retrospective cohort and nested case-control, female breast cancer incidence 1961–1991	Cohort of 2,619 women from Norway working as radio and telegraph operators between 1920 and 1980; 50 breast-cancer cases and 259 matched controls from the cohort	Detailed job history from Norwegian seamen registry; spot measurements in radio rooms of three ships using old-fashioned transmitters; fertility from Central Bureau of Statistics Diagnosis from cancer registry	Significantly elevated risk for all cancers in the cohort (SIR 1.2) and especially for breast cancer (SIR 1.5); case-control study demonstrated an effect especially in those aged 50 and over	Due to high correlation between shift-work and duration of employment these factors are hardly separable; a combined effect of EMF and chronobiological disturbance possible Weak evidence of association
Beall et al. (1996)	Occupational case-control, brain-tumor mortality 1975–1989	149 Brain-tumor cases and 591 matched controls selected from company registry of all U.S. IBM employees dying 1975–1989	Company databases and interviews with personnel was basis for work histories Assessment of VDT development work Review of death certificates	No consistent association between VDT development work and brain-tumor risk; significantly elevated risk for engineering/technical jobs (OR 1.7) and programming jobs (OR 2.8); accounting for latency increased OR to 3.9 for 5 or more years of programming	No assessment of exposures within job categories Programming and engineering jobs may be associated with exposure to ELF and RF fields; low number of relevant cases; only deceased controls Inconclusive

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Grayson (1996)	Occupational nested case-control, brain-cancer incidence	230 Primary brain-cancer cases and 920 matched controls from records of U.S. Air Force (cohort with at least 1 yr of service 1970–1989)	Job-exposure matrix and independent assessment of exposure to RF/MW, ELF fields and ionising radiation; personal dosimetry for ionising radiation Examination of hospital discharge records	Significantly increased risk for RF/MW exposure (OR 1.39) Increase independent of rank and other exposures	Underestimation possible due to loss of follow-up after leaving service; analysis of trend compromised by neglect of latency Limited evidence of association
Hocking et al. (1996)	Ecological brain cancer and leukemia incidence and mortality 1972–1990	740 Adult brain-cancer cases (606 deaths) and 1206 leukemia cases (847 deaths), and 64 childhood (0–14 yr) brain-cancer cases (30 deaths) and 134 leukemia cases (59 deaths) within 4 km of the source of radiation in Sydney, Australia	Three TV towers within a triangular area of 1.5 km side length (broadcasting 63–215 MHz); calculated free-field power density 80 mW/m² to 2 mW/m² for the inner area and 0.2 mW/m² at 12 km distance Cancer registry data	Significantly elevated incidence of adult and childhood leukemia (RR 1.24 and 1.58, resp.); increased leukemia mortality for children (RR 2.32) and adults (RR 1.17 not sign.); brain cancer incidence and mortality not elevated	Ecological bias possible; no heterogeneity found across areas—however, McKenzie et al. (1998) reported evidence that risk increase is mainly due to one area Limited evidence of association
Szmigielski (1996)	Occupational stratified retrospective cohort, cancer incidence 1971–1985	Polish military career personnel (118,500 to 142,200 per year), exposed to RF/MW (mostly pulse modulated 150–3500 MHz fields) were 3400 to 4600 annually	Service records and documented exposure at service posts; data on RF/MW exposure from military safety groups Cancer data from records of central and regional military hospitals	Significantly elevated risk for all cancers (SIR 2.07 relative to not-exposed cohort), for alimentary tract cancers (SIR 3.19–3.24), brain cancer (SIR 1.91), and haematopoietic and lymphatic system (SIR 6.31)	Due to military constraints no crude data reported Occasional high exposure > 6 W/m² possible; elevated risk consistent across age groups; confounders could not be considered. Very limited evidence of association

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Dolk et al. (1997a)	Ecological, cancer incidence 1974–1986	Study area within 10 km of Sutton Coldfield (GB) transmitter; population appr. 408,000	Distance of residence from tower; maximum total power density measured, 13 mW/m² for TV and 57 mW/m² for FM radio Population statistics from 1981 census Cancer registry data	Significantly elevated risk for all cancers (SIR 1.09) within 2 km and 10 km (SIR 1.03) in adults; significantly elevated were leukemia, female breast cancer, and bladder cancer; skin melanoma and brain tumors were insignificantly elevated	Analysis for trend not correctly applied because of no monotonous decline of exposure with distance; calculations indicate highest exposure at ground level in a distance of 2 to 4 km Limited evidence of association
Dolk et al. (1997b)	Ecological, adult leukemia, skin melanoma, and bladder cancer 1974–1986	Study areas within 10 km of 20 high-power transmitters in GB; population approx. 3.4 million	Distance of residence from respective tower Cancer and population registry data	Significantly elevated risk for all leukemias (SIR 1.03) and bladder cancer (SIR 1.09) Pattern of incidence varies with types of transmitters	Conclusions faulty due to wrong assumption of monotonously declining exposure Highest risk found consistently within 2 to 5 km from towers in accordance with exposure estimates Limited evidence of association
Lagorio et al. (1997)	Occupational cohort, mortality 1962–1992	481 Women employed in a plasticware manufacturing plant exposed to RF fields from dielectric heat sealers in Grosseto, Italy; 9 cases of death, 6 neoplasms	Company records to assess department of employment; exposure measurement not possible due to high turnover of machines Vital status and causes of death from Registry Office of municipalities	Insignificantly elevated overall mortality (SMR 1.4) and for neoplasms (SMR 2.0); among neoplasms, one leukemia and one brain cancer case (0.2 and 0.1 expected, respectively)	Very small number of deaths; however, two times more neoplasms than expected Exposure of considerable variance occasionally exceeding guideline levels Exposure to vinyl chlorid monomer and solvents possible Noninformative

TABLE 3. Synopsis of Epidemiological Studies of High-Frequency EMF and Cancer Published Since 1990 (Continued)

Study	Type	Population	Exposure and outcome assessment	Findings	Comments
Finkelstein (1998)	Occupational retrospective cohort, cancer incidence 1970–1995	22,197 Police officers (20,601 males and 1,596 females) of 83 Ontario police departments	Linkage of employment records to Cancer Registry and Ontario Mortality Database	Reduced overall cancer incidence in males; elevated incidence rates for testicular cancer (SIR 1.3) and significantly elevated rates for melanoma (SIR 1.45)	No assessment of exposure possible; nested case-control study planned Inconclusive
Morgan et al. (2000)	Occupational retrospective cohort, cancer mortality (cancer of brain and haematopoietic and lymphatic tissues) 1976–1996	195,775 Workers employed by Motorola in the United States	Classification of RF exposure by job title; vital status from SSA Master Mortality File and National Death Index; death certificates coded according to ICD-9	Significantly reduced overall mortality; insignificantly elevated rate for Hodgkin's disease (SMR 1.28). Internal comparison revealed no association with exposure categories	Not only healthy worker effect but indication of lifestyle differences to general population; no assessment of private use of mobile phones; young cohort and low number of relevant cases Inconclusive
Michelozzi et al. (2002)	Ecological, childhood leukemia incidence and adult leukemia mortality 1987–1998 (1999)	Study area within 10 km of Vatican Radio (Rome, Italy) broadcasting area; approx. 49,700 (~ 9700 children) residents (1991); 40 cases of adult leukemia, 8 cases of childhood leukemia	Measurements from different organizations between 1998 and 2001 (indoor 24-h and outdoor spot measurements); mortality from Lazio Region Geographic Information Mortality System, childhood incidence by direct collection and regional hospital discharge records	Insignificantly elevated leukemia mortality within 2 km (decreasing trend with increasing distance into question; only two measurements in a distance exceeding 1 km were reported, one at 3 km with results similar to those at 1 km and one > 4 km that was lower | Reported results of measurements call decreasing exposure with increasing distance only in males); borderline significant increase of childhood leukemia incidence within 6 km (SIR 2.2)	Very limited evidence of association

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nature of these studies there are only two that have included some measurements of exposure. Consequently these studies provide at most weak support for the hypothesis of an association between exposure to high-frequency EMFs and cancer. Overall 20 studies were reviewed. Of these, one provides weak, six limited, and another six very limited support to the assumption of an association. No study provides support to the assumption of no association. However, no study has been published that could in principle be utilized in this respect. Despite these shortcomings, the vast majority of studies are in line with the hypothesis of an elevated risk of high-frequency EMF and even some of those that were classified as inconclusive or noninformative found some indication of increased risk. Because publication bias is unlikely, these data point rather to the existence of an association between exposure to high-frequency EMFs and cancer.

DISCUSSION

Despite the decade-long controversy about long-term adverse health effects from exposure to low levels of high-frequency EMFs not a single epidemiological study and not a single long-term animal experiment has been conducted that can be used as a firm basis for the resolution of this controversy. Besides the economical, military, and political interest in an unlimited usage of devices leading to such exposures, scientific paradigms that forbid such effects have hampered an open-minded, unemotional, matter-of-fact approach.

While there is a legitimate scientific controversy, this should not lead to neglecting disparate points of view. The concept of absorption of electromagnetic energy and tissue heating developed over the past 40 yr is quite important. There is no doubt that accidental overheating must be prohibited. In fact, exposure to high levels of RF/MW fields may lead to severe damage of tissues or even to death. The great progress that has been made in explaining and modeling absorption of electromagnetic energy by tissues and the dosimetric utilization of these advances have, however, led to a focus on thermal effects that cannot be scientifically defended. The law of thermal effects has been extended to a thermal effect principle that states that there cannot be a relevant adverse health effect if exposure is not associated with a relevant increase of temperature due to absorption of electromagnetic energy. While excessive heating is a sufficient condition for adverse health effects, its necessity has not been established to any degree of certainty.

Still another factor has contributed to the widespread acceptance of the thermal effect principle. It conforms to the energy constraints set up by the thermal noise concept known as the kT theory (Adair, 1991, 2002). Considering signal-to-noise ratio a limit for an effect to occur seems to be derivative from the distribution of thermal movements of molecules within tissues, based on the stochastic theory of equilibrium thermodynamics. While this concept is important insofar as it imposes a condition for alternative models, the kT theory cannot be valid for all biological system responses to external stimulation. For example, signal detection by the human auditory system is close to the quantum limit of measurement (Bialek & Wit, 1984). However, none of the alternative models have been generally accepted so far (see Adey, 1999).

There is a wide range of exposures that have been covered by the earlier studies on high-frequency EMFs and cancer, and therefore, without a sound theory that provides a basis for understanding molecular mechanisms of EMF interactions, these data cannot readily be combined for risk assessment. Exposure to mobile phones is the first type of high-frequency EMF exposure that has been studied in more than a few investigations. Now nine epidemiological studies that focus on mobile phone use are available. Most of these studies focused on brain tumors. One was about intraocular melanoma, and one included additionally salivary-gland cancer and another hematopoietic malignancies.

Considering induction periods and latencies for the development of these cancers, epidemiological investigations are confronted with the problem that the technology has not been in use for a long enough period to study induction at all. As cited earlier, most authors assume that if microwaves are related to development of cancer, they act as promoters. This hypothesis is only weakly corroborated by evidence. It is supported by the observation of Chou et al. (1992) in the first long-term animal experiment of low-level microwave exposure ever conducted that although overall cancer incidence was significantly elevated in exposed Sprague-Dawley rats, no type of cancer was

specifically increased. This is to be expected if microwaves act as promoters. Other supporting evidence is provided by an in vitro experiment (Balcer-Kubiczek & Harrison, 1991) demonstrating that microwaves modulated at 120 Hz enhance the effect of tetradecanoyl phorbol acetate (TPA), an efficient tumor promoter. Results on induction of ornithine decarboxylase (e.g., Byus et al., 1988; Litovitz et al., 1993) point in the same direction.

However, analogy to chemical carcinogenesis might not be an ideal starting point for the discussion of microwave effects. Mode of action of chemical promoters is characterized for only a few substances, but it is hypothesized that they act along pathways regulating gene expression. For example TPA acts by binding to protein kinase C receptor, mediating signal transduction of tyrosine kinase and G-protein linked pathways.

As mentioned earlier, many discussions concerning possible impacts of high-frequency EMF exposure start by stating that photon energy in this range of frequencies is far too low to directly induce DNA damage. However, induction of stable DNA alterations does not require a DNA-damaging agent. DNA damage occurs spontaneously at an estimated frequency of several hundreds per cell per day (Lindahl, 2000). Agents that interfere with either processing of these damages, cell cycle control, or apoptosis of the deviating cell will increase the likelihood of malignant transformation. Furthermore, cooperative processes between cells seem to play an important role (Zhou et al., 2001). Viewed from this perspective, epigenetic carcinogens are much more important than genotoxic ones because their mode of action will increase the impact of both the spontaneous as well as the induced DNA alterations. Concerning effects of high-frequency EMF, the evidence available does not indicate a unique process of interaction with cellular processes, unlike chemical carcinogenesis, where in many cases specific processes are responsible for DNA alteration (alkylation, bulky adducts, intercalation for inductors, and interference with intracellular signal transduction pathways or gap junctional communication for promoters).

Another essential aspect is the relationship between the dynamics of the cancer process and the time point and duration of an agent's interaction. The quite limited evidence available points to a slow action of EMFs. Animal models that lead to a steep and fast decrease of survival are not suited for the study of EMFs. Because at present the mode of action of EMFs during carcinogenesis, if EMFs exert an effect at all, is less than clear, animal models must allow for an interference at all stages of the malignant process.

Unlike typical experimental paradigms of the study of chemical carcinogenicity where exposure doses are chosen that are orders of magnitudes higher than those encountered in human environments and that are just below levels of acute toxicity and where, starting from these high doses, geometrically declining exposure levels are studied down to levels that may occur in occupational settings, such a procedure is not indicated in the study of high-frequency EMFs. The reason for this difficulty in experimental design is the interference with heating. At field strengths only about 3 times higher than occupational exposure limits (ICNIRP, 1998; IEEE, 1999), already whole-body temperature increases of about 1–2 °C occur for exposures in the far field and similar relationships hold for localized exposure. Such heating is accompanied by physiological reactions that could interfere with the carcinogenetic process and cause an ambiguity in the studied endpoints that is similar to that encountered in the study of chemical carcinogens if interference with acute toxicity occurs. Hence, highest exposure levels have to be chosen that are just below those that produce relevant heating. Due to the small margin of safety these levels are not much above those occurring in occupational environments and only a factor of 7 above standards for exposure of the general public. Such conditions afford special considerations for experimental animal studies because these exposure levels cannot dramatically increase rate of malignancies (otherwise there would be no controversy) in wild-type animals (although "wild-type" strains of experimental rodents have often substantially increased spontaneous cancer rates; Pitot & Dragan, 1996). Three different procedures are possible: (1) Strains can be chosen that have habitually increased cancer rates, harbor an oncogenic virus, or that are genetically engineered and overexpress an oncogene; (2) a known carcinogen can be used to induce malignancies, thereby increasing cancer rates; and (3) transplantation of cancer cells can be applied. All these procedures have been used in the study of high-frequency EMFs.

Tumor prone mice have been used by Toler et al. (1997) and Frei et al. (1998a, 1998b), and transgenic mice by Repacholi et al. (1997) and Utteridge et al. (2002). Chemical induction was utilized by Wu et al. (1994), Imaida et al. (1998a, 1998b), Chagnaud et al. (1999), Adey et al. (1999, 2000), Zook and Simmens (2001), and Bartsch et al. (2002). Santini et al. (1988), Salford et al. (1997), and Higashikubo et al. (1999) used implantation of tumor cells. Exposures that were slightly above levels that cause relevant temperature increase (2–8 W/kg, whole-body SAR) were used in early studies of Szmigielski et al. (1982) and Szudzinski et al. (1982).

Only a few of these studies demonstrated a significant effect of exposure. In the early studies (Szmigielski et al., 1982; Szudzinski et al., 1982), a dose-dependent increase of tumor incidence was observed. Repacholi et al. (1997) found in transgenic mice a significant effect of exposure on lymphoma incidence. The latter study is being replicated in several laboratories (using the same mouse strain, but applying a different experimental design and an exposure setup that restricts animals in tubes). One of these studies (Utteridge et al., 2002) has already been published, and reported no increase in lymphoma incidence. However, some questions remain about the implications of these findings (Kundi, 2003; Goldstein et al., 2003; Lerchl, 2003). One study (Adey et al., 1999) applying a paradigm that has been used earlier in teratogenicity studies (Kalter et al., 1980) found a reduction of brain tumor incidence similar to results obtained for low-dose x-ray exposures.

The early studies (Szmigielski et al., 1982; Szudzinski et al., 1982) applied exposures of 2–8 W/kg, and therefore results have been attributed to heating. However, this is in contrast to the antitumorigenic effect of increased tissue temperature (Dunlop et al., 1986), but underlines the problem of experimental design mentioned earlier.

The predominantly negative results of long- and medium-term animal experiments seem to rule out a carcinogenic effect of RF/MW EMFs. However, due to the lack of a well-founded mechanistic hypothesis, most experiments applied procedures that are suitable for the study of chemical carcinogens but may be less efficient for EMFs. Some of the studies (Santini et al., 1988) used induction procedures that led to very fast onset of disease and may be too fast for an effect of EMFs to show up. Other studies (Higashikubo et al., 1999) had slower onset but very steep decline of survival curves indicating the potential to detect any additional effect of an agent unreliable. Another important point is related to the type of exposure. Two studies (Frei et al., 1998a, 1998b) applied continuous-wave (CW) exposure; other studies used pulsed-field or frequency-modulated RF/MW fields. There is some evidence (Balcer-Kubiczek & Harrison, 1991) that pulsed fields are more effective than CW at equal rates of energy deposition. No generally accepted explanation for this observation has been yet proposed (Adey, 2003).

All experiments conducted so far differed in almost all aspects of exposure: frequency of the applied EMF, modulation type, exposure time and duration, distance to the emitting antenna, type of exposure facility, and so on. Considering human exposure conditions, it seems that a continuous exposure at constant levels is highly artificial. Most real-world exposures are time-varying or intermittent. Up to now no experiment has been reported that varied exposure duration. While typically chemical promoters are most efficient if tissue concentrations are maintained at a constantly high level, EMFs may be more effective if applied discontinuously. Chemical promoters act by binding to receptors while EMFs are not considered to mimic such processes. Fractionated exposure could be more effective, as indicated by in vitro studies (Ruediger et al., 2003).

Based on the evidence available to date, an elevated risk of RF/MW fields cannot be excluded. Epidemiological studies that approached reasonable latencies consistently observed elevated risk for the development of neoplastic diseases. Although long-term animal experiments provide only equivocal evidence for an association between EMFs and cancer, these studies are difficult to assess due to the limited range of exposure conditions studied and significant differences in methodology. It is as if one should start to assess carcinogenicity of chemicals by arbitrarily selecting a dozen. No one would conclude that chemicals cannot be carcinogenic based on such a procedure. The scientific community should combine strengths to propose and test possible mechanisms of action of RF/MW fields. These studies should provide a starting point for animal experiments and specification of dose parameters that may be used in epidemiological studies.

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