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Epidemiologic Studies of Cellular Telephones and Cancer Risk – A Review

Statens strålskyddsinstitut
Swedish Radiation Protection Authority

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TITLE: Epidemiologic Studies of Cellular Telephones and Cancer Risk, – A Review.

SUMMARY: Cellular telephones emit and receive radiofrequency (RF) signals between about 450 and 2200 MHz which fall in the microwave region of the electromagnetic spectrum. A RF wave from a cellular telephone contains billions of times less energy than an x-ray and is not capable of inducing ionizations or damaging DNA. The rapid and widespread use of this technology, however, has raised concern over possible adverse health effects, in particular brain cancer. A few studies which addressed this concern in the United States and Sweden are non-informative, either because the follow-up was too short and numbers of cancers too small (USA) or because of serious methodological limitations (Sweden). In contrast, five well-designed epidemiologic studies have been conducted in three countries by investigators using different designs: three hospital-based case-control studies in the United States, a registry-based case-control study in Finland, and a registry-based cohort study of over 400,000 cellular phone users in Denmark. In our view, a consistent picture has emerged from these studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date. No consistent evidence was observed for increased risk of brain cancer, meningioma, acoustic neuroma, ocular melanoma, or salivary gland cancer, examined over a wide range of exposure measures, including type of phone (analogue or digital), duration of use, frequency of use, total cumulative hours of use, tumor location and laterality (concurrence of tumor location with hand normally used during phone conversations). These methodologically sound epidemiologic investigations have limitations associated with any non-experimental study, and although they are not the same across each of the studies, the influence of bias, confounding and uncertainties in exposure assessment cannot be completely discounted. However, increased risks of 20% or higher can be excluded with a high level of confidence. Complementing the human data are the emerging results of experimental studies which have failed to confirm earlier reports of possible adverse outcomes from RF exposure. Moreover, there is no biologically plausible mechanism to support a carcinogenic effect of non-ionizing RF waves. While the current state of the science is reassuring, ongoing case-control studies being conducted in 13 countries using a shared protocol, and continued follow-up of cohorts of cellular phone users, should provide further evidence regarding any possible carcinogenic effect associated with long-term cellular telephone use.

SAMMANFATTNING: Mobiltelefoner sänder och tar emot radiofrekventa signaler i frekvensområdet 450-2200 MHz. Elektromagnetiska vågor vid dessa frekvenser brukar kallas mikrovågor. Energiinnehållet i en elektromagnetisk våg från en mobiltelefon är några miljarder gånger lägre än i t.ex. röntgenstrålning. Den kan inte skada DNA, vilket röntgenstrålningen kan. Den snabbt ökande användningen av mobiltelefonin har emellertid skapat oro för möjliga skadliga hälsoeffekter och i synnerhet för hjärntumörer. I ett antal epidemiologiska studier har man försökt att belysa sådana eventuella samband. Några av studierna, från USA och Sverige, är av begränsat värde. Antingen har uppföljningstiden varit för kort eller antalet cancerfall för litet (USA), eller så har det funnits allvarliga brister i de använda metoderna (Sverige). Mot detta står fem välplanerade epidemiologiska studier gjorda i tre länder där forskarna använt olika metoder; tre sjukhusbaserade fall-kontrollstudier i USA, en registerbaserad fall-kontrollstudie i Finland och en registerbaserad kohortstudie omfattande över 400 000 mobiltelefonanvändare i Danmark. Dessa studier så samstämmiga att man med rimlig grad av säkerhet kan utesluta ett orsakssamband mellan mobiltelefoner och cancer. Man har inte funnit några säkra belägg för ökad risk vare för sig hjärntumör, hjärnhinnetumör, tumör i hörselnerven, malignt melanom i ögat eller spottkörteltumör. Möjliga samband har analyserats med avseende på tumörernas läge eller liksidighet (samstämmighet mellan tumörläge och den sida man hållit telefonen på) eller med avseende på olika mått på exponering såsom typ av telefon (analog eller digital), tids-

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rymd, användningsfrekvens eller sammanlagd telefoneringstid. De metodologiskt välgjorda studierna har samma begränsningar som andra icke-experimentella studier och det går inte att helt utesluta inverkan av bland annat samverkande faktorer eller felklassificering av exponeringen, även om sådana faktorer varit olika i de olika studierna. Man kan med hög grad av säkerhet utesluta en riskökning på 20 % eller mer. Som komplement till data på människor börjar det nu också komma djurexperimentella resultat som inte bekräftar tidigare rapporter om skadlig verkan av radiovågor. Det finns ingen rimlig mekanism som stöder att icke-joniserande radiovågor skulle var cancerframkallande. Pågående fall-kontroll studier som genomförs i 13 länder med ett gemensamt upplägg, liksom fortsatta uppföljningar av befintliga kohortstudier av mobiltelefonanvändare kommer i framtiden att ge ytterligare bevis i frågan om huruvida långvarig användning av mobiltelefoner kan orsaka cancer.

Statens strålskyddsinstitut
Swedish Radiation Protection Authority

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Preface

The Swedish Radiation Protection Authority, SSI, is Sweden's central regulatory authority for radiation protection. SSI supervises many different operations involving radiation with the main aim of ensuring compliance with the Swedish Radiation Protection Act of 1988. The purpose of this act is to protect people and the environment from harmful effects of ionising and non-ionising radiation.

In 1998, the Swedish Parliament established 15 national environmental quality objectives for different environmental sectors to control pollutants and contaminants as well as activities. The objectives focus on protection of humans and the environment, and the overall challenge is to hand over to the next generation a sustainable society in which the major environmental problems have been solved. The objective for radiation, *A Safe Radiation Environment*, concerns both ionising and non-ionising radiation. SSI has the responsibility for formulating the goals and coordinating the follow-up for this environmental quality objective.

Many people today worry about possible adverse health effects of exposure to electromagnetic fields (EMF) from power lines and radiofrequency (RF) waves from cellular telephones and base stations. SSI is of the opinion that there is no scientific support for serious health effects at exposures below the levels recommended by the International Commission on Non-Ionizing Radiation Protection. There are, however, still reasons to take people's concerns seriously and more research in this field is therefore needed.

SSI is going to increase its activities regarding non-ionizing radiation and earlier this year set up an Independent Scientific Group consisting of seven renowned European scientists. This Group shall give SSI advice regarding health effects of EMF and RF signals and related biological issues. In order to obtain more knowledge about published data, SSI has also asked two internationally recognized US epidemiologists to review all published epidemiological studies dealing with cancer risks in relation to the use of cellular telephones. The present report is written by these two epidemiologists, John D. Boice, Jr. and Joseph K. McLaughlin from the International Epidemiology Institute, USA. The conclusions are the authors' and do not necessarily reflect the views of SSI.

I hope that this scientific review will be a useful document in SSI's endeavor to evaluate risk associated with RF exposure from cellular telephones in the proper scientific perspective.

SWEDISH RADIATION PROTECTION AUTHORITY

Lars-Erik Holm
Director General

Introduction

Similar to personal computers, video cassette players, and digital cameras, cellular telephones have become a part of daily life. In many countries they are used by over 75% of the population and use is increasing (GAO 2001). Cellular telephones differ from these other electronic consumer products, though, in that they receive and emit radiofrequency (RF) signals, and questions have been raised over possible adverse health effects, in particular brain cancer, following long-term use. This review will examine the epidemiologic studies that have been conducted on cancer risk among cellular telephone users, with emphasis on strengths, weaknesses and conclusions that can be drawn.

The electromagnetic spectrum covers an enormous range of wavelengths, from extremely small (the size of an atom) to extremely large (the size of a continent). As the wavelength gets shorter, the frequency gets higher and the energy of the wave increases. (Table 1).

Table 1. Characteristics of ionizing and non-ionizing radiation

Type of Radiation[1]	**Approximate Wavelength**	**Approximate Frequency**
Ionizing Radiation		
X-rays and gamma rays	0.03 nm	10^{10} GHz
Non-ionizing Radiation		
Radar	3 cm	10 GHz
Microwave oven	12 cm	2.45 GHz
Cellular telephone	30 cm	1 GHz
Electrical power lines	5,000 km	50-60 Hz

The shortest wavelengths ($<10^{-8}$ m) are those of ionizing radiations such as X-rays and gamma rays which are capable of breaking molecular bonds and causing cancer. Longer wavelengths are associated with electrical power lines (5,000 km), microwaves and radar (1-90 cm) and cellular telephones (16-67 cm) and are of lower frequency and lower energy. For example, the energy of a RF wave from a cellular telephone is *billions* of times lower than the energy of an x-ray photon. Since these longer wavelengths and lower energy waves are not capable of breaking molecular bonds, they are termed non-ionizing. RF signals from cellular phones are thus very different from ionizing radiation.

Cellular telephones and their base stations transmit and receive RF signals of between about 450 to 2200 MHz which fall in the microwave part of the electromagnetic spectrum. The first mobile phone networks were based on analogue technologies which are gradually being replaced by digital systems. The older analogue systems usually operated at higher power levels and at lower frequencies than the newer digital systems. RF radiation at sufficiently high power levels can cause some heating by inducing small electric currents and increasing molecular movement. Protection guidelines are set according to these thermal properties and are in terms of the "specific absorption rate" (SAR) --- defined as the amount of RF energy absorbed per unit mass per unit time and expressed in watts per kilogram (W/kg) (ICNIRP 1998; FCC 1999). A typical GSM digital cellular phone operating at a maximum average power output of about 0.25 watts (W) might results in a SAR of about 0.5-1.5 W/kg averaged over a gram of tissue, and an associated very low rise in brain temperature (maximum 0.1º C) (Anderson and Joyner 1995; Val-

berg 1997; van Leeuwen et al. 1999). Thus any biologic effect from cellular phone use would not be thermal in nature.

Cordless telephones used in the home, i.e., portable phones for which the base stations are also in the home, can emit and receive RF signals similar to cellular telephones in wavelength and frequency but at a much lower power level (maximum 0.01 W) in Sweden and other European countries (http://www.ssi.se/ickejoniserande_stralning/DECTmm.html, Bach Andersen 1999;), i.e., lower than that of a typical GSM digital phone or a typical NMT analogue phone. In the US, early cordless telephones operated at lower frequencies (46 - 49 MHz) and even lower power levels than cellular phones (Rothman et al. 1996b), although cordless telephones today in the US can operate at frequencies and power levels similar to those of cellular phones (FCC 1999). For completion, it is noted that GSM digital cellular phones operate with adaptive power controls that continually regulate power levels according to the distance to the base station. Power levels are usually many times lower than the maximum average of 0.25 W (NRPB 2000).

RF energy deposition from cellular telephones is due to magnetic fields that induce eddy currents in exposed tissue (Rothman et al. 1996b). Energy deposition is highest on the side of the head where the phone is used with exposure on the opposite (contralateral) side being lower by more than a factor of ten (Dimbylow and Mann 1999). Relatively high SARs occur in the temporal lobe (Balzano et al. 1995) and the lower anterior region of the parietal lobe (i.e., the area of the parietal lobe adjacent to the temporal lobe) (Rothman et al. 1996b). SARs would also be relatively high at the surface of the vestibular portion of the acoustic nerve (where acoustic neuromas might arise), in meningeal tissue at the outermost surface of the head near the ear, in the parotid gland (located in the cheek directly below the ear), and in any active bone marrow in cranial bones near the ear. Considerably lower SARs would be expected in other head and neck locations, including the cerebellum, midbrain, eyes and thyroid gland. Most of the frontal and occipital lobes are also outside the area of relatively high RF exposure.

Epidemiologic Studies

Recent epidemiologic investigations conducted in four countries have focused on cancer risk among cellular telephone users. (Table 2). Below we describe these studies with emphasis on their strengths and weaknesses, in an attempt to determine whether a consensus of evidence exists to judge whether cellular telephone use may increase risk of cancer, particularly of the brain. For completion, relevant occupational and geographical correlation studies of RF exposure are briefly discussed.

Table 2. Epidemiologic studies of cellular phone users and cancer risk

Study	Type	Population	Findings	Comment
Rothman et al. Epidemiology 1996	Cohort. Mortality. USA (1994). Linkage of subscriber lists with death records.	60,000 mobile (car or bag) phone subscribers, 50,000 portable (handheld) phone users, 150,000 unknown phone type.	Total mortality RR=0.86 (95 % CI 0.5-1.5) comparing handheld phone users with non-handheld phone users.	Follow-up very short. Only total mortality. Small number of deaths. Limited exposure assessment. Inconclusive.
Dreyer et al. JAMA 1999	Cohort. Mortality. USA (1994). Linkage of subscriber lists with death records	285,561 cellular phone subscribers. Expansion of Rothman et al. (1996)	No dose response for all cancers, brain cancer or leukemia.	Follow-up very short. Number of specific cancers small, e.g., 6 brain cancers. Limited exposure assessment. Non-informative.
Hardell et al. Int J Oncol 1999 MedGenMed 2000 Eur J Cancer Prev 2001	Case-control. Prevalence. Sweden (1994-96). Mail questionnaire.	209 brain tumors, 425 controls.	No association with ever use (OR 0.98), long-term use (OR 1.2) or hours used (OR 0.8). Suggestive associations with "same-side" use (OR 2.42) and with diagnostic x-rays of head and neck (OR 1.64). No dose response for gliomas, meningiomas, acoustic neuromas.	Prevalence studies exclude those who died and are not informative with regard to causality. Small numbers. Interview, selection and response bias likely. Methodology questioned (Ahlbom and Feychting 1999). Non-informative.
Muscat et al. JAMA 2000	Case-control. Incidence. USA (1994-98). Hospital interview conducted shortly after diagnosis using structured questionnaire.	469 brain cancer, 422 controls.	No association with ever use (OR 0.9), years used (OR 0.7), hours used (OR 0.7), temporal lobe (OR 0.9).	Hospital controls. Few long-term users, 88% analogue phones. Broad range of usage for dose-response analysis. No evidence for association.
Inskip et al NEJM 2001	Case-control. Incidence. USA (1994-98). Hospital interview conducted shortly after diagnosis using structured questionnaire.	782 brain tumors, 799 controls.	No association with ever use (OR 0.9), regular use (OR 0.9) or hours used (OR 0.7). No association with gliomas (N=489), meningiomas (N=197), acoustic neuromas (N=96), temporal lobe, or laterality.	Hospital controls. Few long-term users. Mostly analogue phones. Convincing evidence against association (Trichopoulos and Adami 2001).

Table 2 continued. Epidemiologic studies of cellular phone users and cancer risk

Study	Type	Population	Findings	Comment
Muscat et al. Neurology 2002	Case-control. Incidence. USA (1997-1999). Hospital interview conducted shortly after diagnosis using structured questionnaire.	90 acoustic neuromas, 86 controls.	No association with regular use (OR 0.9) or with frequency or duration of use. No association with laterality and handedness.	Hospital controls. Few long-term users. Mainly analogue. Small numbers. Consistent with USA (Inskip et al. 2001) and Danish (Johansen et al. 2001) studies.
Johansen et al. JNCI 2001	Cohort. Incidence. Denmark (1982-95). Linkage of subscriber lists with cancer incidence data.	420,095 subscribers identified from two operating companies.	No association with brain cancer (SIR 0.95, N=154) leukemia (SIR 0.97) or any cancer, including ocular melanoma (SIR 0.59). Brain cancer risk did not vary by type of phone, duration of subscription, histologic subtype or anatomic location.	Nationwide. No response bias. Large numbers but duration and extent of use unknown. User and subscriber may not be same. Small percentage of long-term users. Strong evidence against association (Park 2001).
Auvinen et al. Epidemiology 2002	Case-control. Incidence. Finland (1996). Tumors identified from cancer registry for single year, 1996, and matched against subscriber records.	398 brain tumors, 34 salivary gland cancers. 5 controls per case.	No significant associations for brain tumors (OR 1.3, gliomas and meningiomas) or salivary gland cancers (OR 1.3). Suggested increase for gliomas for analogue phone use, but not supported by tumor location analyses (lobe and laterality did not differ between users and non-users). No associations with digital phones.	Nationwide, registry-based, subscriber lists, no response bias. Usage seems unusually low, only 11%. Few users > 2 y. Inadequate exposure assessment.
Hardell et al Eur J Cancer Prev 2002	Case-control. Prevalence. Sweden (1997-2000). Mail questionnaire.	1,303 matched pairs of brain tumor cases and controls.	No association found for malignant tumors for analogue, digital or cordless phones. Significant association for analogue phones and all tumors (OR 1.3) for >1 y latency but not for >5 y latency (OR 1.1). Sinificant association for analogue phones and acoustic neuroma (OR 3.5). Borderline significant association for cordless phones and all tumors (OR 1.3) for >5 y latency. Increased ipsilateral (same side) risks balanced by decreased contralateral risks for virtually all phones and locations. No evidence of dose response by hours of phone use.	Prevalence studies exclude those who died and are not informative with regard to causality. Interview, selection and response bias likely. Acoustic neuroma increase not consistent with previous study in Sweden or 3 other studies. Non-informative.

USA - ROTHMAN ET AL. (1996A)

Design. A cohort study was conducted of mortality among cellular telephone subscribers residing in one of four metropolitan areas (Boston, Chicago, Dallas, and Washington DC). Cohort members included single phone, noncorporate customers who had active accounts as of January 1, 1994. Social Security numbers (SSN) were sought for 770,390 subscribers. The SSN was the primary matching variable for linkage to the Social Security Administration's Death Master File for deaths occurring in 1994 and the first quarter of 1995. An attempt was made to classify subscribers as to whether they used handheld (portable) or nonhandheld (mobile car or bag) cellular telephones. Car and bag telephones have antennas that are not located next to the user's head. Mortality rates were computed by type of telephone (handheld vs. nonhandheld) and mortality rate ratios were computed contrasting portable (handheld) with mobile (car or bag) phone users. In this early paper Rothman et al. (1996a) used the term "mobile" to describe nonhandheld car or bag cellular telephones, whereas today "mobile" is often used synonymously to mean handheld cellular telephones.

Results. After excluding 514,106 (67%) records because of duplicate SSNs, incorrect SSNs, potential corporate accounts, missing dates of birth or gender, and deaths prior to 1994 (N = 416), and requiring identical identification information from at least two sources (e.g., credit bureaus and subscriber listings), 255,868 persons were selected for mortality linkage: 23% used a nonhandheld telephone, 19% used a handheld telephone, and for 58% the type of phone was unknown. A total of 408 deaths were identified. The overall mortality rate was lower for handheld cellular telephone users than for nonhandheld cellular telephone users (RR =0.89, 95% CI 0.5-1.5). Mortality rates for users of both types of telephones were much lower than corresponding rates for the general population.

Strengths. The cohort design and linkage approach eliminate the possibility of interviewer and recall bias. The use of subscriber lists is a valid approach to identify exposed cohort members. Comparisons of mortality rates between handheld phone users and nonhandheld phone users are more appropriate than comparisons with the general population.

Weaknesses. The follow-up was very short, about 15 months. Total mortality is a non-specific outcome to evaluate possible cancer risks associated with cellular telephone use. The total numbers of deaths was small and the number of deaths due to brain cancer was unknown. Exposure assessment was imprecise in that duration and frequency of use were not known. The low mortality rate compared with the general population suggests that a healthy subgroup was selected and/or that deaths were underascertained. The percentage of unknown phone types (58%) was high.

Summary. This was the first epidemiologic study to evaluate the potential cancer risks associated with cellular telephone use and provided useful information with regard to the methodologic issues involved in evaluating this association (Rothman et al. 1996b; Funch et al. 1996). However, the limited follow-up, small number of deaths, and inadequate exposure assessment renders the study non-informative with regard to cancer risks.

USA - DREYER ET AL. (1999)

Summary. The Rothman et al. (1996a) study was expanded slightly to 285,561 analogue telephone users, in part by incorporating noncorporate customers from another signal carrier. Cause-specific mortality for 1994 was evaluated. The National Death Index was used to ascertain deaths and mortality rates were compared across categories of type of phone and daily minutes of phone use as well as length of subscription. Methodologic details were not provided. There were no significant associations with number of minutes of phone use per day or years of phone ownership, but the numbers of brain cancers deaths (N = 6) and leukemia deaths (N = 15) were small, precluding meaningful interpretation.

SWEDEN - HARDELL ET AL. (1999, 2000, 2001)

Design. A prevalence case-control study was conducted of persons aged 20-80 years and diagnosed with a brain tumor between 1994-96 in two regions in Sweden. Three papers were published based on the data collected in this study (Hardell et al. 1999, 2000, 2001). After excluding over 70% of eligible patients with malignant tumors and one out of three with benign tumors because of death and other reasons (Ahlbom and Feychting 1999 with reply by Hardell et al.; Hardell et al. 2002, Table 8 and discussion on page 383), an additional 37 (or 14%) of the 270 living (prevalent) cases were excluded for medical reasons, resulting in 233 brain tumor cases who were matched to two controls from the Swedish Population Registry. Those cases alive at the start of study and healthy controls from the general population were requested to fill out a self-administered mail questionnaire on a large number of items, including use of cellular telephones. Postal questionnaires were completed by 217 (93%) of the cases and 439 (94%) of the controls. After the mailing of the questionnaire an additional 8 cases and 14 responding controls were excluded because of metastatic or recurrent disease. The final analyses in all three papers were based on 209 (90%) cases (136 malignant, 46 meningiomas, 13 acoustic neuromas, 3 other benign, and 12 with unknown histology: one case had both an acoustic neuroma and an ependymoma) and 425 (91%) controls who responded to the mail questionnaire. Questions included average minutes of phone use per day, years of phone use, type of radiofrequency signaling (digital or analogue), type of phone (handheld, bag or car), laterality (side of head) of phone use, diagnostic and therapeutic x-rays, and occupation. A nurse supplemented incomplete or unclear answers by telephone, and contacted all subjects who reported use of cellular phones "to confirm such exposure and if necessary to qualify answers" (Hardell et al. 1999, page 114).

Results. There was no difference in the use of cellular telephones between cases (37%) and controls (38%) (OR =0.98, 95% CI 0.69-1.41) or in the median number of hours a telephone was used (136 hours for both cases and controls). No significant differences were observed for the use of analogue or digital phones or by histologic subtypes. There were no associations seen for gliomas, meningiomas or acoustic neuromas. There was no evidence for a dose response based on any measure of exposure for any latency period. An increased risk for brain tumors on the same side (ipsilateral) of the head where the telephones were held was reported for tumors in the temporal, occipital or temporoparietal region of the brain (OR=2.4; 95% CI 0.97-6.05); no increased risk was found in this region for brain tumors occurring on the contralateral (opposite) side (OR 1.06) and a deficit (OR 0.65) was reported among persons who varied which side of the head they held the phone (Hardell et al. 2001). Several significant associations were reported for other factors studied. Self-reported exposure to medical diagnostic X-rays of the head and neck was associated with a significant risk of brain tumor (OR 1.64), as was work in the chemical industry (OR 4.10) or in the laboratory (OR 3.21) (Hardell et al. 2001). These univariate risks were highlighted by the authors in their abstract and differed somewhat from those present in their multivariate analysis (Hardell et al. 2001). Work as a physician (OR 6.0; 95% CI 0.6-58) was also highlighted in the abstract, implying that fluoroscopy exposure was a factor. Intake of low-calorie drinks taken as a measure of aspartame, an artificial sweetener found in many consumables, was also linked to an increased risk of malignant brain tumor (OR 1.7; 95% CI 0.8-3.4) (Hardell et al. 2001), which was significant (OR 2.7; 95% CI 1.01-7.0) among those reporting the highest intake (Hardell et al. 2000).

Strengths. Use of the Swedish Central Population Registry should allow for the identification of controls representative of the same population from which the cases were drawn. Participation rates were extremely high, 94%, for completion of a self-administered mailed questionnaire sent to population-based controls. Clinical details of the tumor diagnoses were available.

Weaknesses. Prevalence-based case-control studies such as this one are limited and inferior in design to incidence-based case-control studies and cohort studies. Prevalence-based case-control studies of cancers that have high fatality rates, such as brain tumors, are problematic

since large numbers of patients who have died from the cancer are excluded from the study. Associations based only on comparing cancer survivors with healthy controls may be misleading, and firm causal inferences cannot be made (Breslow and Day 1980; Rothman and Greenland 1998).

The methodology, including case ascertainment and extremely high response rate to a self-administered mailed questionnaire, especially for healthy controls, has been questioned (Ahlbom and Feychting, including reply by Hardell et al. 1999; NRPB 2000). It appears that over 70% of the malignant brain tumors and one out of three benign tumors diagnosed during the study period were not included because of death and other reasons, indicating a serious selection bias. No proxy interviews were reported in this study. Thus the cases had to survive to the start of the study and had to be able to complete and return the mailed questionnaire. Cellular telephone exposure information relied only on the memory of respondents. Other methodological difficulties include the non-standard follow-up telephone contact by the nurse and the selective contact of cellular phone users, raising the possibility of interviewer bias. There were a large number of subgroup comparisons, such as those with respect to tumor location, each based on relatively small numbers of cases, suggesting that some elevated or decreased risks likely arose by chance alone.

The response rate of 94% for healthy population controls mailed a lengthy self-administered questionnaire is unusually high, especially when compared with a recently conducted population-based case-control study in Sweden reporting a response rate of 74% to a mailed questionnaire and face-to-face interview conducted by professional interviewers (Fored et al. 2001). Other recent studies in Sweden involving mail questionnaires with follow-up telephone interviews report population control response rates between 72%-83% (Riman et al. 2002; Fryzek et al. 2001). There is no adequate description of the techniques used by Hardell et al. (1999, 2000, 2001) to achieve such high response rates, which raises questions about how the target population was selected and response rates were defined. Remarkably, it is noted that previous studies of other cancer sites by the authors report even higher control response rates to questionnaires of 99% and 100% (Hardell et al.'s response to Ahlbom and Feychting 1999).

The statistical analysis of risks of brain cancer by laterality is misleading. Positive associations were emphasized between certain brain tumor locations (e.g., temporal, occipital and temporoparietal lobes) and side of the head against which the telephone was held during conversations, but persons with equal phone use on both sides (i.e., those who varied the use of their right and left hands to hold the phone, OR 0.65) should have been combined with ipsilateral use; such a combination would have reduced the OR for cellular telephone exposure on the same side as the tumor, and the significance in the multivariate analysis would have disappeared. Since there was no overall association between brain tumors and cellular phone use (OR 0.98) (Hardell et al. 1999), it is not reasonable to conclude that the use of a cellular telephone would simply change the location in the brain where diagnoses occur, increasing risk in some areas but protecting against the development of tumors in other areas. Further, since the occipital lobe is an area that receives relatively low RF exposure during cellular telephone use (Balzano et al. 1995), it is unclear why it was included in this grouping of supposedly high RF exposure regions. Bias in reporting exposures is also suggested by the significant excess risk associated with medical diagnostic X-rays, which is three times higher than the non-significant risk seen among atomic bomb survivors (RR 1.22 at 1 Gy) exposed to much higher doses of ionizing radiation (UNSCEAR 2000). It also seems misleading for the authors to state that "radiology work, especially fluoroscopy, may increase the risk of brain tumour" (page 527) based on their finding that fluoroscopy work as a physician (N = 3) was associated with a high risk of brain tumor (OR 6.0; 95% CI 0.6-58). They failed to mention that brain cancer was not increased in cohort studies of 1,300 British radiologists (Smith and Doll 1981), 27,000 Chinese medical diagnostic x-ray workers (Wang et al. 1990), or 143,000 US x-ray technologists (Doody et al. 1998).

Recently the Health Council of the Netherlands (2002) questioned the validity of Hardell et al.'s laterality findings. The Committee pointed out that

> "... it is not certain whether people's recollection about the side of the head against which they hold the telephone is accurate enough. [The Committee] also considers it likely that people do not always hold the telephone on the same side of the head, but alternate this. In addition, patients might report on this in a biased way if the object of the research were known. Research on this so-called laterality can better be conducted in a cohort study. In this way, the side of the head to which the telephone is preferably held can be recorded before a brain tumour arises, and thus also without having to trust users' recollections. The Committee considers that, without more accurate and reliable data on laterality, no conclusions can be reached concerning possible links."

Summary. No overall increased risk of brain tumors was associated with use of cellular telephones. An increased risk of tumors of the temporal, temporoparietal and occipital areas was associated with ipsilateral (same side) use of a cellular telephone, but was balanced by a decreased risk in other areas, i.e., the overall OR was 0.98. Small numbers, questionable methodology, multiple subgroup comparisons and exclusion of substantial numbers of cases renders this study non-informative with regard to risk of brain tumor. A similar but larger study than the one described here has been recently reported (Hardell et al. 2002) and is discussed later in this report.

Additional comments. Because the study by Hardell and colleagues encompasses three published papers, additional comments are necessary. The first paper in 1999 covered only cellular phones, whereas the second and third papers published in 2000 and 2001 covered a wide range of exposures in addition to cellular phones. There were few differences between the 2000 and 2001 papers. It is not clear, however, why the emphasis and interpretations of the same cellular phone data by the same authors changed dramatically over the course of two years, especially when three major negative epidemiologic studies were published between the first and the last paper (Muscat et al. 2000; Inskip et al. 2001; Johansen et al. 2001).

The 1999 paper is presented in a convincingly negative tone: "In this study we did not find an overall increased risk for brain tumours associated with exposure to cellular phones. The results were similar both for the analogue and digital system. No dose-response effect could be seen or any effect of tumour induction time" (page 116). "Acoustic neuroma develops in an anatomical area with comparatively high exposure to microwave radiation from a mobile phone. However, we did not find any association in this study" (page 116). With regard to the laterality findings they state: "A non-significantly increased risk for brain tumours located in the temporal or occipital lobe was found for persons who had used a cellular phone on the same side of the head...The results were based on low numbers and must be interpreted with caution" (page 116). The non-significant findings for tumor location and cellular phone use were an OR of 2.45 for right side and an OR of 2.40 for left side concordance based on 8 and 5 tumors, respectively.

In the 2001 paper the interpretation of the findings shifts: the paper highlights in the abstract and in the text only the non-significant combined right and left side laterality findings (without mentioning that the overall findings were negative): "Ipsilateral (same side) use of a cellular telephone increased the risk of tumours in the temporal, temporoparietal and occipital areas, with OR 2.42, 95% CI 0.97-6.05 (i.e. the anatomical areas with highest exposure to microwaves from a mobile phone)" (abstract, page 523). The 2001 paper concludes with "Use of cellular telephones increased the risk in the most exposed part of the brain" (page 528). The negative interpretation of the cellular phone findings in the 1999 paper is left unaddressed in the 2001 publication. The null finding for acoustic neuroma (OR 0.78) which develops in an anatomical area with high RF exposure comparable to the temporal lobe and lower anterior portion of the parietal lobe is also not mentioned; of 13 acoustic neuroma cases, only 5 had exposure to cellular

telephones, and only 1 used the telephone on the same side of the head where the tumor developed (Hardell et al. 1999, page 115).

USA - MUSCAT ET AL. (2000)

Design. A hospital-based incidence case-control study was conducted within five hospitals in New York, Massachusetts and Rhode Island, 1994-98. Cases were 18-80 years of age with primary brain cancer (N = 469) and were matched to 422 hospital controls. A structured questionnaire was used during an interview to ascertain use of handheld cellular telephones and estimate hours per month and years of use. Interviews were conducted shortly after cancer diagnosis. Forty-three (9%) of the case interviews and 6 (1%) of the control interviews were conducted with proxy respondents.

Results. Use of handheld cellular phones was reported by 66 cases (14%) and 76 controls (18%). The mean duration of phone use was 2.8 years for cases and 2.7 years for controls. Phones were used more frequently by men than women, persons aged 30-59 years, and salespersons. Most phones were analogue. Analyses were conducted by years of use, number of hours used per month, cumulative hours used, anatomical location of brain cancer, and histologic type of tumor. No significant associations were found. The odds ratio (OR) for regular past or current use was 0.85 (95% CI 0.6-1.2). All heavy users of cellular telephones had ORs below 1.0, including persons who used the phone for more than four years (OR 0.7), for more than 10 hours per month (OR 0.7), and for more than 480 total hours (OR 0.7). Brain tumors occurred more frequently on the same (ipsilateral) side of the head the telephone was usually held (26 vs 15 cases; P = 0.06), but tumors of the temporal lobe (the region of highest RF exposure) occurred less frequently on the ipsilateral than on the contralateral side (5 vs 9 cases; P=0.33), opposite to the finding of Hardell et al. (1999, 2000, 2001). ORs were less than 1.0 for all histologic types of brain cancer except for neuroepitheliomas, which was elevated but not significantly (OR 2.1, 95% CI 0.9-4.7).

Strengths. The relatively large number of incident cases, the use of a structured questionnaire administered face-to-face within two months of diagnosis and the high response rates for both cases (82%) and controls (90%) are strengths of this study. Trained health professionals administered the questionnaire while cases and controls were still in the hospital. Median monthly use (150 minutes) and highest use category (> 600 minutes per month) were sufficiently broad to provide a wide range of exposures for dose response analysis. Tumors were histologically confirmed and clinical details available. Emphasis was placed on rapid ascertainment of incident cases and interview of study subjects rather than surrogate respondents to minimize possible response and recall biases.

Weaknesses. Only about 5% of subjects reported using a cellular phone for more than four years. There is the possibility of response bias in case-control studies, although it probably was minimized with the use of a structured questionnaire administered shortly after brain cancer diagnosis and use of controls who also were hospitalized. The controls in tertiary care hospitals in large metropolitan areas may not be representative of the same population that gave rise to the cases (Wacholder et al. 1992b). Selection bias is a possibility in hospital based case-control studies, although the authors argued that the percentage of controls who reported cellular telephone use in 1994-1998 (18%) was similar to US population usage in 1998 (25%) (Muscat et al. 2000). Exposure assessment had to rely on memories of persons with brain cancer and matched controls to determine phone use, and it was not possible to validate responses against subscriber records or personal billing records. Digital phones could not be evaluated because of few users.

Summary. The results of this hospital-based study are negative, and are not consistent with an increased risk of tumors in areas of the brain presumed to be most heavily exposed to RF waves during cellular telephone use. The percentage of long-term users of analogue phones, while only 5% of the study population, did allow for dose-response evaluation with no trends of rising

risk detected. Nonetheless, possible associations with slow-growing tumors with long induction periods could not be addressed, nor could use of digital cellular telephones.

USA - MUSCAT ET AL. (2002)

Design. As part of the larger study of brain tumors discussed above (Muscat et al. 2000), an incidence case-control study of acoustic neuroma was conducted between 1997 and 1999. Overall, 90 patients with acoustic neuromas (or acoustic neurilemomas or Schwannomas) were matched to 86 hospital control patients with a variety of nonmalignant conditions. Hospital admissions lists were used to select controls. Personal interviews were conducted shortly after diagnosis using a structured questionnaire containing detailed questions on cellular telephone use and lifestyle characteristics.

Results. Eighteen cases (20%) and 23 controls (27%) reported regular use of a handheld cellular telephone (OR 0.9). Patients diagnosed with acoustic neuroma reported using the mobile phones on average for 4.6 hours (276 minutes) per month for 4.1 years, compared with 6.6 hours (396 minutes) per month and 2.2 years for controls. Risk for acoustic neuroma was not related to frequency or duration of cellular phone use. A nonsignificant elevation was seen for patients reporting cellular phone use for over 3 years (OR 1.7), but these patients were infrequent users and there was no association with cumulative minutes of use. There was no association between tumor laterality and the hand used to hold the cellular phone: only 4 of 11 patients who used the left hand and 1 of 7 patients who used the right hand had ipsilateral (same side) tumors (RR 0.65). [Note that the laterality relative risk (RR) is incorrectly reported by Muscat et al. (2002) as 0.9. The OR for the tumor laterality data in Table 2 of Muscat et al. (2002) is 0.095, and the computation for the laterality RR is straightforward[($\sqrt{OR}+1)\div 2$]; see Inskip et al. (2001) for derivation.]

Strengths. This was a hospital-based case series with clinically confirmed diagnoses, and interviews were conducted shortly after diagnosis using a structured questionnaire, minimizing response and recall bias.

Weaknesses. The number of cases was small. The possibility that controls were not representative of the same population that gave rise to the cases is a concern in tertiary care hospitals in large metropolitan areas (Wacholder et al. 1992b), although controls were comparable on practically all demographic characteristics evaluated. Digital phones and high frequency signals could not be evaluated, nor could long-term use or slow growing tumors of long latency, e.g., an effect of exposure that was delayed for ten or more years. Self-reported use of cellular phones was not validated by billing records.

Summary. Although limited by the small number of cases, this investigation of acoustic neuroma revealed no evidence for an association with the use of a cellular telephone. The absence of an association with acoustic neuroma is consistent with previous studies conducted in the United States and Denmark (Inskip et al. 2001; Johansen et al. 2001). These studies are of interest because RF exposure and associated SARs from mobile phones are relatively high at the surface of the vestibular portion of the acoustic nerve (the eighth cranial nerve) where acoustic neuromas develop (Rothman et al. 1996b).

USA - INSKIP ET AL. (2001)

Design. A hospital-based incidence case-control study was conducted of 782 cases (489 gliomas, 197 meningiomas, 96 acoustic neuromas) and 799 controls residing in Phoenix, Boston, and Pittsburgh (Inskip et al. 1999). Diagnoses occurred between 1994-98 among persons over the age of 18 years. Controls were admitted to the same hospitals but treated for a variety of non-malignant conditions. Controls were frequency-matched to cases on age, race or ethnicity,

sex and proximity of their residence to the hospital. Emphasis was placed on rapid ascertainment of incident cases and interview of study subjects. A personal interview was conducted in the hospital by a research nurse who administered a computer-assisted questionnaire. The interviews were also audiotaped. Ninety-two percent of eligible cases agreed to participate and most (80%) did so within three weeks of their diagnosis. The participation rate of eligible controls was 86%. Proxy respondents were used for 97 cases (12%) and 24 controls (3%).

Results. Overall, 39% of cases vs 45% of controls reported using a cellular telephone and 18% of cases vs 22% of controls reported regular use (at least two calls per week). The OR for regular use of a cellular phone was 0.8 (95% CI 0.6-1.1). Risk did not increase over categories of daily minutes of use (up to > 1 hour per day), duration of use (up to > 5 years), or cumulative hours used (up to > 500 hours). Risk did not vary by histologic type of intracranial tumor of the nervous system, nor by calendar year of first use. 12% of the subjects had used cellular telephones for three or more years. Regular use of a cellular phone for five or more years was reported by 2.6% of cases and 3.3% of controls. Tumors occurred slightly less often on the side of the head (ipsilateral) on which the telephone was typically used. The glioma relative risk for cellular phone use was lower in the exposed temporal lobe (OR 0.8) than in the frontal (OR 0.9) or parietal (OR 1.1) lobes, where exposure is generally considered to be much less. In contrast to the non-significant increase in neuroepitheliomas reported in the Muscat et al. (2000) study, a non-significant decrease in neuroepitheliomas was observed (OR 0.5; 95% CI 0.1-2.0). Most of the phones used were analogue.

The largest of 80 ORs presented for different types of intracranial tumors was for acoustic neuroma following 5 or more years of cellular phone use (OR 1.9; 95% CI 0.6-5.9). However, the observation was not significant (based on 5 cases), and the overall OR for ever use was 0.8. Further, there was no elevated risk for the highest levels of intensity of use (minutes per day); there was no association with cumulative hours of use; and acoustic neuromas were less likely to occur on the side of phone use than on the side opposite phone use.

Strengths. The study included a large number of incident cases and thus had the power to exclude low to moderate levels of risk. Careful attention was given to methodologic issues which minimized potential bias due to the use of hospital controls, such as sampling controls who lived within the same proximity to the hospital as the cases. The computer-assisted questionnaire reduced potential for interviewer bias, as did the audio taping of each interview. Extensive clinical details were available on histologic type and tumor location. Rapid ascertainment of cases and interviews conducted close in time to diagnosis minimized possible selection and recall biases common in studies of rapidly fatal cancers.

Weaknesses. As seen in other studies of this relatively new technology, long-term heavy use of cellular phones could not be adequately addressed, nor could tumors with potentially long induction periods. Differential selection factors between control diagnoses and the case diagnosis are always a potential problem when using large metropolitan tertiary care hospitals as the study setting (Wacholder et al. 1992b). However, the OR estimates for cellular phone use were quite similar in analyses based on different subgroups of control diagnoses. Most of the phones were analogue with frequencies of 800 to 900 MHz and thus potential risks associated with digital phones and higher operating frequencies could not be addressed. Exposure assessment had to rely on memories of persons with brain cancer and matched controls to determine phone use, and it was not possible to validate responses against personal phone bills or subscriber records.

Summary. This large-scale case-control study provides no evidence for an association between brain tumors and the use of cellular phones. The large numbers of cases, careful attention to methodologic issues to reduce potential biases, and absence of any consistent patterns of risk, dose response or tumor location are noteworthy.

DENMARK - JOHANSEN ET AL. (2001)

Design. A nationwide retrospective cohort study of cancer incidence through 1996 was conducted among all private users of cellular telephones in Denmark, 1982-95 (Johansen et al. 1999, 2001). A list of 420,095 mobile phone subscribers was obtained from the two Danish operating companies and matched against the Danish Cancer Registry on the basis of unique personal identification numbers assigned to each Danish citizen. Expected numbers of cancers were generated from general population statistics. Analyses were conducted by duration of mobile phone subscription, time since first subscription, age at first subscription, type of phone (analogue or digital), and type of cancer.

Results. During the time period of this study approximately 15% of the adult Danish population had mobile phone subscriptions. Overall, 3,391 cancers were observed with 3,825 expected, giving a standardized incidence ratio (SIR) of 0.89. No excesses were observed for cancers of the brain or nervous system (SIR 0.95; 95% CI 0.81-1.12; N=154), salivary gland (SIR 0.72; N=7) or leukemia (SIR 0.97; N=84). Risk of these cancers was not found to vary by type of mobile phone (analogue or digital), duration of mobile phone subscription, age at first subscription, or time since first subscription. No significant differences were observed for any subtype of brain tumor or anatomic location. Glioma risk was lowest for tumors of the temporal lobe (SIR 0.86) and the parietal lobe (SIR 0.48), both regions that receive exposure to RF signals during cellular telephone use.

Strengths. In epidemiology, results from a well-conducted cohort study are generally considered less prone to distortion than those from a well-conducted case-control study. A cohort design is generally superior to a case-control approach because of the minimization of selection, interviewer and recall biases. Since all persons within the country of Denmark with a personal subscription to a mobile phone were studied, including those who subsequently died, the possibility of selection bias is effectively removed. Because exposure was identified before the cancer outcome was determined, and the outcome was determined by linkage with previously collected cancer data, the possibility of recall bias is eliminated. The study had high statistical power to detect an effect because of the large numbers studied, the large numbers of person-years of observation (over one million), and the ability for some users to be followed for up to 15 years. Cancer incidence data in general are also of higher quality and may be more etiologically informative, particularly in regard to difficult to diagnose tumors, than mortality data.

Weaknesses. Despite the large numbers, the mean follow-up was 3.1 years, leaving open the possibility that slow growing tumors or those with long latency periods might be missed (although there were over 10,000 long-term subscribers who started using mobile phones in 1982-87 and had used cellular phones for up to 15 years). Exposure assessment was limited and based only on subscription information without validation. Thus the frequency and duration of phone use could not be evaluated. Corporate users were excluded and this group conceivably could be heavy users, although it is likely that corporate and personal subscriptions would also overlap. There was no way to discern car and bag phones from handheld phones which likely resulted in some misclassification of exposure. The general population was not an ideal comparison group as evidenced by the low SIR for lung cancer, suggesting a lower frequency of cigarette smoking among mobile phone users than the general population. Although cigarette smoking is not associated with brain cancer risk, cellular phone users may differ with regard to other factors that could be associated with brain cancer risk.

Summary. This cohort study with large numbers and minimal opportunity for bias is negative and does not support the hypothesis of an association between the use of mobile phones and cancer. Relative risks greater than 1.12 could be excluded with 95 percent confidence for brain cancer following short-term, i.e., less than 5 years of use of mobile phones.

FINLAND - AUVINEN ET AL. (2002)

Design. A registry-based incidence case-control study of cellular telephone use and cancer was recently reported from Finland. All brain tumor cases (198 gliomas, 129 meningiomas, 72 NOS) and salivary gland cancers (N = 34) diagnosed in 1996 between the ages of 20-69 years and reported to the Finnish Cancer Registry were identified and matched to 5 controls using the Central Population Register. Type and duration of cellular telephone use was determined by linkage with cellular phone subscriber lists provided by two signal carriers on the basis of the unique personal identification number assigned to each Finnish citizen. Histologic subtype, lobe and laterality of 32 glioma cases with cellular phone subscriptions were contrasted with a similar number of randomly selected age- and sex- matched glioma cases who did not have a phone subscription. Due to the study design in this linked-registry case-control study, there were no proxy respondents.

Results. Overall, the percentages of cases and controls with subscriptions for a cellular phone were low and not significantly different: 13% of brain tumor cases (OR 1.3; 95% CI 0.9-1.8), 12% of salivary gland cancer cases (OR 1.3; 95% CI 0.4-4.7) and 11% of controls. Subgroup analyses were conducted for three phone categories (analogue, digital, total), five histologic types (all brain, glioma, meningioma, other brain, salivary gland) and four duration of subscription categories (ever, < 1 year, 1-2 years, >2 years). There were no significant findings for digital phone use with any tumor type or for use of any phone with meningiomas, other brain tumors or salivary gland cancers. Gliomas were associated with the use of analogue phones (OR 2.1; 95% CI 1.3-3.4) but not digital phones (OR 1.0; 95% CI 0.5-2.0). There was no significant difference, however, for tumor location (lobe and laterality) between glioma cases who used and who did not use cellular telephones. There was little variation in glioma risk over categories of subscription duration to analogue phones (OR 1.6, 2.4, 2.0 for < 1year, 1-2 years, > 2 years). A significant trend was found when non-exposed persons were included but was not considered evidence of a dose response. It is well known that a plateau response (i.e., similar odds ratios for all exposure categories compared with no exposure), such as that seen here, can give a significant result in a trend analysis when there is in fact no dose response among users (Maclure and Greenland 1992). Analogue phone use was not associated with meningiomas (OR 1.0; 95% CI 0.6-1.5) or salivary gland cancers (OR 1.3; 95% CI 0.7-2.5).

Strengths. No selection bias was likely since cases were incidence-based and identified from the nationwide cancer registry and controls from the nationwide population register. No response bias was possible since exposure was determined from linkage with subscriber lists. The number of brain tumors overall was reasonably large. Analyses were carefully performed and results clearly presented. Potential confounders such as occupation, place of residence and socioeconomic status were evaluated.

Weaknesses. The number of cellular phone users seems low, only 11% among controls in a country instrumental in starting the explosion of world-wide cellular phone use (Bach Andersen 1999). The duration of subscription also seems low, with few subscriptions more than 2 years (about 5%) whereas in Denmark 23% were long-term users (first subscription prior to 1994) (Johansen et al. 2001) and in USA 11% of controls used phones for more than 2 years (Muscat et al. 2000). The low percentages in Finland, especially in comparison with the Danish data, suggest that private cellular phone users might have been underascertained. No data were presented on calendar year of coverage of the two cellular network providers operating in Finland in 1996, i.e., it was not clear whether their coverage began in the 1980s. Duration of subscription is not the same as duration of use and no information was available on frequency or duration of calls. Determination of phone use was possible only for private subscriptions and not for individuals who used a company phone. Thus, both cases and controls may have had more exposure to cellular phones than was estimated based on personal subscriptions. A distinction apparently could not be made between subscriptions for handheld telephones, car telephones, and bag telephones, except that RF signals at 450 MHz were assumed to be for bag telephones and excluded.

Summary. Overall, there was no consistent evidence for an association between brain tumors or salivary gland cancers and cellular phone use. The association between gliomas and analogue phone use overall was not supported by an analysis of tumor location (lobe and laterality did not differ between users and non-users), and might be a chance finding related to multiple comparisons. No associations with gliomas and cellular phone use were reported in the Danish (Johansen et al. 2001) and US incidence studies (Muscat et al. 2000; Inskip et al. 2001) or in the Swedish prevalence studies (Hardell et al. 1999, 2002). Similar to previous studies, long-term use could not be evaluated and exposure assessment was limited. Private cellular telephone users also might have been underascertained.

SWEDEN - HARDELL ET AL. (2002)

Design. Similar in design to their previous study (Hardell et al. 1999, 2000, 2001), Hardell et al. (2002) conducted a prevalence case-control study of persons aged 20-80 years and diagnosed with a brain tumor between 1 January 1997 and 30 June 2000 in four regions in Sweden. Of the 2,561 patients reported with brain tumors from the regional cancer centers, 540 (21%) were excluded because they had died and 404 (16%) were excluded for other reasons, resulting in 1617 brain tumor cases who were matched to one control identified from the Swedish Population Registry. These cases who were still alive at the start of study and healthy controls from the general population were requested to fill out a 21 page self-administered mail questionnaire on a large number of items, including use of cellular and cordless telephones. Postal questionnaires were completed by 1,429 (56% of the source population / 88% of those sent questionnaires) of the cases (588 malignant, 611 meningiomas, 159 acoustic neuromas, and 72 other benign: one case had both a meningioma and an acoustic neuroma) and 1470 (91%) of the controls. An additional 167 cases were excluded because their matched control did not respond to the questionnaire, leaving 1,303 (51% / 81%) matched case-control pairs available for analysis. The questionnaire was based on the one used in the previous study and included questions on the average number and length of calls in minutes per day, years of phone use, type of phone (analogue (450 MHz or 900 MHz), digital or cordless), ear most frequently used during phone calls (laterality), car phone use with external antenna and earpiece use. Questions were also asked about diagnostic and therapeutic x-rays, organic solvents, pesticides, asbestos, reproductive history, and heredity. Only results for telephone usage were presented in this paper. A nurse supplemented incomplete or unclear answers by telephone, and contacted all subjects who reported use of cellular phones if the "quality of the answers" failed to meet unspecified "criteria for assessment of exposure" see also (Hardell et al. response to Ahlbom and Feychting 1999). Assistance in completing the questionnaire was required from the relatives of 456 (35%) of the cases and 137 (11%) of the controls.

Results. Odds ratios (ORs) for brain tumor were presented by 3 types of phones (analogue, digital, cordless), 10 brain tumor locations, 3 latency periods (>1, >5, > 10 years), 3 lateralities (ipsilateral, contralateral, both), and 11 different histologies. Specific analyses for the temporal area of the brain and multivariate analyses were also conducted. The paper reports over 200 ORs.

Cases reported similar or slightly more use than controls of analogue phones (17% vs 15%), digital phones (30% vs 30%), and cordless phones (28% vs 27%). Overall, there were no associations between either analogue, digital or cordless phone use and malignant tumors (ORs 1.1, 1.1 and 1.1, respectively). Overall, there was no evidence for a dose response by hours of phone use with analogue (OR 1.3 and 1.2 for $\leq$85 h vs > 85 h), digital (OR 1.0 and 0.9 for $\leq$55 h vs >55 h) or cordless (OR 0.9 and 1.1 for $\leq$183 h vs >183 h) phones. The only significant finding in analyses of all brain tumors by histology was an association between analogue phone use and acoustic neuroma (OR 3.5; 95% CI 1.8-6.8); however, there was no variation in risk by latency periods (OR 3.5, 3.7 and 3.5 for > 1 year, > 5 year and > 10 year latencies, respectively). Another benign tumor, meningioma, was associated with analogue phone use in the temporal lobe (OR 4.5; 95% 0.97-21), but again the ORs declined with increasing latencies (OR 4.5, 3.0 and 1.0 for > 1 year, > 5 year and > 10 year latencies, respectively); and there was no association for

meningiomas in all brain locations (OR 1.1). Significant associations for all brain tumors with analogue phones for >1 year (OR 1.3), > 5 year (OR 1.4) and > 10 year (OR 1.8) latencies were reported in a univariate analysis, but a multivariate analysis revealed no statistical significance and lower risks for the >5 year (OR 1.1) and >10 year (OR 1.3) latencies. Further, there was no evidence that those who used the phones for the longest time had higher risks than those who occasionally used the phone, i.e., there was no dose response by hours of phone use.

For latencies > 5 years, significant associations were reported between all tumors occurring in the temporal lobe for analogue (OR 1.9) and cordless phones (OR 1.9). However, inverse risks were seen between analogue phones and tumors occurring in the occipital (OR 0.6) and temporo-parietal (OR 0.8) regions, i.e., in the regions combined by Hardell et al. (2001) with the temporal lobe in earlier papers and presented together as the areas of the brain having the "highest exposure to microwaves".

Laterality analyses revealed significant ipsilateral (brain tumor occurring on the same side of the head as ear used during conversations) associations for brain hemisphere and analogue (OR 1.8) and cordless (OR 1.3) phone use; for temporal area tumors and analogue phone (OR 2.5) use; and "other than temporal area" for analogue (OR 1.5), digital (OR 1.4) and cordless (OR 1.4) phone use. However, the ORs for tumors occurring on the opposite (contralateral) side of the head of phone use were virtually all less than 1. Significantly low contralateral ORs were seen for brain hemisphere and cordless (OR 0.7) phone use and reduced contralateral ORs of borderline significance were seen for temporal area and cordless (OR 0.7) phone use and for "other than temporal area" and analogue (OR 0.6), digital (OR 0.8) and cordless (OR 0.7) phone use.

If one assumes that type of phone can act as a crude surrogate measure of "dose" then cordless phones would result in lowest brain exposure to RF waves, with successively higher exposure for digital and then analogue phones. For malignant tumors in the temporal lobe (the lobe with highest RF exposure from cellular phones), the observed "dose" response would be inverse with ORs of 1.6, 0.8 and 0.8 for cordless, digital and analogue phones, respectively. For benign tumors in the temporal lobe the "dose" response would be positive with ORs of 0.8, 1.0 and 3.8 for cordless, digital and analogue phones, respectively. Moreover, in the multivariate analyses of all brain tumors, there was no evidence of dose response within latency categories: for >1 year latency ORs were 1.0, 1.0 and 1.3, whereas for the longer-term users the patterns were reversed, i.e., for >5 years latency ORs were 1.3, 0.9 and 1.1 and for >10 years latency ORs were 1.8, n/a (digital phone use did not exceed 10 years) and 1.3 for cordless, digital and analogue phone use, respectively. The only significant finding in the multivariate analysis was for analogue phones and > 1 year latency (OR 1.3; 95% CI 1.04-1.6), although a borderline significant association was seen for cordless phones and > 5 year latency (OR 1.3; 95% 0.95-1.8).

Interestingly, twice as many cases reported having been diagnosed with a previous cancer than controls (176 vs 86) prior to completing the questionnaire. It is unclear how this noncomparability between cases and controls would affect cellular telephone use or how treatments for the prior cancer would have affected brain tumor occurrence or even questionnaire response.

Strengths. Use of the Swedish Central Population Registry allowed for the identification of controls representative of the same population from which the cases arose. Reported participation rates were high, over 91%, for completion of a mailed questionnaire by control subjects. Clinical details of the tumor diagnoses were available. The questionnaire was designed to obtain detailed information on use of cellular and cordless telephones.

Weaknesses. As discussed previously (see the section on weaknesses of the Hardell et al. 1999, 2000, 2001 study), prevalence-based case-control studies such as this one are limited and inferior in design to incidence-based case-control studies and cohort studies (Breslow and Day 1980; Rothman and Greenland 1998). Over 500 subjects with brain tumor died prior to the questionnaire mailing and resulted in a non-representative distribution of tumors overall, i.e.,

among the patients studied, 36% had malignant, 42% benign, and 16% acoustic neuromas, compared with the expected distribution of brain tumors, where most are malignant (Ahlbom and Feychting 1999; Inskip et al. 2001). Study results based only on survivors are likely to be distorted since the surviving cases represent a highly selected group (Gordis 1982).

There is further evidence of distorting biases in this study which preclude meaningful interpretations. It is not biologically plausible that cordless telephones, which operate at power levels some 25 - 100 times lower than cellular telephones in Sweden, would show the same level of risk as cellular telephones, yet this is reported in the paper (e.g., in the multivariate analysis for > 5 year latency the OR was 1.1 for analogue and 1.3 for cordless; for >10 year latency the ORs were 1.3 and 1.8 respectively). It is noteworthy that the multivariate analyses resulted in substantial reductions of the OR estimates for analogue phones (compared with univariate analyses), but resulted in little or no such reduction of the OR estimates for cordless phones. The authors speculate that cordless phones may increase risk because they are used more frequently than cellular phones, but this increase in duration of use of only 2-3 times is minuscule when compared to the 25 to 100 times higher operating power levels of cellular phones. The most likely explanation of the positive findings for cordless phones is response bias on the part of brain tumor patients and their relatives. Such bias would also be expected to be present in analyses of cellular phones.

Recall bias is a potential problem in all case-control interview studies, but seems particularly likely in investigations of tumor location and cellular phone use (Health Council of the Netherlands 2002). For analyses of analogue, digital and cordless telephones, nine positive associations (increased risks) were reported between brain tumor location and side of the head (ipsilateral) most frequently exposed to radiofrequency waves during cellular telephone conversations. However, these positive associations were counter-balanced by eight deficits of tumors (i.e., decreased risks with OR < 1.0) on the opposite (contralateral) side of the head of phone use, suggesting a bias in the reporting or collection of these data. It is not reasonable to conclude that the use of a cellular telephone would simply change the location in the brain where diagnoses occur, or that cellular telephones would protect against the development of tumors on the opposite side of the head. Thus, in this study it seems plausible that a person with a brain tumor was prone to incorrectly report telephone use on the side of the head in which the tumor occurred, leading to a positive bias in the laterality analyses. Such a reporting bias will affect all tumors for all types of telephones, as was seen even for cordless telephones.

The authors fail to define what they mean by latency and whether a person who used a phone just a few times 10 or more years prior to tumor diagnosis would be classified in the >10 year latency category. The laterality analysis involved assuming a "tumor" location for the control, i.e., each matched control was assumed to have a "tumor" occurring in the same region of the brain as the brain tumor that occurred for the corresponding case. 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). None of the self-reported phone use was validated with billing or subscription records. There are other methodological difficulties such as the non-standard follow-up telephone contact by the nurse and the selective telephoning of cellular phone users, raising the possibility of interviewer bias. Furthermore, with over 200 comparisons presented, it is likely that many of the "significant" findings are due to chance alone.

There were also questionable and inconsistent statements throughout the paper. It is claimed that the results are consistent with the previous study (Hardell et al. 1999, 2000, 2001) but this appears not to be the case. The previous study (Hardell et al. 1999, 2000, 2001) was negative overall (OR 0.98), with no association between cellular phone use and acoustic neuroma (OR 0.78). The only significant association in the current study was for acoustic neuroma (OR 3.5), although latency and dose response analyses were not consistent with a causal relationship. The previous study (Hardell et al. 1999, 2000, 2001) reported an increased risk for tumors occurring

in the temporal, occipital and temporoparietal regions of the brain, but the current study found the increase only for the temporal lobe with decreased risks in the other two regions (OR 0.6 and 0.8, respectively). It is unclear why the two studies focused on different brain regions to make inferences about potential risks, except that using the earlier definition within the 2002 study would have reduced the risk estimates, suggesting that the brain region grouping in the earlier study might have been data driven. The abstract highlights the >10 year latency risk estimate (OR 1.8; 95% CI 1.1-2.9) from the univariate analysis, whereas the multivariate analysis risk estimate was neither significant (OR 1.3; 95% CI 0.8-2.3) nor "increased further" over the >1 year latency risk estimate (OR 1.3). One consistent finding that is not mentioned, however, is that no statistically significant increased risk was seen for malignant tumors. Furthermore, in reviewing the three major studies conducted to date (Muscat et al. 2000; Inskip et al. 2001; and Johansen et al. 2001) the authors correctly state that "one major shortcoming of these studies is the short tumour induction period" (page 385). However, in their multivariate analysis there are no statistically significant findings for any type of telephone within the > 5 year or > 10 year latency categories, presumably those with the longest tumor induction period. In fact, it is only the > 1 year latency period for analogue phone use that provides a significant result in the multivariate analysis, i.e., when including those with the shortest tumor induction period. Moreover, for this one statistically significant category of >1 year latency for analogue phone use, there was no evidence for a dose response over categories of cumulative hours of use.

Finally, the first paragraph of the Discussion (Hardell et al. 2002, page 383) is unusual in epidemiology. It has little to do with the current study, but addresses a 1999 published correspondence by Ahlbom and Feychting (1999) about the earlier study (Hardell et al. 1999). Hardell et al. (2002) note that the number of eligible brain cancer cases reported by Ahlbom and Feychting (1999) is much larger than the actual number of cases eligible for the earlier study, but this discrepancy is a result of the inadequate study description in Hardell et al. (1999), not of an error in counting registry cases by Ahlbom and Feychting. Ahlbom and Feychting assumed (as readers of Hardell et al. 1999 would) that all patients with benign brain tumors were eligible in both study areas during the entire study period. Only in the response letter to Ahlbom and Feychting (1999) and in subsequent publications (Hardell et al. 2000, 2001) was it revealed that benign tumors were only ascertained for one year in Stockholm. Hardell et al. (2002, page 383, second and third sentences) also imply that diagnostic issues are the major problem leading to exclusion of cases identified from registries. The data provided, however, document that mortality is the major source of exclusion (Hardell et al. 2002, Table 8). Of 476 patients with malignant tumors who met the inclusion criteria for the first study, only 45% were alive at the end of 1996 and only 29% were alive at the end of 1997. Since interviews for the first study were begun some time in 1996 (Hardell et al. 2002, page 383), a large percentage of patients would have died before they could be interviewed. Death is also the major reason for exclusion in the second study; 57% of excluded cases (with benign or malignant tumors) were excluded because of death prior to the start of the study and 6% for medical reasons, compared to 14% who were excluded because their tumors were metastases and 11% because of diagnostic errors or missing histopathology records (Hardell et al. 2002, Table 1).

Summary. An association between the use of analogue cellular telephones and benign brain tumors, but not malignant brain cancers, was reported in a prevalence case-control questionnaire study. Because only living cases were interviewed and well over 500 cases were excluded, and because there is evidence of selection and information bias, this study of cancer survivors cannot provide the basis for causal inferences. The high risks for cordless telephones which operate at power levels up to 100 times lower than analogue telephones in Sweden indicate a reporting bias. The increase for ipsilateral (same side) phone use is balanced by a decrease for contralateral (opposite side) phone use, suggesting a reporting bias; ie., it is not biologically plausible that RF signals would simply change the location in the brain where a tumor is diagnosed or that they would protect against the development of tumors on the opposite side of the head. There was no evidence of a dose response. The only significant finding was for acoustic neuromas and analogue phone use, but there was no evidence from the latency or dose response analyses

to support a causal association. Further, acoustic neuromas have not been linked to cellular phone use in the previous study conducted in Sweden (Hardell et al. 1999), nor in the US (Inskip et al. 2001; Muscat et al. 2002), or Danish (Johansen et al. 2001) studies. Because of the above listed shortcomings and the large number of comparisons made, over 200, bias and chance are the most likely explanations of the significant associations reported in this paper.

Melanoma of the Eye

STANG ET AL. (2001); JOHANSEN ET AL. (2002)

Two incidence case-control interview studies were conducted in Germany on occupational risk factors for 8 rare cancers, including uveal melanoma, and results were pooled (Stang et al. 2001). A total of 118 cases of uveal melanoma and 475 matched controls were evaluated (Table 3). Workers had been asked "Did you use radio sets, mobile phones, or similar devices at your workplace for at least several hours per day?" Based on a subsequent evaluation of this response and categorization by one of the authors, a significant four-fold increased risk of malignant melanoma of the eye was reported for "probable or certain exposure to mobile phones", based on 12 exposed cases. This study is largely non-informative with regard to cellular phone use because it was not designed to address cellular phone exposures. Exposure assessment was extremely limited and did not include personal (non-occupational) use of phones, responses were not validated, it is unclear how mobile phone use could be separated from "radio sets or similar devices" based on "author review", tumor laterality with regard to side of phone use was not considered and important confounders, such as UV exposure, were not taken into account.

If use of cellular phones increases the relative risk of uveal melanoma by a factor of four as reported in the German study, it was postulated that increases in incidence over time should be observable (Inskip 2001). To test this hypothesis, the incidence rates of ocular melanoma 1943-1996 were correlated with the number of mobile phone subscribers in Denmark (Johansen et al. 2002). No increasing trend in the incidence rates was observed, which was in sharp contrast to the exponentially increasing number of mobile phone subscribers (Figure 1).

In addition to the absence of an increasing trend in incidence of melanoma of the eye, no association between this cancer and cellular phone use was observed in the Danish cohort study of over 420,000 users of mobile telephones between 1982 and 1995 (Johansen et al. 2001). Eight cases of ocular cancer were observed compared with 13.5 cases expected (SIR 0.59; 95 % CI 0.25 – 1.17). Thus the Danish studies provide no support for an association between mobile phones and ocular melanoma. Further, an association seems somewhat improbable given the very low level of exposure to the eye from RF signals emanating from mobile phones (Rothman et al. 1996b, Anderson and Joyner 1995).

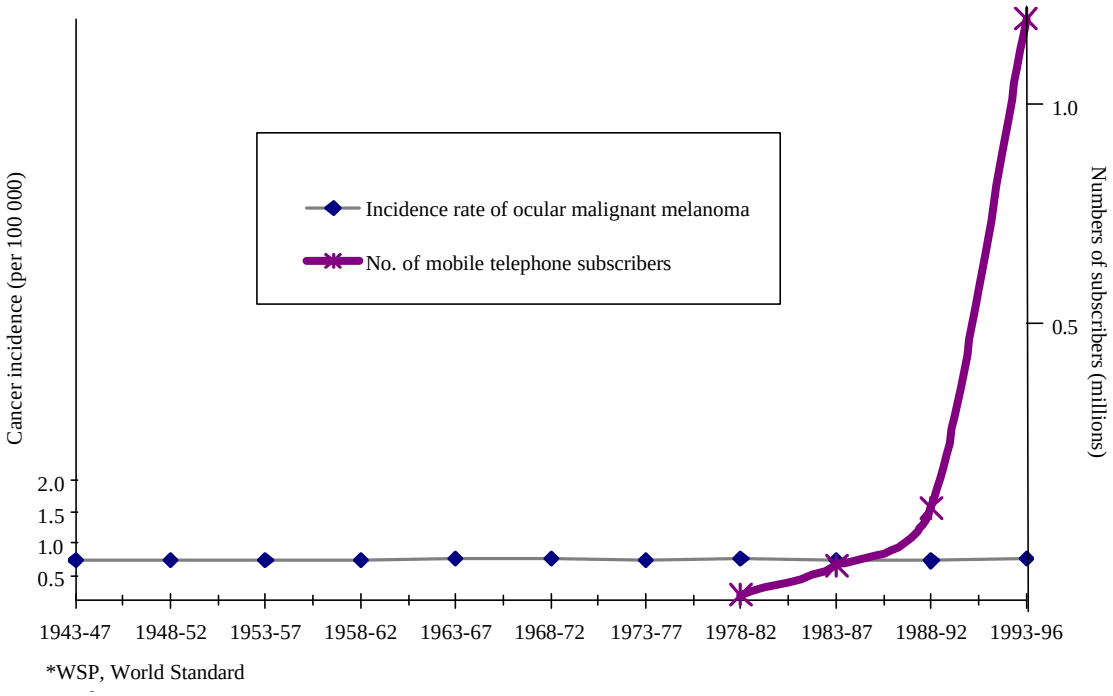

Figure 1. Age Standardized (WSP) annual incidence (cases per 100,000) of ocular malignant melanoma in Denmark 1943-96 and number of subscribers to cellular telephones, Denmark 1982-96* (Johansen et al. 2002).

Table 3. Recent occupational and geographical correlation studies of radiofrequency (RF) exposure and cancer risk

Study	Type	Population	Findings	Comment
Stang et al. Epidemiology 2001	Case-control incidence. Germany (1994-1997). Two case-control studies of occupational exposures, one hospital based, pooled. Interview.	118 uveal melanomas, 475 controls.	Association with ever exposure to "mobile phones, radio sets or similar devices".	Occupational studies not designed for cellular phone evaluation. Response bias possible. Low participation rate (48%). Inadequate exposure assessment. UV exposure not taken into account (Inskip 2001). Inconclusive.
Johansen et al. Br J Cancer 2002	Incidence time trend. Denmark (1943-96). Cohort incidence analysis among subscribers.	Incidence of melanoma of the eye over time. Cohort of 420,095 subscribers.	No changes in incidence trend. No excess, SIR=0.6 (N=8), in cohort of subscribers.	No evidence to support association in either the time trend or cohort analyses. RF exposure to eye very low.
Morgan et al. Epidemiology 2000	Cohort mortality. USA (1976-96). Occupational study.	195,775 workers engaged in manufacturing and testing cellular telephones.	No association between RF-exposure and brain cancer (SMR 0.60, N=51). Internal analyses showed no associations with exposure duration or latency. No association between highest RF-exposure and brain cancer (SMR 0.53, N=7).	Large cohort. Qualitative job matrix for exposure assessment Small number of brain cancer deaths among heavily exposed. No information on personal phone use. No association between heavily RF exposed group and cancer risk.
Groves et al. Am J Epidemiol 2002	Cohort mortality. USA (1950-96). Korean War Veterans.	20,021 sailors with high radar exposure potential during 1950-54 (Korean War) 20,560 sailors with low radar exposure potential during 1950-54.	No increase in brain cancer (SMR 0.9, N=88) overall or in high exposure occupations (SMR 0.7, N=37).	40 year follow-up. High potential exposure to radar frequencies (300 MHz - 300 GHz). Exposure assessment only for 1950-54. Other exposures (e.g., solvents) unknown. Follow-up uncertainties. No evidence for increased cancer risk.

Other RF Occupational Studies

MORGAN ET AL. (2000); GROVES ET AL. (2002)

Occupational studies of RF exposure and cancer risk have been limited and their results are inconsistent, in part due to small numbers, inadequate or only qualitative measures of RF exposure, and absence of information on other occupational exposures such as chemicals (Rothman 1996b, 2000; Elwood 1999). Further, the wide range of signal frequencies and variations in anatomical exposure (whole body vs head) complicates comparisons with cellular telephones (Rothman 2000). One recent occupational study, however, dealt directly with RF exposures from wireless communication technologies. No association between RF exposure and cancer of the brain (N = 51) and leukemia (N=79) was seen among 195,775 Motorola workers, who were engaged in manufacturing and testing of cellular telephones between 1976-96 (Morgan et al. 2000). Exposure assessment was based on a qualitative job matrix, with about 72% of workers with no RF exposure above background levels. The SMR for brain cancer among 24,621 RF-exposed workers was 0.53 based on 7 cases. Internal analyses revealed no associations with exposure duration or latency. Limitations include the use of a qualitative job matrix for exposure assessment, the relatively small number of cancer deaths among the RF-exposed workers, and the absence of information on personal (non-occupational) use of cellular phones. On the other hand, although domestic phone use was not addressed, it could be expected to be much higher than in the general population among these wireless communication workers (Owen 2000), and thus the negative findings might be even more informative.

A recent cohort mortality study addressing the possible health effects of RF waves was conducted among 40,581 US Navy veterans of the Korean War (1950-54) (Groves et al. 2002). Radar frequencies range between 300 MHz to 300 GHz, and 20,021 sailors were judged to have high radar exposure potential based on job categories. There was no evidence of increased brain cancer in the entire cohort (SMR 0.9; N=88) or in the high exposure occupations (SMR 0.7; N=37); neither were risks elevated for leukemia deaths for the entire cohort (SMR 0.8; N=113) or for the high exposure occupations (SMR 1.1; N=69). A slight increase was seen for nonlymphocytic leukemia among sailors with high radar exposure potential (SMR 1.2) but was limited to only one of the three high-exposure occupations (SMR 2.2, electronics technicians in aviation squadrons) and was likely a chance finding among multiple comparisons. Ocular cancer was not increased; only one case occurred and it was in the low-exposure group. The 40 year follow-up, the potential for very high RF exposure during military conflict, and the existence of comparable comparison groups of low exposure potential are strengths of this study. Limitations include the use of job categories during one moment in time to characterize exposures, the potential for exposure to other occupational agents (such as solvents), the absence of SSNs for half the cohort (which likely led to some underascertainment of deaths), and the wide range of microwave frequencies associated with radar work. Overall, however, radar exposure had little effect on mortality among US Navy veterans.

There have been a number of geographical correlation studies conducted on cancer risk and proximity to radio or television transmission towers. There have been no consistent findings of increased cancer risk and all studies exhibit problems with exposure assessment (Schüz and Mann 2000; Blettner et al. 2000) and geographically-related confounding (Elwood 1999; Rothman 2000).

Brief Overview of Experimental Studies

It is generally accepted that RF signals from cellular telephones do not possess enough energy to break chemical bonds or damage DNA (FCC 1999; NRPB 2000), and some have argued on physical grounds alone that the extremely low intensities and associated low energy from these non-ionizing radiations are not capable of causing cancer, either by initiation or promotion or progression (Moulder et al. 1999; Park 2001). Scientific interest was raised when Lai and Singh (1995) reported increased numbers of DNA breaks in rat brain cells after two hour exposures to RF radiation of 2.45 GHz (SAR 0.5-2.0 W/kg). Subsequent studies, however, failed to replicate these findings (Malyapa et al. 1998). Similarly, it was reported that micronuclei were inducible in human lymphocytes *in vitro* by relatively high power density microwave radiation of 2.45 GHz and 7.7 GHz (Zotti-Martelli et al. 2000). Subsequent studies at cellular telephone frequencies did not replicate these findings and found no evidence for induction of chromosome aberrations or micronuclei in human blood lymphocytes exposed *in vitro* for 24 h to 835.62 MHz or 847.74 MHz RF radiation at SARs of 4.9 or 5.5 W/kg (Vijayalaxmi et al. 2001a, 2001b). A recent study reported that micronuclei were induced in human lymphocytes *in vitro* at an average SAR of at least 5.0 W/kg at 837 MHz and1909.8 MHz (Tice et al. 2002). However, these findings were not consistent with several previous ones (Vijayalaxmi et al. 2001a, 2001b) nor were they replicated in a more recent study of C3H 10T (½) cells exposed to RF waves (835.62 MHz or 847.74 MHz) at SARs of 3.2 to 5.1 W/kg (Bisht et al. 2002). It was postulated that the positive findings might be related to thermal effects resulting from hot spots due to significant inhomogeneities in the SAR distributions (Bisht et al. 2002). RF signals in the frequency range of relevance to mobile phones have been judged not to be directly mutagenic and adverse effects from such exposures are predominantly the result of thermal effects caused by high power intensities (Brusick et al. 1998).

One provocative experimental study found an excess of lymphoma in mice genetically predisposed to develop lymphoma that were exposed one hour per day for eighteen months to pulsed 900 MHz RF radiation (Repacholi et al. 1997). The relevance of the findings for human health has been questioned as well as the possibility that an unusually low lymphoma rate among control animals contributed to the reported excess in the exposed animals. Nonetheless, this was the only experimental evidence suggesting a carcinogenic effect from RF exposures and replication of the finding was needed. It took five years for such a study to be completed (Utteridge et al. 2002). The authors of the new study noted that the Repacholi et al. (1999) study was conceived as a pilot study and had shortcomings (such as variable SARs and the potential for thermal hot spots to arise) that they were able to overcome under more stringent and controlled conditions. The Utteridge et al. (2002) study used the same strain of genetically modified mice as Repacholi et al. (1997) but found that long-term exposure of these lymphoma-prone animals to 898.4 MHz at SARs of 0.25, 1.0, 2.0 or 4.0 W/kg had no significant effects compared with sham-irradiated mice. The SARs in the Repacholi et al. (1997) study averaged only 0.13-1.4 W/kg, and thus were lower than the highest two energy levels used in the more recent experiment (Utteridge et al. 2002). Thus it can be concluded that the Repacholi et al. (1997) study has been refuted, which is of importance because this was the only experimental evidence suggesting a carcinogenic effect from RF exposure in the animal literature.

The ability for RF signals to act as a tumor promoter has subsequently been evaluated in several other experimental designs involving a wide range of cellular phone frequencies. Neoplastic transformation in C3H 10T (½) cells induced by 4.5 Gy of x-rays was not enhanced by RF exposures to 835.62 MHz or 847.74 MHz (SAR=0.6 W/kg) (Roti Roti et al. 2001). Animal experiments found no evidence for cancer promotion by RF signals emitted from mobile phones for brain cancers induced by nitrosourea (Adey et al. 1999, 2000; Zook and Simmens 2001), brain tumor due to implanted gliosarcoma cells (Higashikubo et al. 1999), breast cancer induced by DMBA (Bartsch et al. 2002), or any tumor induced by benzo(a)pyrene (Chagnaud et al. 1999) or by X-rays (Heikkinen et al. 2001). Several studies lasted two years and exposed ex-

perimental animals to mobile telephone signals for 4 to 6 hours a day, 5 days a week with resulting SAR in the brain of 1.0-1.6 W/kg (Adey et al. 1999, 2000; Zook and Simmens 2001). It is also informative to contrast the laboratory evidence for carcinogenesis between ionizing and non-ionizing radiations. There is incontrovertible evidence from animal and cell studies that ionizing radiation causes cancer, damages DNA, and transforms cells (UNSCEAR 2000; IARC 2000, 2001). In contrast, for non-ionizing forms of radiation the overwhelming evidence is against a carcinogenic potential with only occasional and unreplicated positive reports found in the literature.

Ongoing Research

The Interphone Project, coordinated by the International Agency for Research on Cancer (IARC), involves 13 population-based incidence case-control studies in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the United Kingdom (Cardis and Kilkenny 1999; Blettner et al. 2000). A common protocol, including comprehensive exposure measurements and assessment, is being used to evaluate the carcinogenic potential of cellular telephones to cause tumors arising in the tissues most exposed to RF from the phones, specifically gliomas, meningiomas, acoustic neurinomas and parotid gland tumors. Additional studies in the U.K. following the Stewart Report on Mobile Phones and Heath (NRPB 2000) have recently been initiated (News 2002). Because these are all case-control in design, it will be particularly important that the problems of selection and information bias and confounding be carefully addressed (Wacholder et al. 1992a, 1992b; Wacholder 1995). Attention to exposure assessment is an important component of these studies but nonetheless will be problematic if reliance is predominantly on interview responses. The emphasis is on possible effects related to phone use 5 or more years prior to tumor diagnosis for which information on number of calls and duration of calls will be difficult to recall accurately. Validation studies are planned to contrast self-reported phone usage with subscriber billing records when available. Because each of these 13 studies will be published separately before a pooled analysis is performed, care must be taken in evaluation of individual study findings. The pooling of studies of nuclear industry workers with low-dose exposure to ionizing radiation, for example, smoothed out the inconsistencies and apparent statistical aberrations that arose from smaller previously published individual studies (Cardis et al. 1995).

It is unfortunate that apparently few cohort investigations are being conducted or planned. Such studies are less susceptible to the biases that can influence case-control studies and they can evaluate a large array of disease outcomes and not just those pre-specified in a case-control design. The Danish cancer incidence study of cellular telephone subscribers ended follow-up in 1996 (Johansen et al. 2001), the US mortality study ended follow-up in 1994 (Rothman et al. 1996a), and the US mortality study of Motorola RF-exposed workers ended follow-up in 1996 (Morgan et al. 2000). Consideration should be given to extending follow-up of these cohorts. Conceivably the subscriber lists used in the Finnish case-control study (Auvinen et al. 2002) could form the basis of a cellular telephone user cohort study. These cohorts could also provide an ongoing research platform to evaluate new hypotheses that may develop in the future, a research flexibility not shared by case-control studies.

Exposure assessment is a generic problem for this field of inquiry because of the absence of any plausible biological mechanism for a carcinogenic effect. The relevant "dosimetric quantity" to measure is thus unknown. It is assumed that the SAR, i.e., the energy absorbed per second by 1 kg in target tissue, is relevant, but power absorption in body tissues may not be estimated accurately based on phone usage measures such as minutes per month, years of use and type of phone. Actual SARs vary by distance to the cellular base station, physical obstacles interfering with connections (e.g., buildings), type of phone (analogue and older phones are usually of higher power), position of a cellular phone antenna and perhaps even wearing wire-rimmed glasses (Rothman et al. 1996b; Frumkin et al. 2001; Anderson and Joyner 1995). In fact, the amount of power sent from a base station to a particular cellular phone can vary even during a single telephone call. Thus it should be realized that only surrogate measures of exposure are being estimated and reported, and not actual tissue absorption. A useful analogy might be with studies of indoor radon, where actual radiation dose to lung is not measured, but only the concentration of radon in a home. Such inherent exposure misclassification may cloud the results, even for any future pooled analysis.

The problem of multiple comparisons and multiple subgroup analyses should not be underestimated. When there are 15 to 20 epidemiologic studies being conducted on two types of phones

(analogue and digital), at least seven classifications of tumors (brain malignant, brain non-malignant, acoustic neuroma, meningioma, leukemia, non-CLL, salivary gland), two lateralities (side of head tumor developed and side of head phone normally used), two latencies (recent usage, more distant usage), two genders, and at least three age categories (young, middle aged, elderly), there will be a number of significant findings arising by chance alone. It will be the consistency of findings across studies that will be most important in identifying any patterns possibly related to health risks.

Summary

Since 1996, there has been a flurry of scientific activity to evaluate the possibility that cellular telephone use may cause brain tumors, reflecting the rapid increase in the use of these phones throughout the world. Results from analytic investigations examining the association between cellular phone use and brain tumor risk have been published: four in the United States, two in Sweden, and one each in Denmark and Finland. The designs ranged from cohort (two), population-based incidence case-control (one), hospital-based incidence case-control (three), and population-based prevalence case-control (two). No significant associations overall were seen between all brain tumors combined and cellular telephone use with estimates of relative risk ranging from 0.9 to 1.3. Subgroup analyses of different types of phones (analogue, digital), tumor histologies (gliomas, meningiomas, acoustic neuromas), durations of use, and laterality (whether the tumor developed on the same side of the head normally used during telephone conversations) showed no consistent patterns of increased risk.

Overall, the epidemiologic and laboratory studies to date have ruled out with a reasonable degree of certainty that cellular telephones cause cancer, at least for durations of use up to 5 years. Cellular phones have only recently come into common use, so long-term effects are not well evaluated, but no well-founded clues to adverse effects have yet arisen. It is very difficult for epidemiologic studies to rule out the possible existence of a small risk in certain subsets of the populations, but are such risks biologically plausible? At this time the answer appears to be no. RF signals from cellular telephones are not genotoxic and cannot directly damage DNA, and are thus unlikely to be initiators; hence the risk of cancer from a thermal or non-thermal mechanism would be one that, if anything, promotes tumor growth. However, there is no convincing evidence from animal experiments or epidemiologic research that RF signals can promote tumor growth. If RF exposure is assumed to act by promoting the growth of an underlying lesion, then the large numbers of recent cellular phone users who have been studied are likely to have been sufficient to detect such an effect, but none has been found.

There are no incontrovertible rules for determining whether a particular exposure is carcinogenic in man (Adami et al. 2002), but the practical, common sense criteria of Sir Austin Bradford Hill are often invoked, the most important being consistency across epidemiologic studies, evidence of a dose response, strength of the association, and biological plausibility. To date evidence for cellular phones come up wanting: the methodologically sound epidemiologic studies, both of cellular phone use and occupational RF exposures, are consistent in finding no evidence for excess brain tumors; there has not been a single reported dose-response relation based on any measure of phone use; the strength of the association, if it exists, is very weak and most studies rule out relative risks greater than 1.2 to 1.3; and there is no known biological mechanism that supports a causal relation and no evidence of adverse effects in laboratory animals. A series of papers by one group in Sweden (Hardell et al. 1999, 2000, 2001, 2002) have reported associations between analogue phone use and brain tumors but the studies have serious methodological weaknesses with evidence of selection, response, and interviewer bias. Their results have found no support in the research of other investigators.

The Center for Devices and Radiological Health of the US Food and Drug Administration concluded that "the available scientific evidence does not demonstrate any adverse health effects associated with the use of mobile phones" (FDA 1999, Frumkin et al. 2001). Similar conclusions are reached by other authoritative committees and agencies reviewing the possible carcinogenicity of cellular phone use and RF signals, such as the UK National Radiologic Protection Board Advisory Group on Non-ionizing Radiation (NRPB 1999, 2000), the US Federal Communications Commission (FCC 1999), the US Government Accounting Office (GAO 2001), and the Health Council of the Netherlands (2002).

Nonetheless, this new technology is being widely used throughout the world with new users being added at a rate of over one million per month. It is prudent to conduct studies to evaluate potential impact on human health. Clearly there is an immediate impact from increased car accidents associated with the distractions of using a mobile phone while driving (Redelmeier and Tibshirani 1997). Presently, however, there is no evidence that cellular telephones pose a cancer risk and ongoing studies should provide further data on any possible carcinogenic effects from long-term usage of cellular phones.

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SSI Rapport

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SSI är ansvarig myndighet för det av riksdagen beslutade miljömålet *Säker strålmiljö*.

SSI sätter gränser för stråldoser till allmänheten och för dem som arbetar med strålning, utfärdar föreskrifter och kontrollerar att de efterlevs. Myndigheten inspekterar, informerar, utbildar och ger råd för att öka kunskaperna om strålning. SSI bedriver också egen forskning och stöder forskning vid universitet och högskolor.

SSI håller beredskap dygnet runt mot olyckor med strålning. En tidig varning om olyckor fås genom svenska och utländska mätstationer och genom internationella varnings- och informationssystem.

SSI medverkar i det internationella strålskyddssamarbetet och bidrar därigenom till förbättringar av strålskyddet i främst Baltikum och Ryssland.

Myndigheten har idag ca 110 anställda och är beläget i Stockholm.

THE SWEDISH RADIATION PROTECTION AUTHORITY (SSI) is the government regulatory authority for radiation protection. Its task is to secure good radiation protection for people and the environment both today and in the future.

The Swedish parliament has appointed SSI to be in charge of the implementation of its environmental quality objective *Säker strålmiljö* ("A Safe Radiation Environment").

SSI sets radiation dose limits for the public and for workers exposed to radiation and regulates many other matters dealing with radiation. Compliance with the regulations is ensured through inspections.

SSI also provides information, education, and advice, carries out its own research and administers external research projects.

SSI maintains an around-the-clock preparedness for radiation accidents. Early warning is provided by Swedish and foreign monitoring stations and by international alarm and information systems.

The Authority collaborates with many national and international radiation protection endeavours. It actively supports the on-going improvements of radiation protection in Estonia, Latvia, Lithuania, and Russia.

SSI has about 110 employees and is located in Stockholm.

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