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

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Abstract

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

**Methods:** Two cohort studies and 16 case–control studies on this topic were identified. 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 tumor size was significantly larger among users. Six studies gave results for malignant brain tumors in that latency group. All gave increased odd ratios (OR), especially for ipsilateral exposure. In a meta-analysis, ipsilateral cell phone use for acoustic neuroma was OR=2.4 (95% CI 1.1 to 5.3) and OR=2.0, (1.2 to 3.4) for glioma using a tumor latency period of ≥10 years.

**Conclusions:**

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

- DECT, digital enhanced cordless telecommunications
- RF, radiofrequency
- SIR, standardized incidence ratio
- UMTS, universal mobile telecommunication system
- mobile phones
- acoustic neuroma
- glioma
- ipsilateral exposure

Over the past few decades, there has been rapid worldwide development of wireless technology, including increasing use of wireless telephone communication. This has raised concerns about health risks, primarily increased risk for brain tumors, owing to the proximity of the brain to the radiation antenna, with the potential for absorbing a comparatively large amount of electromagnetic energy.

An increased risk for brain tumors 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. Initial studies
on brain tumor risk had insufficiently long latency periods to give a meaningful interpretation of long-term risk. However, during recent years, studies have been published that enable evaluation of ≥10-year latency period risk, although still mostly based on low numbers. A 10-year latency period for development of tumors seems to be a reasonable minimum period to indicate long-term carcinogenic risks from exposure to radiofrequency (RF) fields during use of cellular or cordless phones.

In this paper, we present results from cohort and case–control studies published to date on this topic. In tables we give 10-year latency period results, and if presented, ipsilateral use of cellular phones, i.e. same side of tumor and microwave exposure. This gives a “worst-case scenario” that may predict increasing incidence of brain tumors in the future, as the use of cellular phones is globally widespread, 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 possible future health problems in other countries. The technology is briefly discussed in the following using the Swedish experience as a model.

The analogue system has been used from the early 1980s using 450 or 900 MHz RF fields. The digital system has been increasingly used since the beginning of the 1990s and currently dominates the market. This system uses dual-band, 900 and 1800 MHz frequencies for communication. Over recent years the third generation of mobile phones, 3G or universal mobile telecommunication system (UMTS), using 1,900 MHz RF fields has been introduced worldwide.

Desktop cordless phones (digital enhanced cordless telecommunications; DECT) also use wireless technology. Initially, in the late 1980s, analogue 800–900 MHz was used but since the early 1990s, the digital 1900 MHz system has been used. Our research group has also assessed use of DECT phones in all of our tumor investigations, whereas no such data have been presented in publications from other research groups.

**METHODS**

We scrutinized the literature for published studies using PubMed and personal knowledge of this area as we are involved in current research in this field. We used mobile/cellular/cordless telephone and brain tumor/neoplasm/acoustic neuroma/meningioma/gloma 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 analyzed 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 Finland, five from Sweden, one from the UK, one from Germany, one from Japan and two from study groups partly overlapping some of these studies.

**Statistical methods**

For statistical analyses, Stata V.8.2 was used (StataCorp, College Station, Texas). Random effects model was used for all meta-analyses, based on test for heterogeneity.

**RESULTS**

Tables 1–3 summaries the studies. The first study, by Hardell et al., included cases and controls from the Uppsala-Örebro region during 1994–96 and the Stockholm region during 1995–96 in Sweden. Only living cases were included. Two controls were selected for each case from the Swedish Population Registry. The questionnaire was answered by 217 (93%) cases and 439 (94%) controls. A high response rate was obtained because the study was hospital-based (relationship between study subjects and physicians). Two reminders were sent after the postal
questionnaires if unanswered, and finally a telephone interview was conducted if possible. The population registry holds updated contact details, so it is easy to trace participants. Overall, no association between mobile phone use and brain tumors was found. However, an increased risk was seen for ipsilateral phone use, especially for tumors in the temporal, occipital or temporoparietal lobe (OR=2.4, 95% CI 0.97 to 6.1).

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Table 1
Summary of eight studies on acoustic neuroma and use of wireless (cell) telephones

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

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

The study by Muscat et al included patients with malignant brain tumors from five different hospitals in USA. Controls were hospital patients and except for those from two hospitals, were 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 cases and 2.7 years for controls. Only 17 cases (4%) and 22 controls (5%) had used a mobile phone for ≥4 years. Overall, no association was found: OR=0.9 (95% CI 0.6 to 1.2) for handheld cellular phones, and OR=2.1 (0.9 to 4.7) for neuroepithelioma. Of 41 assessable tumors, 26 occurred at the side of the head mostly used during calls (ipsilateral) and 15 on the contralateral side (p=0.06). The study is inconclusive because no data were available on long-term users (≥10-year latency period).

Johansen et al performed a population-based cohort study of mobile phone users in the period 1982–1995 in Denmark. In total over 700 000 users were included. Subjects with phones supplied by their company (about 200 000) were excluded. Of digital (Global System for Mobile Communications; GSM) subscribers, only nine cases had used the phone for ≥3 years. This produced a slightly increased standardized incidence ratio (SIR) of 1.2 (95% CI 0.6 to 2.3). Digital phone users with previous use of an analogue phone yielded SIR=1.3 (0.8 to 2.1). No subjects with 10-year use were reported.

The study by Inskip et al from the USA also had few long-term users of mobile phones: only 11 patients with glioma, 6 with meningioma and 5 with acoustic neuroma had ≥5 years’ regular use, and no subjects had ≥10 years’ use. The study enrolled 782 (92%) hospital cases with 489 malignant brain tumors, 197 with meningioma and 96 with acoustic neuroma. Most (80%) were interviewed within 3 weeks of diagnosis. In total, 799 (86%) hospital-based controls were used. Regular use of mobile phones gave OR=0.8 (95% CI 0.6 to 1.2) for glioma, OR=0.8 (0.4 to 1.3) for meningioma and OR=1.0 (0.5 to 1.9) for acoustic neuroma. Duration of use ≥5.0 years did not increase the risk for glioma and meningioma, but OR increased to 1.9 (0.6 to 5.9) for acoustic neuroma. Regarding different types of glioma, OR=1.8 (0.7 to 5.1) was found for anaplastic astrocytoma.

In the study by Muscat et al, 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 for 1–2 years produced OR = 0.5 (95% CI 0.2 to 1.3; n = 7), increasing to OR = 1.7 (0.5 to 5.1; n = 11), in the group with 3–6 years’ use.

A register based case–control study on brain and salivary gland tumors was performed in Finland by Auvinen et al. All cases aged 20–69 years diagnosed in 1996 were included, a total of 398 brain tumor cases and 34 salivary gland tumor cases. The duration of use was very short, for analogue users 2–3 years and for digital cell phone users <1 year. No association was found for salivary gland tumors. An increased risk for glioma (OR = 2.1, 95% CI 1.3 to 3.4), was found for analogue phones, whereas for digital phones OR was 1.0 (0.5 to 2.0). Duration of use was used as a continuous variable and yielded for analogue phones and glioma OR = 1.2 (1.1 to 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. 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 ≥ 5 years since first use gave OR = 1.2 (95% CI 0.7 to 2.1). No subjects were reported with ≥ 10 years’ use of a digital phone. Use of an analogue phone gave OR = 1.3 (0.6 to 2.9) for a duration of 5–9 years, and OR = 1.8 (0.8 to 4.3) for ≥ 10 years. Ipsilateral use of a mobile phone with ≥ 10 years since first use gave OR = 3.9 (1.6 to 9.5), whereas contralateral use gave OR = 0.8 (0.2 to 2.9).

In Denmark a case–control study on acoustic neuroma was performed by Christensen et al. It comprised 106 (82%) hospital-based incident cases and 212 (64%) population-based controls. Overall OR = 0.9 (95% CI 0.5 to 1.6) was obtained for regular use. Time since first regular use of ≥ 10 years yielded OR = 0.2 (0.04 to 1.1) based on two cases. Shorter time intervals did not increase the risk. Significantly larger tumors were found among cellular phone users: 1.66 cm³ compared with 1.39 cm³ among non-users, p = 0.03.

Lönn et al., the group from the Karolinska Institute in Sweden, also performed 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 OR = 0.8 (95% CI 0.6 to 1.0) for glioma and OR = 0.7 (0.5 to 0.9) for meningioma. Time since first regular use of ≥ 10 years gave OR = 1.6 (0.8 to 3.4) for ipsilateral glioma and OR = 0.7 (0.3 to 1.5) for contralateral glioma. The corresponding results were OR = 1.3 (0.5 to 3.9) for ipsilateral meningioma and OR = 0.5 (0.1 to 1.7) for contralateral meningioma.

Schoemaker et al. presented results for acoustic neuroma as part of the Interphone study performed in six different regions in the Nordic countries and the UK. The Swedish and Danish parts have been reported previously. Cases were obtained from hospitals, and if possible, also from cancer registries. In the Nordic countries controls, were selected from population registries and in the UK from general practitioners’ practice lists. In total, 678 (82%) cases and 3553 (42%) controls were interviewed. Regular use of a mobile phone yielded OR = 0.9 (95% CI 0.7 to 1.1). Lifetime use for ≥ 10 years gave OR = 1.8 (1.1 to 3.1) for ipsilateral acoustic neuroma, and OR = 0.9 (0.5 to 1.8) for contralateral tumor.

The Danish part of the Interphone study on brain tumors comprised 252 (71%) people with glioma, 175 (74%) with meningioma and 822 (64%) controls. Cases were hospital-based and controls were selected from the Danish Central Population Register. Statistical analyses gave OR = 0.8 (95% CI 0.5 to 1.3) for meningioma, OR = 1.1 (0.6 to 2.0) for low-grade glioma, and OR = 0.6 (0.4 to 0.9) for high-grade glioma. Use for ≥ 10 years yielded OR = 1.0 (0.3 to 3.2) for meningioma, OR = 1.6 (0.4 to 6.1) for low-grade glioma and OR = 0.5 (0.2 to 1.3) for high-grade glioma. For high-grade glioma 17 ORs were presented and all showed OR < 1.0.
Hepworth et al\textsuperscript{13} presented results from England as part of the Interphone study on glioma. It comprised 966 (51%) cases and 1716 (45%) controls. Cases were ascertained from multiple sources including hospital departments and cancer registries. The controls were randomly selected from general practitioners’ lists. The overall OR for regular phone use was 0.9 (95% CI 0.8 to 1.1). Ipsilateral phone use was OR = 1.2 (1.02 to 1.5), and contralateral OR = 0.8 (0.6 to 0.9). Ipsilateral use for ≥10 years produced OR = 1.6 (0.9 to 2.8), and contralateral OR = 0.8 (0.4 to 1.4).

The Interphone Study Group with Schüz et al\textsuperscript{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 1494 (61%) were included in the analyses. Overall, no association was found between use of cellular telephones and brain tumor. For glioma OR = 1.0 (95% CI 0.7 to 1.3), and for meningioma OR = 0.8 (0.6 to 1.1), were obtained. However, for users of cellular telephones for ≥10 years OR = 2.2 (0.9 to 5.1) was calculated for glioma and OR = 1.1 (0.4 to 3.4) for meningioma. For women with “ever” use of a cell phone OR = 2.0 (1.1 to 3.5) was calculated for high-grade glioma.

Our group\textsuperscript{15} reported in a pooled analysis the results for benign brain tumors from two case–control studies. Cases were reported from Cancer Registries and controls were population-based. The questionnaire was answered by 1254 (88%) cases and 2162 (89%) controls. Use of cordless desktop phones was assessed. Use of cellular phones gave for acoustic neuroma OR = 1.7 (95% CI 1.2 to 2.3), and cordless phones OR = 1.5 (1.04 to 2.0). Using a >10-year latency period for cellular telephones gave OR = 2.9 (1.6 to 5.5), and cordless phones OR = 1.0 (0.3 to 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 (1.3 to 3.8). For meningioma, cellular phones gave OR = 1.1 (0.9 to 1.3) and cordless OR = 1.1 (0.9 to 1.4). Using a >10-year latency period, ORs increased: for cellular telephones OR = 1.5 (0.98 to 2.4), and for cordless phones OR = 1.6 (0.9 to 2.8). Ipsilateral exposure gave OR = 2.0 (0.98 to 2.9) for cellular phones, and OR = 3.2 (1.2 to 8.4) for cordless phones 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.

Our later study\textsuperscript{16} presented results for malignant brain tumors. Answers were obtained from 905 (90%) cases, and the same control group as for benign tumors was used (2162; 89%). Overall, the study found for low-grade astrocytoma OR = 1.4 (95% CI 0.9 to 2.3) for cellular phones and OR = 1.4 (0.9 to 3.4 for) cordless phones. The corresponding results for high-grade astrocytoma were OR = 1.4 (1.1 to 1.8) and OR = 1.5 (1.1 to 1.9), respectively. Using a >10-year latency period gave results for low-grade astrocytoma of OR = 1.5 (0.6 to 3.8) for use of cellular phones (ipsilateral OR = 1.2, 0.3 to 5.8), and OR = 1.6 (0.5 to 4.6) for cordless phones (ipsilateral OR = 3.2, 0.6 to 16). For high-grade astrocytoma in the same latency period, cellular phones had OR = 3.1 (2.0 to 4.6) (ipsilateral OR = 5.4, 3.0 to 9.6), and cordless phones OR = 2.2 (1.3 to 3.9) (ipsilateral OR = 4.7, 1.8 to 13). The multivariate analysis of high-grade astrocytoma gave OR = 2.2 (1.6 to 3.1) for cellular phones, and OR = 1.3 (0.8 to 2.3) cordless phones, with a >10-year latency period. Results were also presented for analogue and digital phones separately.

The Danish cohort study on mobile phone subscribers\textsuperscript{4} was updated with follow-up through 2002 for cancer incidence.\textsuperscript{17} As previously, >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 giving a very skewed sex distribution. There seemed to be a “healthy worker” effect in the study, as SIR was significantly decreased to 0.95 (95% CI 0.9 to 0.97) for all cancers. In the group with ≥10 years since first subscription, significantly decreased SIR of 0.7 (0.4 to 0.95) was found for brain and nervous system tumors indicating methodological problems in the study. Temporal glioma yielded SIR=1.2 (0.9 to 1.6). This finding was based on 54 people. No latency data were given or laterality of phone use in relation to tumor 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 using random digit dialling. Of 120 eligible cases, 101 (84%) participated in the study. In total, 647 controls were selected but only 339 (52%) were interviewed. Regular mobile phone use yielded OR=0.7 (95% CI 0.4 to 1.2). For use >8 years OR=0.8 (0.2 to 2.7) was obtained. A somewhat increased risk was found for 300–900 hours cumulative call time, with OR=1.4 (0.5 to 3.5). The >900 hours group gave OR=0.7 (0.3 to 1.8). No effect of laterality was seen, ipsilateral mobile phone use OR=0.9 (0.5 to 1.6), and contralateral use OR=0.9 (0.6 to 1.6).

A report on mobile phone use and risk of glioma in Denmark, and parts of Finland, Norway, Sweden and UK gave summary results for these Interphone studies.19 In the report, three previously published studies were included from Sweden,10 Denmark12 and the UK.13 Of 2530 eligible cases, 1521 (60%) participated. Overall, no increased risk was found for regular mobile phone use, OR=0.8 (95% CI 0.7 to 0.9). However, cumulative hours of use gave OR=1.006 (1.002 to 1.010) per 100 hours. For ≥10 years, OR=1.4 (1.01 to 1.9), p for trend=0.04 was found for ipsilateral mobile phone use. Contralateral use gave OR=1.0 (0.7 to 1.4) in the same group.

Using a latency period of ≥10 years (for definitions see tables) we performed 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 to 2.8) was obtained,8,11,15 and for ipsilateral mobile phone use OR=2.4 (1.1 to 5.3) was calculated.8,11,15 For glioma, OR=1.2 (0.8 to 1.9) was calculated in the whole group10,12–14,16,19 increasing to OR=2.0 (1.2 to 3.4) for ipsilateral use.10,13,16,19 The corresponding results for meningioma were OR=1.3 (0.9 to 1.8)10,12,14,15 and OR=1.7 (0.99 to 3.1)10,15 respectively.

**DISCUSSION**

This review included 18 studies: 2 cohort and 16 case–control studies.

Some of the studies were part of the Interphone investigation and two publications included results from different studies.11,19 The conclusions on the risk for brain tumors associated with use of cellular phones have to date been based mostly on studies with an insufficiently long latency period in carcinogenesis. As we are now seeing results from studies with long-term users (i.e. ≥10 years), it is pertinent to compile the data to see if a pattern of association with brain tumors is emerging. It should be noted that only the studies by our group15,16 also give results for use of cordless phones. It is necessary to assess such use in case–control studies, which has been discussed in our publications, thus, an association between cordless phones and brain tumors 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 from the tables. Brain tumors are a heterogenic group of tumors including both malignant and benign types. Thus, it is reasonable to separate the results for malignant and benign tumors, as has been carried out in the various studies. The Danish cohort study4 is not very informative, owing to the limits in study design, analysis and follow-up, and will not be discussed further. The same methodological limitations are present in the updated version.12
Acoustic neuroma might be a “signal” tumor type for increased brain tumor risk from microwave exposure, as it is located in an anatomical area that receives high exposure during calls with cellular or cordless phones. In fact, an increasing incidence of acoustic neuroma has been noted in Sweden. In table 1, results are presented from seven case–control studies on acoustic neuroma and use of cellular phones. Three studies did not have follow-up of at least 10 years, but two of them showed a somewhat increased risk for shorter latency periods. Three of the four 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 two cases. The tumors were significantly larger among mobile phone users. In our previous study, an increased risk was also found with a 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 tumor 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. No case was reported with a latency period ≥10 years.

Meningioma results were given in five case–control studies. No consistent pattern of an association was found, although ipsilateral exposure in the >10-year latency group increased the risk in one of the studies. For a definite conclusion, longer follow-up studies are needed.

Results for glioma are given in nine studies (table 2). One was register-based 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. For glioma, increased OR was found, which was more pronounced for ipsilateral use of the cell phone. This pattern of association was consistent in the various studies, except for the Danish study by Christensen et al. In that study, all 17 ORs for high-grade glioma were <1.0, indicating systematic bias in assessment of exposure. The Interphone study 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 a ≥10-year latency period gives a consistent pattern of association between use of mobile phones and malignant brain tumors, especially high-grade glioma.

In spite of the heterogeneity between the different studies, we performed a meta-analysis for use of mobile phones with a latency period of ≥10 years. We calculated OR for the whole group and for ipsilateral use of mobile phones. For both acoustic neuroma and glioma, OR was increased in the whole group, but significantly increased for ipsilateral exposure. No significantly increased risk was found for meningioma, although the highest OR was calculated for ipsilateral use. These results are certainly of biological relevance, as the highest risk was found for tumors 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 OR=1.0 (95% CI 0.8 to 1.4) for contralateral tumors and for ipsilateral tumors OR=1.3 (0.99 to 1.9). No analysis was performed for >10-year latency time. 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 analyzed in the Interphone study. It was concluded that actual use was underestimated by light users and overestimated by 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 tumors. In a following article from the same study group, it was concluded that random recall bias could lead to substantial underestimation in the risk of brain tumors 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 ≥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, as an increased risk for other types of brain tumors cannot be ruled out.** From these studies, it is not clear at what stage microwaves act in carcinogenesis.

**Main message**

- **Results in case–control studies on brain tumors 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 tumor occurred) yielded highest risk.**

**Policy implications**

- These results indicate that the caution is needed in the use of mobile phones.
- More research is necessary for risk assessment based on higher number of long-term users.

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- Original article
  1. Lennart Hardell1,
  2. Michael Carlberg2,
  3. Fredrik Söderqvist3,
  4. Kjell Hansson Mild4,
  5. L. Lloyd Morgan5

+ Author Affiliations

1. 1Department of Oncology, University Hospital, Örebro and Department of Natural Sciences, Örebro University, Örebro, Sweden
2. 2Department of Oncology, University Hospital, Örebro, Sweden
3. 3Department of Oncology, University Hospital and Institute of Clinical Medicine, Örebro University, Örebro, Sweden
4. 4National Institute for Working Life, Umeå and Department of Natural Sciences, Örebro University, Örebro, Sweden
5. 5Francisco Street, Berkeley, California, USA

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