Downloaded from oem.bmj.com on 11 April 2007

Long-term use of cellular phones and brain tumours - increased risk associated with use for > 10 years

Lennart O Hardell, Michael Carlberg, Fredrik Söderqvist, Kjell Hansson Mild and Lloyd L Morgan

Occup. Environ. Med. published online 4 Apr 2007;
doi:10.1136/oem.2006.029751

Updated information and services can be found at:
http://oem.bmj.com/cgi/content/abstract/oem.2006.029751v1

These include:

Rapid responses You can respond to this article at:
http://oem.bmj.com/cgi/eletter-submit/oem.2006.029751v1

Email alerting service Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

Online First contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

To order reprints of this article go to:
http://www.bmjjournals.com/cgi/reprintform

To subscribe to *Occupational and Environmental Medicine* go to:
http://www.bmjjournals.com/subscriptions/

Downloaded from oem.bmj.com on 11 April 2007
OEM Online First, published on April 4, 2007 as 10.1136/oem.2006.029751

Long-term use of cellular phones and brain tumours - increased risk associated with use for ≥ 10 years

Lennart Hardell, MD, PhD, Professor
Department of Oncology, University Hospital, SE-701 85 Örebro and Department of Natural Sciences, Örebro University, SE-701 82 Örebro, Sweden

Michael Carlberg, MSc
Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden

Fredrik Söderqvist, MSc
Department of Oncology, University Hospital and Institute of Clinical Medicine, Örebro University, SE-701 85 Örebro, Sweden

Kjell Hansson Mild, PhD, Professor
National Institute for Working Life, SE-907 13 Umeå and Department of Natural Sciences, Örebro University, SE-701 82 Örebro, Sweden

L. Lloyd Morgan, BSc
2022 Francisco Street, Berkeley, CA 94709, USA

Correspondence to:
Dr L Hardell, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden
lennart.hardell@orebroll.se

Running title: Mobile phones, brain tumours, latency

Copyright Article author (or their employer) 2007. Produced by BMJ Publishing Group Ltd under licence.

Downloaded from oem.bmj.com on 11 April 2007

Abstract

Aim: To evaluate brain tumour risk among long-term users of cellular telephones.

Methods: Two cohort studies and 16 case-control studies were identified on this topic. Data were scrutinized for use of mobile phone for ≥ 10 years and ipsilateral exposure if presented.

Results: The cohort study was of limited value due to methodological shortcomings in the study. Of the 16 case-control studies, 11 gave results for ≥ 10 years use or latency period. Most of these results were based on low numbers. An association with acoustic neuroma was found in four studies in the group with at least 10 years use of a mobile phone. No risk was found in one study, but the tumour size was significantly larger among users. Six studies gave results for malignant brain tumours in that latency group. All gave increased OR especially for ipsilateral exposure. In a meta-analysis ipsilateral cell phone use gave for acoustic neuroma OR = 2.4, 95 % CI = 1.1-5.3 and for glioma OR = 2.0, 95 % CI = 1.2-3.4 using a latency period of 10 years or more.

Conclusions: Results from present studies on use of mobile phones for ≥ 10 years give a consistent pattern of an increased risk for acoustic neuroma and glioma. The risk is highest for ipsilateral exposure.

Key words: mobile phones, acoustic neuroma, glioma, ipsilateral exposure

Downloaded from oem.bmj.com on 11 April 2007

Main message:
Results in case-control studies on brain tumours and use of mobile phones for ≥ 10 years gave a consistent pattern of an increased risk for acoustic neuroma and glioma. Ipsilateral exposure (same side as the tumour occurred) yielded highest risk.

Policy implications:
These results indicate that the precautionary principle should be applied for the use of mobile phones. More research is necessary for risk assessment based on higher number of long-term users.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Occupational and Environmental Medicine editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://oem.bmjjournals.com/misc/ifora/licenceform.shtml).

Downloaded from oem.bmj.com on 11 April 2007

Introduction

During the most recent decades there has been a rapid worldwide development of wireless technology and along with that an increasing use of wireless telephone communication. This has raised concern of health risks, primarily an increased risk for brain tumours, since the brain is due to the vicinity to the radiation antenna absorbing a comparatively large amount of electromagnetic energy. An increased risk for brain tumours would be an indication of other potential health effects, but it would also imply that the current guidelines for microwave exposure during phone calls are inappropriate. The initial studies on brain tumour risk had too short latency periods to give a meaningful interpretation of long-term risk. However, during recent years studies have been published that enable evaluation of $\geq$ 10-year latency period risk, although still mostly based on low numbers. A 10-year latency period seems to be a reasonable minimum period to indicate long-term carcinogenic risks from exposure to radio frequency (RF) fields during use of cellular or cordless phones.

In the following we present results from cohort and case-control studies published so far on this topic. In Table 1 we give 10-year latency period results and if presented ipsilateral use of the cellular phones, i.e. same side of tumour and microwave exposure. This gives a "worst-case scenario" that may predict increasing incidence of brain tumours in the future, since the use of cellular phones is globally wide-spread with high prevalence among almost all age groups in the population. If the study did not have users with a 10-year latency period only the overall results are presented.

The Nordic countries were among the first to introduce this new technology, and may serve as a test market for health problems foregoing other countries. This technology is briefly discussed in the following using the Swedish experience as a model.

The analogue system has been used since early 1980's using 450 or 900 MegaHertz (MHz) fields. The digital system has been increasingly used since the beginning of the 1990's and dominates the market currently. This system uses dual band, 900 and 1,800 MHz, for communication. During recent years the third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900 MHz RF fields has been introduced worldwide.

Desktop cordless phones (DECT) also use wireless technology. At the start in late 1980's analogue 800-900 MHz RF fields were used but since early 1990's digital 1,900 MHz system is used. Our research group has in all of our tumour investigations also assessed use of DECT phones, whereas no data are presented in publications from other research groups.

Materials and Methods

We have scrutinized the literature for published studies using Pub Med database (**www.ncbi.nlm.nih.gov**) and personal knowledge of this area since we are involved in current research in this field. We used mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. If a study had several publications on certain aspects we used the latest publication giving the most relevant data. In total we identified 18 studies for this presentation. Two publications were cohort studies (one study analysed twice with longer follow-up) and 16 were case-control studies. No mortality studies were included. Three studies came from USA, four from Denmark, one from

Downloaded from oem.bmj.com on 11 April 2007

Finland, five from Sweden, one from UK, one from Germany, one from Japan and two from study groups partly overlapping previously mentioned studies.

Statistical Methods

For statistical analyzes Stata 8.2 was used (Stata/SE 8.2 for Windows; StataCorp, College Station TX). Random effects model was used for all meta-analysis, based on test for heterogeneity.

Results

Tables 1-3 give reference to the studies with main author, years for subject inclusion, type of study (case-control or cohort), age of the subjects, tumour type, number of cases, odds ratio (OR), 95 % confidence interval (CI) and comments. The number of included subjects and response rate (in parenthesis) are given in the following text.

The first study by Hardell et al[1,2] included cases and controls from the Uppsala-Örebro region during 1994-96 and Stockholm region during 1995-96 in Sweden. Only living cases were included. Two controls were selected to each case from the Population Registry. The questionnaire was answered by 217 (93 %) cases and 439 (94 %) controls. A high response rate was obtained since the study was hospital based (relation study subjects and physicians), two reminders were sent of the postal questionnaires and finally if possible a telephone interview was conducted. Furthermore, Sweden has good coverage of current address and phone number in the Population Registry so it is easy to trace participants. Overall no association between mobile phone use and brain tumours was found. However, somewhat increased risk was seen for ipsilateral phone use, especially for tumours in the temporal, occipital or temporoparietal lobe yielding OR = 2.4, 95 % CI = 0.97-6.1.[2]

The study by Muscat et al[3] included patients with malignant brain tumours from five different hospitals in USA. Controls were hospital patients and except for two hospitals not cancer patients. Data from 469 (82 %) cases and 422 (90 %) controls were available. Mean duration of use of cellular telephones was 2.8 years for the cases and 2.7 years for the controls. Only 17 cases (4 %) and 22 controls (5 %) had used a mobile phone for 4 years or longer. Overall no association was found, OR for handheld cellular phones was 0.9, 95 % CI = 0.6-1.2. For neuroepithelioma OR = 2.1, 95 % CI = 0.9-4.7, was reported. Of 41 evaluable tumours, 26 occurred at the side of the head mostly used during calls and 15 on the contralateral side (p=0.06). The study is inconclusive since no data were available on long-term users ($\geq$ 10 years latency period).

Johansen et al[4] performed in Denmark a population based cohort study of mobile phone users during 1982 to 1995. In total over 700,000 users were included. Subjects with company paid phones, about 200,000, were excluded. Of digital (GSM) subscribers only nine cases had used the phone for $\geq$ 3 years duration. This produced slightly increased standardised incidence ratio (SIR) of 1.2, 95 % CI = 0.6-2.3. Digital phone users with previous use of an analogue phone yielded SIR = 1.3, 95 % CI = 0.8-2.1. No subjects with 10-year use were reported.

Also the study by Inskip et al[5] from USA had few long-term users of mobile phones, only 11 cases with glioma, 6 with meningioma and 5 with acoustic neuroma with $\geq$ 5 years regular use. No subjects had $\geq$ 10 years use. The study enrolled 782 (92 %) hospital cases with 489

Downloaded from oem.bmj.com on 11 April 2007

malignant brain tumours, 197 with meningioma and 96 with acoustic neuroma. Most of them (80 %) were interviewed within 3 weeks after diagnosis. In total 799 (86 %) hospital-based controls were used. Regular use of mobile phones gave for glioma OR = 0.8, 95 % CI = 0.6-1.2, for meningioma OR = 0.8, 95 % CI = 0.4-1.3, and for acoustic neuroma OR = 1.0, 95 % CI = 0.5-1.9. Duration of use $\geq$ 5.0 years did not increase the risk for glioma and meningioma whereas for acoustic neuroma OR increased to 1.9, 95 % CI = 0.6-5.9. Regarding different types of glioma OR = 1.8, 95 % CI = 0.7-5.1 was found for anaplastic astrocytoma.

In another study by Muscat et al[6] results were presented from a hospital based case-control study on acoustic neuroma including 90 (100 %) patients and 86 (100 %) control subjects with non-malignant diseases. Cases used a mobile phone on average for 4.1 years and controls for only 2.2 years. Use of cell phone during 1-2 years produced OR = 0.5, 95 % CI = 0.2-1.3 (n=7 cases), increasing to OR = 1.7, 95 % CI = 0.5-5.1 (n=11 cases), in the group with 3-6 years use.

A register based case-control study on brain and salivary gland tumours was performed in Finland by Auvinen et al.[7] All cases aged 20-69 years diagnosed in 1996 were included, in total 398 brain tumour cases and 34 salivary gland tumour cases. The duration of use was very short, for analogue users 2-3 years and for digital cell phone users less than one year. No association was found for salivary gland tumours. An increased risk for glioma, OR = 2.1, 95 % CI = 1.3-3.4, was found for analogue phones, whereas for digital phones OR was 1.0, 95 % CI = 0.5-2.0. Duration of use was used as a continuous variable and yielded for analogue phones and glioma OR = 1.2, 95 % CI = 1.1-1.5 per year of use.

From the Karolinska Institute in Sweden results on a case-control study of acoustic neuroma were reported by Lönn et al.[8] Cases were identified in collaboration with hospitals and also checked with the cancer registry. Controls were randomly selected from the population registry. Exposure data were collected from 148 (93 %) cases and 604 (72 %) controls. Use of digital phones with time $\geq$ 5 years since first use gave OR = 1.2, 95 % CI = 0.7-2.1. No subjects were reported with use of a digital phone $\geq$ 10 years. Use of an analogue phone gave for duration of 5-9 years OR = 1.3, 95 % CI = 0.6-2.9, and for $\geq$ 10 years OR = 1.8, 95 % CI = 0.8-4.3. Ipsilateral use of a mobile phone $\geq$ 10 years time since first use gave OR = 3.9, 95 % CI = 1.6-9.5, whereas contralateral use gave OR = 0.8, 95 % CI = 0.2-2.9.

In Denmark a case-control study on acoustic neuroma was performed by Christensen et al.[9] It included 106 (82 %) hospital based incident cases and 212 (64 %) population based controls. Overall OR = 0.9, 95 % CI = 0.5-1.6 was obtained for regular use. Time since first regular use $\geq$ 10 years yielded OR = 0.2, 95 % CI = 0.04-1.1 based on two cases. Neither did shorter time intervals increase the risk. Significantly larger tumours were found among cellular phone users, 1.66 cm^3 compared with 1.39 cm^3 among non-users, $p = 0.03$.

The group from Karolinska Institute in Sweden, Lönn et al[10], also made a study on glioma and meningioma. Cases were recruited from hospitals and controls from the population registry. Data were obtained for 371 (74 %) glioma and 273 (85 %) meningioma cases. The control group consisted of 674 (71 %) subjects. Regular phone use gave for glioma OR = 0.8, 95 % CI = 0.6-1.0, and for meningioma OR = 0.7, 95 % CI = 0.5-0.9. Time since first regular use of $\geq$ 10 years gave for ipsilateral glioma OR = 1.6, 95 % CI = 0.8-3.4, and for contralateral glioma OR = 0.7, 95 % CI = 0.3-1.5. The corresponding results were for ipsilateral meningioma OR = 1.3, 95 % CI = 0.5-3.9, and for contralateral meningioma OR = 0.5, 95 % CI = 0.1-1.7.

Downloaded from oem.bmj.com on 11 April 2007

Schoemaker et al[11] presented results for acoustic neuroma as part of the Interphone study performed in 6 different regions in the Nordic countries and UK. The Swedish and Danish parts have been reported previously.[8,9] Cases were obtained from hospitals and if possible also from cancer registries. In the Nordic countries controls were selected from population registries and in UK from general practioners' practice lists. In total 678 (82 %) cases and 3,553 (42 %) controls were interviewed. Regular use of a mobile phone yielded OR = 0.9, 95 % CI = 0.7-1.1. Lifetime use for $\geq$ 10 years gave for ipsilateral acoustic neuroma OR = 1.8, 95 % CI = 1.1-3.1, and for contralateral tumour OR = 0.9, 95 % CI = 0.5-1.8.

The Danish part of the Interphone study on brain tumours included 252 (71 %) persons with glioma, 175 (74 %) with meningioma and 822 (64 %) controls.[12] Cases were hospital based and controls were selected from the Danish Central Population Register. Statistical analyses gave for meningioma OR = 0.8, 95 % CI = 0.5-1.3, low-grade glioma OR = 1.1, 95 % CI = 0.6-2.0, and for high-grade glioma OR = 0.6, 95 % CI = 0.4-0.9. Use for $\geq$ 10 years yielded for meningioma OR = 1.0, 95 % CI = 0.3-3.2, low-grade glioma OR = 1.6, 95 % CI = 0.4-6.1 and for high-grade glioma OR = 0.5, 95 % CI = 0.2-1.3. Regarding high-grade glioma 17 ORs were presented and all showed OR < 1.0.

Hepworth et al[13] presented results from England as part of the Interphone study on glioma. It included 966 (51 %) cases and 1,716 (45 %) controls. Cases were ascertained from multiple sources including hospital departments and cancer registries. The controls were randomly selected from general practioners' lists. The overall OR for regular phone use was 0.9, 95 % CI = 0.8-1.1. Ipsilateral phone use yielded OR = 1.2, 95 % CI = 1.02-1.5, and contralateral OR = 0.8, 95 % CI = 0.6-0.9. Ipsilateral use for $\geq$ 10 years produced OR = 1.6, 95 % CI = 0.9-2.8, and contralateral OR = 0.8, 95 % CI = 0.4-1.4.

The Interphone Study Group with Schüz et al[14] from Germany presented results for glioma and meningioma. Incident cases from four different neurosurgery clinics were included. The results were based on interviews of 366 (80%) glioma cases and 381 (88 %) meningioma cases. Controls were randomly selected from population registries and in total 1,494 (61 %) were included in the analyses. Overall no association was found between use of cellular telephones and brain tumour. For glioma OR = 1.0, 95 % CI = 0.7-1.3, and for meningioma OR = 0.8, 95 % CI = 0.6-1.1, were obtained. However, for users of cellular telephones $\geq$ 10 years OR = 2.2, 95 % CI = 0.9-5.1, was calculated for glioma and OR = 1.1, 95 % CI = 0.4-3.4 for meningioma. For women with "ever" use of a cell phone OR = 2.0, 95 % CI = 1.1-3.5, was calculated for high-grade glioma.

Hardell et al[15] reported in a pooled analysis results for benign brain tumours from two case-control studies. Cases were reported from Cancer Registries and controls were population based. The questionnaire was answered by 1,254 (88 %) cases and 2,162 (89 %) controls. Also use of cordless desktop phones was assessed. Use of cellular phones gave for acoustic neuroma OR = 1.7, 95 % CI 1.2-2.3, and cordless phones OR = 1.5, 95 % CI = 1.04-2.0. Using > 10 year latency period for cellular telephones gave OR = 2.9, 95 % CI = 1.6-5.5, and cordless phones OR = 1.0, 95 % CI 0.3-2.9. Results were also presented for analogue and digital cellular telephones separately. In a multivariate unconditional regression analysis using > 10 year latency period only analogue phones were significant risk factors, OR = 2.2, 95 % CI = 1.3-3.8. Regarding meningioma cellular phones gave OR = 1.1, 95 % CI = 0.9-1.3, and cordless OR = 1.1, 95 % CI = 0.9-1.4. Using > 10 year latency period ORs increased, for cellular telephones OR = 1.5, 95 % CI = 0.98-2.4, and for cordless phones OR = 1.6, 95 % CI = 0.9-2.8. Ipsilateral

Downloaded from oem.bmj.com on 11 April 2007

exposure gave for cellular phones OR = 2.0, 95 CI % = 0.98-2.9, and for cordless phones OR = 3.2, 95 % CI = 1.2–8.4, in the > 10 year latency group. In the multivariate analysis neither cellular nor cordless phones were significant risk factors for meningioma. Also for meningioma results were reported for both analogue and digital cell phones.

In Hardell et al[16] results were presented for malignant brain tumours. Answers were obtained from 905 (90%) cases and the same control group as for benign tumours was used, 2,162 (89 %) subjects. Overall for low-grade astrocytoma cellular phones gave OR= 1.4, 95 % CI = 0.9-2.3 and cordless phones OR = 1.4, 95 % CI = 0.9-3.4. The corresponding results for high-grade astrocytoma were OR = 1.4, 95 % CI = 1.1-1.8, and OR = 1.5, 95 % CI = 1.1-1.9, respectively. Using > 10 year latency period gave for low-grade astrocytoma and use of cellular phones OR = 1.5, 95 % CI = 0.6-3.8 (ipsilateral OR = 1.2, 95 % CI = 0.3-5.8), and for cordless phones OR = 1.6, 95 % CI = 0.5-4.6 (ipsilateral OR = 3.2, 95 % CI = 0.6-16). For high-grade astrocytoma in the same latency period cellular phones gave OR = 3.1, 95 % CI = 2.0-4.6 (ipsilateral OR = 5.4, 95 % CI = 3.0-9.6), and cordless phones OR = 2.2, 95 % CI = 1.3-3.9 (ipsilateral OR = 4.7, 95 % CI = 1.8-13). In the multivariate analysis of high-grade astrocytoma cellular phones gave OR = 2.2, 95 % CI = 1.6-3.1, and cordless phones OR = 1.3, 95 % CI = 0.8-2.3, in the > 10 years latency period. Results were also presented for analogue and digital phones separately.

The Danish cohort study on mobile phone subscribers[4] was updated with follow-up through 2002 for cancer incidence.[17] As previously, more than 200,000 (32 %) company subscribers were excluded and apparently instead included in the population based comparison group. The expected numbers were based on the general population. However, a large part of the population does use mobile phones and/or cordless phones, the latter use not assessed at all in the study. There was no truly unexposed group for comparison. Of the subscribers 85 % were men and 15 % were women, thus a very skewed sex distribution. There seemed to be a “healthy worker” effect in the study since SIR was significantly decreased to 0.95, 95 % CI = 0.9-0.97 for all cancers. In the group with $\geq$ 10 years since first subscription significantly decreased SIR of 0.7, 95 % CI = 0.4-0.95 was found for brain and nervous system tumours indicating methodological problems in the study. Temporal glioma yielded SIR = 1.2, 95 % CI = 0.9-1.6. This finding was based on 54 persons. No latency data were given or laterality of phone use in relation to tumour localisation in the brain.

As part of the Interphone study a case-control study was performed on acoustic neuroma in Tokyo.[18] The cases were recruited from hospitals including 23 wards and controls by using random digit dialling. Of 120 eligible cases 101 (84.2%) participated in the study. In total 647 controls were selected but only 339 (52.4 %) were interviewed. Regular mobile phone use yielded OR = 0.7, 95 % CI = 0.4-1.2. For length of more than 8 years OR = 0.8, 95 % CI = 0.2-2.7 was obtained. Somewhat increased risk was found in the 300-900 hours cumulative call time with OR = 1.4, 95 % CI = 0.5-3.5. The > 900 hours group gave OR = 0.7, 95 % CI = 0.3-1.8. No effect of laterality was seen, ipsilateral mobile phone use OR = 0.9, 95 % CI = 0.5-1.6, and contralateral use OR = 0.9, 95 % CI = 0.6-1.6.

A report on mobile phone use and risk of glioma in Denmark, and parts of Finland, Norway, Sweden and United Kingdom gave summary results for these Interphone studies.[19] Of these results had been published for Sweden,[10] Denmark[12] and UK.[13] Of 2,530 eligible cases 1,521 (60%) participated. Overall no increased risk was found for regular mobile phone use, OR = 0.8, 95 % CI = 0.7-0.9. However, cumulative hours of use gave OR = 1.006, 95 % CI = 1.002-1.010

Downloaded from oem.bmj.com on 11 April 2007

per 100 hours. For ≥ 10 years ipsilateral mobile phone use OR = 1.4, 95 % CI = 1.01-1.9, *p* trend = 0.04 was found. Contralateral use gave in the same group OR = 1.0, 95 % CI = 0.7-1.4.

Using a latency period of 10 years or more (for definitions se tables) we made a meta-analysis of the risk for acoustic neuroma, glioma and meningioma. For acoustic neuroma in the total group OR = 1.3, 95 % CI = 0.6-2.8 was obtained,[8,9,11,15] and for ipsilateral mobile phone use OR = 2.4, 95 % CI = 1.1-5.3 was calculated.[8,11,15] Regarding glioma OR = 1.2, 95 % CI = 0.8-1.9 was calculated in the whole group[10,12,13,14,16,19] increasing to OR = 2.0, 95 % CI = 1.2-3.4 for ipsilateral use.[10,13,16,19] The corresponding results for meningioma were OR = 1.3, 95 % CI = 0.9-1.8[10,12,14,15] and OR = 1.7, 95 % CI = 0.99-3.1[10,15] , respectively.

Discussion

This review included 18 studies, two cohort studies and 16 case-control studies. Some of the studies were parts of the Interphone investigation and two publications included results from different studies.[11,19] The conclusions on the risk for brain tumours associated with use of cellular phones have so far been based mostly on studies with too short latency period in carcinogenesis. Since we are now facing results from studies with long-term users, i.e. ≥ 10 years it is pertinent to compile the data in order to see if a pattern of an association with brain tumours is emerging. It should be noted that only the studies by the Hardell group[15,16] give results also for use of cordless phones. It is necessary to assess such use in case-control studies, which has been discussed in the publications by these authors. Thus, an association between cordless phones and brain tumours is not discussed further here.

Of the 16 case-control studies 11 gave results for ≥ 10 years use or latency period. Most of these results were based on low numbers as can be seen in tables. Brain tumours are a heterogenic group of tumours including both malignant and benign types. Thus it is reasonable to separate the results for malignant and benign tumours, as has been done in the various studies. The Danish cohort study[4] is not very informative due to limits in study design, analysis and follow-up and is not discussed further. The same methodological limitations are present in the up-dated version.[17]

Acoustic neuroma might be a “signal” tumour type for increased brain tumour risk from microwave exposure, since it is located in an anatomical area with high exposure during calls with cellular or cordless phones. In fact, an increasing incidence of acoustic neuroma has been noted in Sweden.[20] In Table 1 results are presented from 7 case-control studies on acoustic neuroma and use of cellular telephones. Three studies[5,6,18] did not have at least 10-year follow-up but two of them showed a somewhat increased risk for shorter latency periods. Three of the 4 studies with data on ≥ 10 years use showed a statistically significantly increased risk overall or for ipsilateral exposure to microwaves. In one study no association was found but the result was based on only 2 cases.[9] The tumours were significantly larger among mobile phone users. In the Hardell et al study[15] an increased risk was also found with shorter latency period. The mechanism for the increased risk for acoustic neuroma from microwave exposure is unknown. An effect might exist at different stages in tumour development. These results on acoustic neuroma are consistent with an association with use of cellular phones. However, a recent study from Tokyo could not confirm an association.[18] No case was reported with a latency period ≥ 10 years.

Downloaded from oem.bmj.com on 11 April 2007

Regarding meningioma results were given in five case-control studies.[5,10,12,14,15] No consistent pattern of an association was found, although ipsilateral exposure in the > 10 years latency group increased the risk in one of the studies.[15] For a definite conclusion longer follow-up studies are needed.

Results for glioma are given in 9 studies, see Table 2. One was register based[7] and showed an increased risk associated with analogue phone use. The risk of glioma increased significantly per year of use. Six studies gave results for use of cell phone for 10 years or more. For glioma increased OR was found that was more pronounced for ipsilateral use of the cell phone. This pattern of association was consistent in the different studies, except for the Danish study by Christensen et al.[12] In that study all 17 odds ratios for high-grade glioma were < 1.0 indicating systematic bias in assessment of exposure. The Interphone study[19] found a significantly decreased risk for glioma associated with mobile phone use, although the risk for ipsilateral use increased significantly with latency period and cumulative hours of use. As the authors discuss the preventive overall result indicates methodological problems in the study. It is concluded that using $\geq$ 10 years latency period gives a consistent pattern of an association between use of mobile phones and malignant brain tumours, especially high-grade glioma.

In spite of the heterogeneity[21] between the different studies we made a meta-analysis for use of mobile phones with a latency period of 10 years or more. We calculated OR for the whole group and for ipsilateral use of mobile phones. For both acoustic neuroma and glioma OR was somewhat increased in the whole group, but increased significantly for ipsilateral exposure. No significantly increased risk was found for meningioma, although highest OR was calculated for ipsilateral use. These results are certainly of biological relevance since the highest risk was found for tumours in the most exposed area of the brain using a latency period that is relevant in carcinogenesis. In another study meta-analysis was performed on mobile phone use yielding for contralateral tumours OR = 1.0, 95 % CI = 0.8-1.4 and for ipsilateral tumours OR = 1.3, 95 % CI = 0.99-1.9. No analysis was performed for > 10 year latency time.[21] Our findings stress the importance of longer follow-up to evaluate long-term health risks from mobile phone use.

The validity of short-term recall of mobile phone use was analysed in the Interphone study.[22] It was concluded that actual use was underestimated in light users and overestimated in heavy users. There was a substantial heterogeneity between countries and the inter-individual variation was larger increasing with level of use. The authors stated that this large random error might reduce the power of the Interphone study to detect an increased risk of brain tumours. In a following article from the same study group[23] it was concluded that random recall bias could lead to substantial underestimation in the risk of brain tumours associated with mobile phone use. According to the authors there was a selection bias in the Interphone study resulting in under selection of unexposed controls with decreasing risk at low to moderate exposure levels. It was concluded that the validation studies would play an important role in the interpretation of the Interphone studies. It should be noted that some studies had a low response rate, especially among controls. Participants tended to be of higher socioeconomic status and therefore more likely to have used a mobile phone for prolonged periods of time.

We conclude that results from present studies on use of mobile phones for $\geq$ 10 years give a consistent pattern of an increased risk for acoustic neuroma and glioma. The risk is highest for ipsilateral exposure. Longer follow-up is needed, however, since an increased risk also for other

Downloaded from oem.bmj.com on 11 April 2007

types of brain tumours cannot be ruled out. From these studies it is not clear at what stage microwaves act in carcinogenesis.

Acknowledgements
Supported by grants from Cancer- och Allergifonden and Örebro University Hospital Cancer Fund.

Downloaded from oem.bmj.com on 11 April 2007

References

1. **Hardell L,** Näsman Å, Påhlson A, *et al*. Use of cellular telephones and the risk for brain tumours: A case-control study. *Int J Oncol* 1999;**15:**113-6.
2. **Hardell L,** Hansson Mild K, Påhlson, *et al*. Ionizing radiation, cellular telephones and the risk for brain tumours. *Eur J Cancer Prev* 2001;**10:**523-9.
3. **Muscat JE**, Malkin MG, Thompson S, *et al*. Handheld cellular telephone use and risk of brain cancer. *JAMA* 2000;**284**:3001-7.
4. **Johansen C**, Boice JD Jr, McLaughlin JK, *et al*. Cellular telephones and cancer – a nationwide cohort study in Denmark. *J Natl Cancer Inst* 2001;**93**:203-7.
5. **Inskip PD**, Tarone RE, Hatch EE, *et al*. Cellular-telephone use and brain tumors. *New Engl J Med* 2001;**344**:79-86.
6. **Muscat JE**, Malkin MG, Shore RE, *et al*. Handheld cellular telephones and risk of acoustic neuroma *Neurology* 2002;**58**:1304-6
7. **Auvinen A**, Hietanen M, Luukonen R, *et al*. Brain tumors and salivary gland cancers among cellular telephone users. *Epidemiology* 2002;**13**:356-9.
8. **Lönn S**, Ahlbom A, Hall P, *et al*. Mobile phone use and the risk of acoustic neuroma. *Epidemiology* 2004;**15:** 653-9.
9. **Christensen HC**, Schüz J, Kosteljanetz M, *et al*. Cellular telephone use and risk of acoustic neuroma. *Am J Epidemiol* 2004;**159**:277-83.
10. **Lönn S**, Ahlbom A, Hall P, *et al*. Long-term mobile phone use and brain tumor risk. *Am J Epidemiol* 2005;**161**:526-35.
11. **Schoemaker MJ**, Swerdlow AJ, Ahlbom A, *et al*. Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer* 2005;**93(7):**842-8.
12. **Christensen HC**, Schüz J, Kosteljanetz M, *et al*. Cellular telephones and risk for brain tumors. A population-based, incident case-control study. *Neurology* 2005;**64**:1189-95.
13. **Hepworth SJ**, Schoemaker MJ, Muir KR, *et al*. Mobile phone use and risk of glioma in adults: case-control study. *BMJ*. 2006;**332(7546**):883-7.
14. **Schüz J**, Böhler E, Berg G, *et al*. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). *Am J Epidemiol* 2006;**163(6)**:512-20.
15. **Hardell L**, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997-2003. *Int J Onco*l 2006;**28**:509-18.
16. **Hardell L**, Hansson Mild K, Carlberg M. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. *Int Arch Occup Environ Health* 2006;**79:**630-9. DOI 10.107/s00420-0088-5.
17. **Schüz J,** Jacobsen R, Olsen JH, *et al*. Cellular telephone use and cancer risks: An update of a nationwide Danish cohort. *J Natl Cancer Inst* 2006;**98:**1-7.
18. **Takebayashi T,** Akiba S, Kikuchi Y, *et al*. Mobile phone use and acoustic neuroma risk in Japan. *Occup Environ Med* 2006;**63:**802-7.
19. **Lahkola A,** Auvinen A, Raitanen J, *et al*. Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 2007;**120(8):**1769-75.
20. **Hardell L,** Hansson Mild K, Sandström M. Vestibular schwannoma, tinnitus and mobile telephones. *Neuroepidemiology* 2003;**22**:124-9.
21. **Lahkola A,** Tokola K, Auvinen A. Meta-analysis of mobile phone use and intracranial tumors. *Scand J Work Environ Health* 2006;**32(3):**171-7.

Downloaded from oem.bmj.com on 11 April 2007

22. **Vrijheid M,** Cardis E, Armstrong BK, *et a*l. Validation of short term recall of mobile phone use for the Interphone study. *Occup Environ Med* 2006;**63:**237-43.
23. **Vrijheid M,** Deltour I, Krewski D, *et al*. . The effects of recall errors and selection bias in epidemiologic studies of mobile phone use and cancer risk. *J Expo Sci Environ Epidemiol* 2006;**16(4):**371-84.

Downloaded from oem.bmj.com on 11 April 2007

Table 1. Summary of eight studies on acoustic neuroma and use of wireless telephones

Study	Years Study Type	Age	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Inskip et al 2001 USA[5]	1994-1998 Case-control	≥ 18 years	5	OR 1.9 (0.6-5.9)	≥ 5 years of cell phone use
Muscat et al 2002 USA[6]	1997-1999 Case-control	≥ 18 years	11	OR 1.7 (0.5-5.1)	3-6 years of cell phone use
Lönn et al 2004 Sweden Interphone[8]	1999-2002 Case-control	20-69 years	14	OR 1.8 (0.8-4.3)	≥10 years since first "regular" cell phone use, result for either side of head
			12	OR **3.9** (1.6-9.5)	≥10 years since first "regular" cell phone use on same side of head as tumour
Christensen et al 2004 Denmark Interphone[9]	2000-2002 Case-control	20-69 years	45	OR 0.9 (0.5-1.6)	Regular use
			2	OR 0.2 (0.04-1.1)	≥10 years since first "regular" cell phone use. Use on same side of head as tumour correlation ***p*=0.02**. Significantly larger tumours among cellular phone users 1.66 cm^3 *versus* 1.39 cm^3, ***p*=0.03**.
Schoemaker et al 2005 Denmark, Finland, Sweden, Norway, Scotland, England, Interphone[11]	1999-2004 Case-control	18-69 years (variable)	360	OR 0.9 (0.7-1.1)	Regular use
			23	OR **1.8** (1.1-3.1)	≥ 10 lifetime years of cell phone use on same side of head as tumour
			31	OR 1.3 (0.8-2.0)	≥10 years since first cell phone use on same side of head as tumour
			12	OR 0.9 (0.5-1.8)	≥ 10 lifetime years of cell phone use on opposite side of head as tumour
			20	OR 1.0 (0.6-1.7)	≥10 years since first cell phone use on opposite side of head as tumour

Downloaded from oem.bmj.com on 11 April 2007

Study	Years Study Type	Age	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al 2006a Sweden[15]	1997-2003 Case-control	20-80 years	130	OR **1.7** (1.2-2.3)	> 1 year latency of cell phone use
			20	OR **2.9** (1.6-5.5)	> 10 years latency of cell phone use
			10	OR **3.5** (1.5-7.8)	> 10 years latency of ipsilateral cell phone use
			4	OR 1.0 (0.3-2.9)	> 10 years latency of cordless phone use
			3	OR 3.1 (0.8-12)	> 10 years latency of ipsilateral cordless phone use
Schüz et al 2006 Denmark[17]	1982-2002 Cohort	$\geq$ 18 years	32	SIR 0.7 (0.5-1.03)	No data on latency or laterality of tumour and use of mobile phone
Takebayashi et al 2006 Tokyo[18]	2000-2004 Case-control	30-69 years	51	OR 0.7 (0.4-1.2)	Regular use
			4	OR 0.8 (0.2-2.7)	Length of use > 8 years
			20	OR 0.9 (0.5-1.6)	Ipsilateral use

Downloaded from oem.bmj.com on 11 April 2007

Table 2: Summary of nine studies on glioma and use of wireless telephones

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Inskip et al 2001 USA[5]	1994-1998 Case-control	≥ 18 years	Glioma	11	OR 0.6 (0.3-1.4)	≥ 5 years of cell phone use
Auvinen et al 2002 Finland[7]	1996 Case-control, register based	20-69 years	Glioma	119	OR **1.5** (1.0-2.4)	Analogue and digital cell phone ”ever” use
				40	OR **2.1** (1.3-3.4)	Analogue cell phone ”ever” used
				11	OR **2.4** (1.2-5.1)	Analogue cell phone use 1-2 years
				11	OR **2.0** (1.0-4.1)	Analogue cell phone use, >2 years
Lönn et al 2005 Sweden Interphone[10]	2000-2002 Case-control	20-69 years	Glioma	214	OR 0.8 (0.6-1.0)	Regular use
				15	OR 1.6 (0.8-3.4)	≥10 years since first “regular” cell phone use on same side of head as tumour
				11	OR 0.7 (0.3-1.5)	≥10 years since first “regular” cell phone use on opposite side of head as tumour.
Christensen et al 2005 Denmark Interphone[12]	2000-2002 Case-control	20-69 years	Low-grade glioma	47	OR 1.1 (0.6-2.0)	Regular use
				6	OR 1.6 (0.4-6.1)	≥10 years since first “regular” use of cell phone
			High-grade glioma	59	OR 0.6 (0.4-0.9)	Regular use
				8	OR 0.5 (0.2-1.3)	≥10 years since first regular use of cell phone 17 odds ratios for high-grade glioma, all < 1.0, indicate systematic bias.

Downloaded from oem.bmj.com on 11 April 2007

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Hepworth et al 2006 UK Interphone[13]	2000-2004 Case-control	18-69 years	Glioma	508	OR 0.9 (0.8-1.1)	Regular use
				Not given	OR 1.6 (0.9-2.8)	≥10 years of cell phone use on same side of head as tumour.
				Not given	OR 0.8 (0.4-1.4)	>10 years of cell phone use on opposite side of head as tumour.
Schüz et al 2006 Germany Interphone[14]	2000-2003 Case-control	30-59 (2000-2001) 30-69 years (2001-2003)	Glioma	138	OR 1.0 (0.7-1.3)	Regular use
				12	OR 2.2 (0.9-5.1)	≥ 10 years since first "regular" use of cell phone
				30	OR **2.0** (1.1-3.5)	Female regular use of cell phone (glioma, high-grade)
Hardell et al 2006b Sweden[16]	1997-2003 Case-control	20-80 years	Glioma, high-grade	281	OR **1.4** (1.1-1.8)	> 1 year latency of cell phone use
				71	OR **3.1** (2.0-4.6)	> 10 years latency of cell phone use
				39	OR **5.4** (3.0-9.6)	> 10 years latency of ipsilateral cell phone use
				23	OR **2.2** (1.3-3.9)	> 10 years latency of cordless phone use
				10	OR **4.7** (1.8-13)	> 10 years latency of ipsilateral cordless phone use
			Glioma, low-grade	65	OR 1.4 (0.9-2.3)	> 1 year latency of cell phone use
				7	OR 1.5 (0.6-3.8)	> 10 years latency of cell phone use
				2	OR 1.2 (0.3-5.8)	> 10 years latency of ipsilateral cell phone use
				5	OR 1.6 (0.5-4.6)	> 10 years latency of cordless phone use
				3	OR 3.2 (0.6-16)	> 10 years latency of ipsilateral cordless phone use

Downloaded from oem.bmj.com on 11 April 2007

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Schüz et al 2006 Denmark[17]	1982-2002 Cohort	≥ 18 years	Glioma	257	SIR 1.0 (0.9-1.1)	No laterality of tumour and mobile phone given.
				54	SIR 1.2 (0.9-1.6)	Temporal lobe
Lahkola et al Denmark, Norway, Finland, Sweden, UK Interphone[19]	September 2000-February 2004 (differed between countries) Case-control	20-69 years (Nordic countries), 18-59 years (UK)	Glioma	867	OR 0.8 (0.7-0.9)	Regular use
				77	OR 1.4 (1.01-1.9)	Ipsilateral mobile phone use, ≥ 10 years since first use, *p* for trend = 0.04

Downloaded from oem.bmj.com on 11 April 2007

Table 3. Summary of nine studies on other brain tumour types or not specified and use of wireless telephones

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al 1999, 2001 Sweden[1,2]	1994-1996 Case-control	20-80 years	Brain tumours	78	OR 1.0 (0.7-1.4)	Analogue and digital cell phone use
				34	OR 1.1 (0.6-1.8)	Ipsilateral use
				16	OR 1.2 (0.6-2.6)	> 10 year latency, analogue cell phone
Muscat et al 2000 USA[3]	1994-1998 Case-control	18-80 years	Brain tumours	66	OR 0.9 (0.6-1.2)	Regular use Mean duration of use, 2.8 years
			Neuorepithelioma	35	OR 2.1 (0.9-4.7)	
Johansen et al 2001 Denmark[4]	1982-1995 Cohort	> 18 years	Brain tumours	20	SIR 1.3 (0.8-2.1)	Analogue and digital cell phone use
				9	SIR 1.2 (0.6-2.3)	≥ 3 years duration of digital subscription
Inskip et al 2001 USA[5]	1994-1998 Case-control	≥ 18 years	Meningioma	6	OR 0.9 (0.3-2.7)	≥ 5 years of cell phone use
Lönn et al 2005 Sweden Interphone[10]	2000-2002 Case-control	20-69 years	Meningioma	118	OR 0.7 (0.5-0.9)	Regular use
				5	OR 1.3 (0.5-3.9)	≥10 years since first "regular" cell phone use on same side of head as tumour
				3	OR 0.5 (0.1-1.7)	≥10 years since first "regular" cell phone use on opposite side of head as tumour.
Christensen et al 2005 Denmark Interphone[12]	2000-2002 Case-control	20-69 years	Meningioma	67	OR 0.8 (0.5-1.3)	Regular use
				6	OR 1.0 (0.3-3.2)	≥10 years since first regular use of cell phone
Schüz et al 2006 Germany Interphone[14]	2000-2003 Case-control	30-(59)-69 years (see above)	Meningioma	104	OR 0.8 (0.6-1.1)	Regular use
				5	OR 1.1 (0.4-3.4)	≥ 10 years since first "regular use" of cell phone

Downloaded from oem.bmj.com on 11 April 2007

Study	Years Study Type	Age	Tumour type	No. of Cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al 2006a Sweden[15]	1997-2003 Case-control	20-80 years	Meningioma	347	OR 1.1 (0.9-1.3)	> 1 year latency of cell phone use
				38	OR 1.5 (0.98-2.4)	> 10 years latency of cell phone use
				15	OR 2.0 (0.98-3.9)	> 10 years latency of ipsilateral cell phone use
				23	OR 1.6 (0.9-2.8)	> 10 years latency of cordless phone use
				9	OR **3.2** (1.2-8.4)	> 10 years latency of ipsilateral cordless phone use
Schüz et al 2006 Denmark[17]	1982-2002 Cohort	≥ 18 years	Brain and nervous system	28	SIR 0.7 (0.4-0.95)	≥ 10 years latency