ENVIRONMENTAL FACTORS
AND RISK OF ACOUSTIC NEUROMA

David Pettersson

Stockholm 2014
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Environmental Factors and Risk of Acoustic Neuroma

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ABSTRACT

The aim of this thesis was to increase the knowledge about environmental risk factors of acoustic neuroma and to increase the understanding of the methodological problems encountered when studying this tumor.

Acoustic neuroma is a benign, usually slow growing, intracranial tumor of the vestibulocochlear nerve (cranial nerve VIII), the nerve that transmits information about hearing and balance from the inner ear to the brain. Acoustic neuroma is usually not life threatening, the most common symptoms are unilateral hearing loss and balance problems, but more severe symptoms like hydrocephalus may occur because of its intracranial location. Very little is known about acoustic neuroma etiology. The only well-established environmental risk factor is ionizing radiation, but associations have been observed with non-smoking, income, and education.

This thesis includes studies that investigated the associations between acoustic neuroma and mobile and cordless phone use, occupational and leisure time exposure to loud noise, and occupational exposure to chemical agents. In addition, a validation of self-reported start year of mobile phone use was performed, using operator data as gold standard. The thesis is based on a Swedish nationwide population based case-control study of acoustic neuroma risk factors. The study includes 451 cases of acoustic neuroma and 710 controls, matched on age, sex and residential region. Postal questionnaires were used to collect exposure information about environmental and lifestyle factors.

No evidence was found for an association between use of mobile phones and acoustic neuroma risk. Odds ratios for regular use and for long-term use of mobile phones were close to unity. An elevated odds ratio was found for the highest quartile of lifetime cumulative duration of calls but no corresponding increase in the highest quartile of cumulative number of calls. An association was found for regular use of cordless phones, but not for long term use. Also for cordless phones an increased odds ratio was found in the highest quartile of cumulative duration of calls but not for number of calls. The increased odds ratios were confined to cases without histological confirmation of the tumor, which may indicate that mobile and cordless phone use increases the probability of detection of the acoustic neuroma tumors. Odds ratios were generally higher for mobile phone use on the non-tumor side of the head and the laterality analyses indicated that laterality specific analyses suffered from reversed causality as cases changed the preferred side of use because of hearing loss on the tumor side. The validation showed large random errors in the self-reported information about start year of mobile phone use. Associations were found between acoustic neuroma and exposure to leisure time loud noise, but not with occupational noise, and associations were found for occupational exposure benzene, diesel engine exhaust, gasoline, and methylene chloride.
LIST OF PUBLICATIONS

The thesis is based on the following original papers. They will be referred to in the text by their Roman numerals (I–IV).


II. Pettersson D, Bottai M, Mathiesen T, Prochazka M, Feychting M. Validation of self-reported start year of mobile phone use in a Swedish case-control study on radiofrequency fields and acoustic neuroma risk. Submitted


*J.L.F. and D.P. contributed equally to this manuscript.
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<th>Description</th>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>IARC</td>
<td>Agency for Research on Cancer</td>
</tr>
<tr>
<td>ICD-10</td>
<td>The International Classification of diseases, tenth revision</td>
</tr>
<tr>
<td>ICD-O-2</td>
<td>The International Classification of diseases for Oncology,</td>
</tr>
<tr>
<td></td>
<td>Second Edition</td>
</tr>
<tr>
<td>JEM</td>
<td>Job-exposure matrix</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis type 2</td>
</tr>
<tr>
<td>NOCCA</td>
<td>Nordic Occupational Cancer Study</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 ACOUSTIC NEUROMA

1.1.1 Acoustic neuroma tumors

Acoustic neuroma is a benign intracranial tumor of the vestibulocochlear nerve (cranial nerve VIII). The name acoustic neuroma derives from the appearance and histological structure of the tumor which lead early investigators to suggest a neuronal origin, and an involvement of the acoustic branch of the nerve was indicated since the most common symptom is hearing loss on the affected side.\(^1\) However, the tumors arise from myelin-forming cells and the tumors are more common on the vestibular than on the acoustic part of the nerve. The name acoustic neuroma is a misnomer and it is widely accepted that the term vestibular schwannoma should be preferred for this tumor. In this thesis, I will nevertheless refer to the tumor as acoustic neuroma since this is the name that has been most widely used in the epidemiological literature.

Acoustic neuroma occurs in a sporadic form or associated with neurofibromatosis type II (NF2), an autosomal-dominant genetic disorder. The damaged gene is located on chromosome 22q. The gene product, termed schwannomin or merlin, has a tumor suppressing function. The mutation can be inherited, but de novo mutations are equally common. Mosaic genotypes are common in the latter case.\(^2,3\) People with this condition are very likely to develop acoustic neuromas, typically on both sides (bilateral acoustic neuromas is the most common diagnostic criterion), but they are also at increased risk of developing other nervous system tumors such as meningiomas, ependymomas and astrocytomas.\(^2\)

This thesis focuses on risk factors for the more common sporadic form of the tumor, which comprises the absolute majority of acoustic neuromas.\(^4\) However, damage of the NF2 gene is very common also in sporadic acoustic neuroma tumors\(^5,6\) and probably plays a role in the development of many of these tumors.

The vestibulocochlear nerve (cranial nerve VIII), from which the acoustic neuroma tumors develop, carries sensory information from the cochlea and the vestibular organ to the brain. It passes through the internal auditory canal (meatus) alongside the facial nerve (cranial nerve VII) and enters the brain stem in the cerebellopontine angle.\(^7\) The vestibulocochlear nerve is divided in one cochlear and two vestibular branches. Acoustic neuroma tumors may arise anywhere along the peripheral part of the nerve, from the glial-schwann cell junction to the cochlea or vestibule organ.\(^8\) The tumors almost exclusively occur on the vestibular branch of the nerve, usually on the inferior branch of the vestibular nerve.\(^8\text{--}10\) It has recently been argued that the majority of acoustic neuromas are associated with the sensory ganglia of the vestibular nerve in the internal auditory canal, while earlier beliefs located the origin
close to the glial-schwann cell junction at the border between the central and peripheral nervous system. \cite{8, 11, 12}

1.1.2 Clinical aspects

Acoustic neuroma is usually not life threatening. The most common symptom is hearing loss, followed by tinnitus and vertigo.\cite{13, 14} More severe complications include hydrocephalus due to compression, and obstruction, of cerebrospinal fluid pathways, or extensive protein secretion.\cite{15} Acoustic neuroma tumors are usually slow growing,\cite{16} and may exist a long time before clinical diagnosis. The diagnosis is usually based on magnetic resonance imaging (MRI), or occasionally, computed tomography. Gadolinium enhanced MRI is considered to be the gold-standard for detection of acoustic neuroma tumors.\cite{17} The majority of small acoustic neuromas does not grow after detection,\cite{1} and can be managed with serial MRI scanning. Treatment is indicated for larger or growing tumors, and sometimes for preservation of hearing. Treatment options are microsurgery or stereotactic radiosurgery, in the latter case, provided that the tumor is not too large. Treatment aims at controlling the tumor and preserving function, but further hearing loss, and facial paresis due to damage of the facial nerve, are possible complications.\cite{18}

1.1.3 Incidence of acoustic neuroma

The true incidence of acoustic neuroma is difficult to assess. The number of diagnosed acoustic neuromas has increased with increased quality and availability of diagnostic imaging. Stangerup and colleagues reported a linear relationship between the number of MRI scanners and diagnoses of intrameatal tumors in Denmark.\cite{19} Tumor size at diagnosis has decreased over the last decades while hearing acuity has increased.\cite{20} Recent estimation of the acoustic neuroma incidences for US, UK and Denmark were 12, 14 and 19 cases per million population, respectively.\cite{4, 20, 21} The discrepancy could reflect real differences in the incidence of acoustic neuroma, but may at least in part depend on differences in the completeness of the registration and/or diagnostic routines of the tumor.

1.2 ACUSTIC NEUROMA ETIOLOGY

Acoustic neuroma etiology is sparsely studied. Environmental associations with exposures such as mobile phones, noise, smoking, occupational exposure to chemicals, socioeconomic factors, parity, and hormone replacement therapy have been analyzed.

So far the only well-established risk factor for the sporadic (non-neurofibromatosis type II) form of acoustic neuroma is ionizing radiation.\cite{22-24} Inverse associations have been consistently reported for current smoking in two case-control studies\cite{25, 26} and one cohort study.\cite{27} Associations with income and education have been reported in
one case-control,\textsuperscript{28} and one cohort study.\textsuperscript{29} Parity\textsuperscript{26} and hormone replacement therapy\textsuperscript{30} have also been associated with increased risks.

1.2.1 Radiofrequency exposure

The first generation’s mobile phone technology, the Nordic Mobile Telephony (NMT) was introduced in Sweden 1981 and the first hand held mobile phones became available on the Swedish market 1987. The Global System for Mobile Communications (GSM), the second generation’s (2G) mobile phone technology, was then introduced in Sweden 1992. Mobile phones became increasingly popular and the market started to grow exceptionally fast in the mid 1990’s. The number of subscriptions per 100 inhabitants in Sweden grew from 9 to nearly 100 between 1994 and 2004.\textsuperscript{31} The third generation (3G) of mobile phone technology, Universal Mobile Telecommunications System (UMTS), was introduced in Sweden 2003.

NMT phones operated in the 450 or 900 MHz-band (NMT450 and NMT900, respectively). The average output power from the NMT450 and NMT900 phones were 900 mW and 600 mW, respectively. The NMT networks are no longer in use. NMT900 was shut down 1999 and the NMT450 network in 2007. GSM phones operate in the 900 and 1800 MHz-bands (GSM900 and GSM1800, respectively) and have a lower average output power (240 and 140 mW for GSM900 and GSM1800, respectively), although the peak power is higher. The reason for this is that GSM phones and subsequent technologies employ adaptive power control (APC) technology which down regulates power when possible. The third generation’s mobile phones have a peak effect of 125 mW, but the average output power is very low due to efficient adaptive power control.\textsuperscript{32, 33} Cordless phones, i.e. phones with a cordless handset connected via radio link to a fixed telephone line, have considerably lower output power than NMT and GSM phones, average output power for both the older analogue cordless phones and digital cordless (DECT) phones are 10 mW.\textsuperscript{33}

There has been a long standing concern in society about possible adverse health effects from the radiofrequency fields emitted from mobile and cordless phone antennas. The intensity of the radiofrequency fields from mobile and cordless phones is highest close to the antenna, and the short distance to the vestibulocochlear nerve sheet tissue brings attention to acoustic neuroma. The association between acoustic neuroma and radiofrequency fields from mobile phones has been in addressed in a number studies since the late 1990’s. Most of the studies have been of case-control design with retrospectively collected self-reported exposure information.\textsuperscript{34-36} Prospectively collected exposure information was used in one subscription list cohort study\textsuperscript{37}, and one cohort with prospectively collected self-reported exposure information.\textsuperscript{38, 39}

The case-control studies can be divided into the early US-studies,\textsuperscript{40-42} the Hardell group studies,\textsuperscript{36, 43-45} and the INTERPHONE study, a large multicenter case-control
study conducted in 13 countries between 2000 and 2004. No overall increased risks were reported from the US and INTERPHONE studies, while large risk increases were reported from the studies by the Hardell group. The reason for this discrepancy is unclear. Methodological differences have been proposed as an explanation. The odds ratio for ever regular use reported from the large multicenter INTERPHONE study was 0.85 (95% confidence interval 0.69–1.04) and for ≥10 years since first regular mobile phone 0.76 (95% CI: 0.52–1.11). The results from the two available cohort studies did not support an increased acoustic neuroma risk. The combined relative risk from the two cohort studies was 0.97 (95% confidence interval 0.65–1.46) for at least 10 years of use. It has however been stated that the epidemiological evidence concerning potential long term effects is insufficient for slow growing tumors like acoustic neuromas.

One of the main problems when studying the association with mobile phones is exposure assessment. A particular concern for case-control studies using retrospectively collected self-reported exposure information is the susceptibility to recall bias. Implausible reports of cumulative hours of mobile phones and inconsistent exposure response patterns in the INTERPHONE analyses raised concerns about recall bias; elevated odds ratios were observed in the highest decile of cumulative calling time for both glioma and acoustic neuroma, while the lowest odds ratios were found in the 9th deciles for both outcomes.

A number of studies have been conducted to assess the accuracy in the self-reported history of mobile phone use in healthy subjects but only one study on adults and one on children and adolescents have been conducted with data from both cases and controls in a case-control study and can therefore provide information about possible differences in recall between cases and controls. The study of adult respondents reported an increased tendency among cases to overestimate both called time and number of calls with increased time before interview, which was not observed for the controls, although no overall difference between cases and controls was seen. Self-reported information about the start of mobile phone use has to our knowledge never been validated for adult respondents.

1.2.2 Noise exposure

The first report of an association between loud noise and acoustic neuroma was from a case-control study published by Preston-Martin and colleagues in 1989. Three case-control studies and one register based study have been conducted since to assess the relationship between loud noise and acoustic neuroma.

The Preston-Martin study, which assessed exposure through self-reported occupational histories linked to a National Occupational Hazards Survey data base, found an odds ratio of 2.2 (95% CI: 1.12–4.67) for the association between acoustic neuroma and occupational exposure to loud noise. The Swedish part of the
INTERPHONE study\textsuperscript{55} found an odds ratio of 1.55 (95% CI: 1.04–2.30) for the association between acoustic neuroma and loud noise exposure from any type of source (occupational and/or leisure time); the German INTERPHONE study\textsuperscript{57} found an odds ratio of 2.31 (95% CI: 1.15–4.66) for exposure to persistent occupational noise; and the French INTERPHONE\textsuperscript{56} reported an odds ratio of 2.55 (95% CI 1.35–4.82) for the association with loud noise exposure (any kind of setting). A Swedish register based study using census information on occupation together with a job-exposure matrix found no association between occupational loud noise exposure and acoustic neuroma; odds ratio for exposure to ≥ 85 dB was 0.89 (95% CI: 0.64–1.23).\textsuperscript{58} The lack of association in the latter study may suggest that recall bias was the explanation for the associations seen in the earlier studies that used self-reported information on past loud noise exposure. However, recall bias is less likely to explain the findings in the earliest study that used self-reported occupational histories linked to the National Occupational Hazards Survey data base.\textsuperscript{54}

1.2.3 Occupational exposures

Three studies have addressed acoustic neuroma risk in relation to occupational title.\textsuperscript{59-61} One of them also used a job-exposure matrix to assess associations with exposure to specific agents,\textsuperscript{59} and another early study investigated associations with self-reported occupational exposure to different agents.\textsuperscript{54}

Two case-control studies,\textsuperscript{60, 61} and one register based study\textsuperscript{59} that used data on acoustic neuroma diagnoses from the Swedish cancer register and occupational information from national censuses, have found associations between several occupational titles and acoustic neuroma. However, no evident patterns emerge when comparing the results. The latter study, which also employed a job-exposure matrix to assess exposure to specific occupational agents, found associations between acoustic neuroma and job-exposure matrix derived exposure to asbestos, textile dust and benzene.\textsuperscript{59} An association between acoustic neuroma and self-reported benzene exposure has also been reported.\textsuperscript{54}
2 AIMS OF THE THESIS

2.1 OVERALL AIM

The overall objective is to increase the knowledge about environmental risk factors for acoustic neuroma and to increase the understanding of the methodological problems encountered when studying this tumor.

2.2 SPECIFIC AIMS

I. To study the association between acoustic neuroma and use of mobile phones and cordless phones, and to investigate the effect of possible differences between cases and controls regarding changes of the preferred side of mobile phone use on laterality specific estimates

II. To assess long-term recall of mobile phone use and possible differential recall between cases and controls

III. To study the association between acoustic neuroma and loud noise in occupational and leisure settings

IV. To study the association between acoustic neuroma and exposures in the work environment
3 METHODS

3.1 THE SOTAN STUDY

The papers in this thesis are based on data from the SOTAN case-control study, a study that was initiated as a response to results from the Swedish part of the INTERPHONE study, which found indications of associations between acoustic neuroma and long-term mobile phone use and loud noise.\textsuperscript{55,62}

The SOTAN study is a population based case-control study conducted in Sweden between September 1, 2002 and August 31, 2007. Postal questionnaires were used to collect information about exposure to radiofrequency fields from mobile and cordless phones, loud noise, and occupational exposures. In addition, network operator information about subscriptions and use of mobile phones was available for a subset of the participants.

3.1.1 Case ascertainment

Eligible cases had their first acoustic neuroma diagnosis (ICD-10 D33.3 and ICD-O-2 9560.0) in the ages 20 to 69 years. Acoustic neuroma cases were identified in collaboration with treating clinics located in Göteborg, Linköping, Lund, Stockholm, Umeå and Uppsala. Local acoustic neuroma registers were available at the otorhinolaryngology clinics in Linköping and Uppsala. In addition to patients reported from the clinics, the regional cancer registers were searched for cases of acoustic neuroma (ICD-10 code C72.4 is used for acoustic neuroma in the Swedish cancer registers). The regional cancer registers constitute the basis for the national register but are earlier updated.\textsuperscript{62}

Diagnoses of acoustic neuroma were either histologically confirmed or based on diagnostic imaging, in most cases an MRI-scan. Date of diagnosis was defined as the date of the first medical examination resulting in a diagnosis of acoustic neuroma. Information about date of diagnosis, histological confirmation and tumor laterality was collected from medical records. A physician’s permission to contact the patient was obtained from treating physicians or heads of the clinics.

3.1.2 Selection of controls

The controls were selected randomly from the Swedish population registry matched to cases on sex, age in five year strata, and residential area according to the catchment areas of the six regional cancer registries. If none of the controls that were first selected decided to participate, two new controls were invited.
3.1.3 Data collection

Information about exposure to mobile and cordless phone use, noise, occupational exposures, and lifestyle factors was collected with postal questionnaires. Starting in October 2007, cases and controls were sent an invitation letter with information about the study. The questionnaires were sent two weeks later. The case and the two controls that were first selected were mailed at the same time. Two mail reminders and one telephone reminder were used with two weeks interval. Cases and controls were invited to complete a non-participant survey if they during the telephone reminder declared that he or she did not intend to participate. The survey included four short questions: (1) Have you ever used a mobile phone? (2) Have you ever used a mobile phone at least once per week for six months or more? (3) When did you start using the mobile phone at least once per week? (4) What is your highest completed education?

3.1.4 Ethical approval and informed consent

The study was approved by the Ethical review board at Karolinska Institutet (registration number (Dnr): 2006/1558-31/1). Data was collected with the written informed consent of the participants. Patients were contacted with the permission of the treating physician or head of the clinic.

3.2 EXPOSURE ASSESSMENT

The date of diagnosis was used as reference date for exposure assessment. The controls were assigned a reference that corresponded to the date of diagnosis of their matched case.

3.2.1 Radiofrequency exposure (Study I and II)

3.2.1.1 Self-reported use of mobile and cordless phones

The study participants were asked if they had ever been “regular users” of mobile phones defined as having used a mobile phone on average once per week for at least six months. In that case, they were then asked to report the start year of regular use. Matrix questions were used to collect information about the frequency and duration of calls, in predefined categories every three years, starting 1987, when hand-held mobile phones were introduced in Sweden. Number of calls was reported in the categories 1–2 per week, 3–6 per week, 1–4 per day, 5–10 per day, and ≥10 per day. Duration of calls was reported in the categories <5 min per week, 5–10 min per week, 1–10 min per day, 11–30 min per day, and ≥ 60 min per day. Figure 1 shows an example of the questions used. For mobile phones, information about the use of hands-free devices were collected for the same years by asking about the proportion of the time a hands-free device was used in the categories never/almost never, less than half the time, about half the time, more than half the time and always/almost
always. For cordless phones, information was collected only about which years hands-free devices had been used.

Lifetime cumulative number of calls and duration of calls were calculated. The mid-points of the intervals were used for in the calculations except for the highest, open, interval, 10 or more calls, for which the lower bound were used. This decision was made after analyzing network operator data available for a subset of the participants. According to this data, it was very rare to have made or received on average more than 10 calls per day or having used the phone for voice calls on average more than 60 min per day.

**How many times did you talk on a mobile phone in the following years?**

<table>
<thead>
<tr>
<th>Year</th>
<th>1-2 calls per week</th>
<th>3-6 calls per week</th>
<th>1-4 calls per day</th>
<th>5-10 calls per day</th>
<th>10 or more calls per day</th>
<th>Not relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>☐</td>
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<tr>
<td>1990</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>1993</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>1996</td>
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<td>1999</td>
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<td>☐</td>
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<td>2005</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>2007</td>
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<td>☐</td>
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</tbody>
</table>

**Figure 1.** Example of the matrix questions used to collect information about lifetime cumulative use of mobile and cordless phones.

The participants were asked on which side of the head they usually hold the mobile phone, if they had ever changed the preferred side of use, and in that case, the year of the change and how they held the phone before. We also asked for the reason of the change in the categories: practical reasons (e.g. started using the mobile phone while writing), hearing problems, headache, cosmetic reasons (e.g. ear piercing), or other/no particular reason. Information about the laterality of cordless phone use was not collected.

3.2.1.2 *Exposure assessment*

The following exposure indices were used to quantify the use of mobile and cordless phones: time since first use, duration of use, lifetime cumulative number of calls, and lifetime cumulative duration of calls. Time since first regular use and duration of regular use was categorized as < 5, 5-9, or ≥ 10 years, lifetime cumulative measures of calls and call duration were categorized with cut-points chosen approximately at the quartiles of the distribution among controls. For mobile phones, the reported use
of hands-free devices was accounted for by subtracting 25%, 50%, 75% or 100% of the exposure for reported use of hands-free devices less than half the time, about half the time, more than half the time and always/almost always, respectively. For cordless phones, we did not ask for the proportion of the time that hands-free devices were used. Instead we adjusted for use of hands-free devices in the analyses. A one year induction period was used in all analyses of the association between acoustic neuroma and use of mobile and cordless phones. People that reported ever regular use before the induction period were considered exposed. Non-regular users, that is, participants that did not report regular use before the induction period, were defined as unexposed and used as reference group in the analyses.

3.2.1.3 Laterality analyses

Participants were considered exposed on the tumor side of the head – ipsilateral exposure – if they reported having used the mobile phone on the same side of the tumor or on both sides of the head any time between first regular use and the start of the induction period. If a participant reported having changed the preferred side of use, because of hearing problems, within 5 years from the reference date, the participant was considered exposed as he or she held the phone before the change. This condition was used because unilateral hearing loss is a common early symptom of acoustic neuroma and hearing dependent side changes would be expected among the cases. Contralateral use was defined using the same criteria, but for holding the phone on the non-tumor side of the head. The unexposed group was defined as “never regular mobile phone use” also in the laterality analyses. Thus, participants who used the phone only on the contralateral side were excluded from analyses of ipsilateral exposure, and participants who used the phone only on the ipsilateral side were excluded from analyses of contralateral exposure.

In addition to the main laterality analysis, we also analyzed the effect of side changes on the laterality specific estimates by doing laterality specific analyses of regular use with laterality information that reflected how they reported preferred side at the time of interview, at reference date, and 1, 5, and 10 years before reference date. Regular users were included in the analyses even if they were not regular users 5 and 10 years before reference date. We only varied the time point for which the information about laterality was determined.

3.2.1.4 Self-reported information on past subscriptions

Participants who reported regular use were asked to enter information about the start date, stop date, network operator, phone number, and type of network for past and present mobile phone subscriptions in a mobile phone calendar (Figure 2). We also asked if the subscriptions were written in the participants name and if the subscriptions were used by someone else.
3.2.1.5 *Operator recorded information*

The participants were asked if they were willing to sign a permission to request information about mobile subscriptions’ start date and stop date, and number and duration of calls from the network operators.

Two (TeliaSonera and Telenor) of the four major network operators in Sweden provided subscription and traffic data for participants that signed the permission form. The other two network operators had the data stored in a way that made historical data complicated to access. Both TeliaSonera and Telenor could provide data about subscriptions start and stop dates for the whole period they had been active on the Swedish market. TeliaSonera that also have operated under the names Televerket and Telia introduced mobile phone services on the Swedish market in the 1980s and is still the largest provider (43% of the subscriptions 2007). Telenor, formerly Vodafone and Europolitan, has operated since 1992 as the third largest mobile phone service provider on the Swedish market (17% of the subscriptions in 2007). Voice call traffic data was available from January 1999 for Telenor subscriptions, while TeliaSonera could provide traffic data only from Mars 2006.

![Mobile phone-calendar](image)

**Figure 2.** Mobile phone calendar used to collect information about the participants past and present subscriptions.

Self-reported data on mobile phone subscriptions and personal identification numbers were sent to the collaborating network operators. The operators sent back information about subscriptions’ start and stop date together with traffic data, for subscriptions that matched the participants’ personal identification numbers or reported phone numbers.
3.2.1.6 Matching of self-reported and operator recorded information

Eligible for validation were participants who reported ever having used mobile phones regularly at least one year before the reference date. Operator recorded data and self-reported information were compared up to one year before reference date. Operator recorded information were linked to self-reported information only if the participant had specified the network operator in question as provider of the subscription.

Self-reported and operator recorded information about number and duration of calls could only be unequivocally linked for 19 cases and 32 controls, equivalent to 5.8% and 6.3% of the regular user cases and controls, respectively. The proportions were judged too small for reliable results and we did not pursue further analysis of this data.

For the validation of start year of mobile phone use, the reported first mobile phone subscription was matched to the earliest subscription in operator records. Subscriptions were matched on personal number or phone number (or both). In order to make the assumption that the first subscription in the calendar referred to the subscription that the participant used when becoming a regular user, we used the criterion that the start year of regular use had to match the start year of the self-reported first subscription.

3.2.2 Noise exposure (Study III)

For the assessment of occupational noise, both job-exposure matrix derived and self-reported exposure to workplace loud noise were used, while the assessment of leisure time noise only relied on self-reported exposure.

The participants were asked if they had ever regularly been exposed to leisure time or occupational loud noise, defined as a level at which a conversation must be held with raised voices. In that case, they were asked to report the jobs and activities in question, and the start and stop year of the jobs or activities. We also asked about the frequency of the leisure time activities. Information about the use of hearing protection was collected for each leisure activity and job in the categories rarely, less than half the time, about half of the time, more than half the time, and always or almost always. Furthermore, a full occupational history was collected, detailing information about occupational title, major work tasks, start year, and stop year for jobs of more than one year’s duration of after the age of 15.

The self-reported occupational noise exposure was categorized as exposure with hearing protection and exposure without hearing protection. Hearing protection was defined as having used hearing at least half the time in the exposed occupations.
The job-exposure matrix used gave an estimated eight-hour time-weighted average sound level in dB(A) (A-weighted sound pressure level) categorized in <75 dB, 75-84 dB, or ≥85 dB for each combination of occupational title and time period, in 5-year periods from 1970 to 2004.63 The occupational histories in the questionnaires were coded for use in the job-exposure matrix according to a three digit coding system based on the Nordic Occupational Classification System of 1983 (NYK 83).64 Job-exposure derived noise exposure was categorized as ≥75 dB with hearing protection, 75–84 dB without protection, and ≥85 dB without protection. No exposure was defined as occupational noise levels lower than 75 dB. Duration of exposure was categorized in Ever exposure, at least 5 years exposure, at least 10 years exposure, and at least 15 years exposure.

Exposure less than 5 years before the reference date was not considered. Acoustic neuroma is a slow growing tumor.16 We considered 5 years to be a reasonable time to allow for initiation growth and detection of the tumor. Only people ever working before a 5-year induction period were included in the analyses. People working before, but unexposed to occupational noise before the 5-year induction period was considered unexposed and constituted the reference group in the analyses.

Leisure time noise was categorized as exposed without hearing protection, exposed with hearing protection (use more than half of the time), or mixed use of protection (use of protection differing between activities). A lifetime cumulative number of loud leisure exposures without protection was calculated and categorized according to the tertiles of the controls distribution. A 5-year induction period was applied in the analyses.

3.2.3 Chemical exposure (Study IV)

Occupational exposure to 21 chemical agents and ionizing radiation were assessed with a job-exposure matrix. In addition, we asked the participants to report workplace exposure to solvents and gasoline, and if they had worked with spray painting (e.g. automotive painting), painting (e.g. painting of buildings or interiors), or metal degreasing.

The NOCCA job-exposure matrix was used to assess the occupational exposure to 22 agents based on the occupational history collected as described under “Noise exposure” above. The occupational histories were coded according to a three digit system based on the Nordic Occupational Classification of 1978 (NYK 78).65 The NOCCA job-exposure matrix gives an estimation of the probability and level of occupational exposure to each agent for each combination of 296 occupational titles and 4 time periods (1945 to 1959, 1960 to 1974, 1975 to 1984, and 1985 to 1994). The NOCCA job-exposure matrix provides exposure estimates for a particular agent if the estimated probability of exposure in the occupation was at least 5% under any of the time periods.66 Job-exposure matrix derived exposure was categorized in
5-24%, 25-49%, and ≥ 50% probability of workplace exposure and evaluated as ever exposed, exposed less than 10 years, or exposed 10 years or more. Lifetime cumulative exposures to the agents were calculated as the sum over the products of probability, level, and duration of exposure for each job held by the participant. The cumulative exposures were classified as low and high exposure with the cut point at the 50th percentile of the controls’ exposure distribution. Self-reported occupational exposures were evaluated as ever exposed, exposed < 10 years, or exposed ≥ 10 years. Exposure up to 5 years from the reference date was considered.

Only people ever working before a 5-year induction period were included in the analyses. People that worked but never exposed to the particular agent before the 5-year induction period was considered unexposed and constituted the reference group in the analyses.

### 3.3 STATISTICAL ANALYSIS

The analyses were performed using SAS statistical software package version 9.3 (SAS Institute, Inc., Cary, North Carolina).

#### 3.3.1 Associations with acoustic neuroma (Study I, III and IV)

Odds ratios for the associations between acoustic neuroma and different indices of exposure to mobile and cordless phones, noise, and chemicals were calculated using conditional logistic regression models. In addition to the matching variables age, sex and residential area, the analyses of noise and workplace chemicals were adjusted for smoking and education. This was decided a priori because a potential association of education and smoking with occupational title is evident and associations with acoustic neuroma have been reported for both education and non-smoking. The regression models for the associations with mobile and cordless phones were only controlled for the matching variables. The effects of adjusting for smoking, education, marital status and parity in these models were assessed but odds ratios were essentially unaffected. Separate analyses for women and men were performed. Separate analyses were also performed for strata with histologically confirmed cases and strata with non-histologically confirmed cases.

Tables presenting odds ratios from the conditional logistic regression models all show only the frequencies of cases and controls in complete matched strata, i.e. one case and at least one control must contribute exposure information in the strata. As a consequence the number of cases and controls may differ from what is expected considering the number of matched participants in Table 1 and in the frequency tables of the main models. This is in particular the case in the laterality analyses where we do not assume a particular exposure level for the contralateral side in the analysis of ipsilateral use or an exposure level for the ipsilateral side in the analysis of contralateral use. This means that whole strata are sometimes not included in the
analyses, for example if the strata consists only of a case and a control (or controls) with opposite laterality of use.

### 3.3.2 Validation of self-reported start year of mobile phone use (Study II)

The error expressed as the difference between self-reported and operator recorded start year was analyzed univariately. Arithmetic mean, standard deviation, median and inter quartile range were calculated. Sensitivity analyses stratifying on type of matching (i.e. matching on personal identification number or subscription phone number) were also performed. In addition, the ratio between the time from self-reported start to questionnaire date, and operator start to questionnaire date was calculated. Operator data were plotted against self-reported data and linear regression models were fitted. The correlations of the error with operator and self-reported start, respectively, were also investigated. All analyses were also performed for cases and controls separately to investigate possible differences in recall.
4 RESULTS

4.1 PARTICIPATION AND BASE LINE CHARACTERISTICS

Over the study period 542 eligible cases and 1095 controls were identified, of which, 451 (83%) and 710 (65%) participated, respectively. The most common reason for non-participation was subject refusal (cases, 9%; controls, 31%), followed by physician’s refusal to allow contact with the patient (6% of eligible cases). Only participants in complete matched strata, 423 cases and 645 controls, could contribute information in the conditional logistic regression models used. Table 1 shows basic characteristics of eligible, participating, and matched cases and controls.

Demographic characteristics differed only slightly between cases and controls, while current smoking was considerably more common among cases. About half of the cases (47%) had a histologically confirmed tumor.

<table>
<thead>
<tr>
<th>Age at reference date (years)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>52.3 (11.6)</td>
<td>51.6 (12.1)</td>
</tr>
<tr>
<td>20-39</td>
<td>96 (18)</td>
<td>210 (19)</td>
</tr>
<tr>
<td>40-49</td>
<td>111 (20)</td>
<td>221 (20)</td>
</tr>
<tr>
<td>50-59</td>
<td>159 (29)</td>
<td>348 (32)</td>
</tr>
<tr>
<td>60+</td>
<td>176 (32)</td>
<td>316 (29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>249 (46)</td>
<td>484 (44)</td>
</tr>
<tr>
<td>Men</td>
<td>293 (54)</td>
<td>611 (56)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compulsory school</td>
<td>123 (27)</td>
<td>197 (28)</td>
</tr>
<tr>
<td>Vocational/secondary</td>
<td>113 (25)</td>
<td>177 (25)</td>
</tr>
<tr>
<td>At least 3 year secondary</td>
<td>92 (21)</td>
<td>118 (17)</td>
</tr>
<tr>
<td>University/College</td>
<td>122 (27)</td>
<td>212 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>250 (55)</td>
<td>341 (48)</td>
</tr>
<tr>
<td>Past</td>
<td>147 (33)</td>
<td>220 (31)</td>
</tr>
<tr>
<td>Current</td>
<td>48 (11)</td>
<td>137 (19)</td>
</tr>
</tbody>
</table>

Table 1. Basic characteristics\(^a\) of acoustic neuroma cases and controls

\(^a\)No. (%); except where otherwise indicated

\(^b\)The number of observations varies over characteristics because of missing values

\(^c\)The highest completed education translated from the Swedish educational system
4.2 MOBILE AND CORDLESS PHONES AND ACOUSTIC NEUROMA
(STUDY I)

4.2.1 Mobile phones and acoustic neuroma

The proportion of regular users according to the definition used (at least one call/week for 6 months or more before the induction period) was 70% among controls and 71% among cases over the whole period. The prevalence of regular use increased over the course of the study period, from 62% for the controls with a reference date in 2002 to 81% for controls with a reference date in 2007 (Table 2). The proportion of regular users was similar among non-participating controls that answered the non-participant survey (67%, n=93). The non-participant survey was only answered by 7 cases (of which 4 were regular users) and cannot give any indication about regular use among non-participating cases.

<table>
<thead>
<tr>
<th>Reference year</th>
<th>Number of controls</th>
<th>Prevalence of regular use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>55</td>
<td>62%</td>
</tr>
<tr>
<td>2003</td>
<td>124</td>
<td>61%</td>
</tr>
<tr>
<td>2004</td>
<td>179</td>
<td>71%</td>
</tr>
<tr>
<td>2005</td>
<td>140</td>
<td>72%</td>
</tr>
<tr>
<td>2006</td>
<td>157</td>
<td>73%</td>
</tr>
<tr>
<td>2007</td>
<td>52</td>
<td>81%</td>
</tr>
</tbody>
</table>

*aAt least 1 mobile phone call/week for 6 months or more before the 1-year induction period

No association was found between acoustic neuroma and regular use of mobile phones (OR = 1.18, 95% CI: 0.88–1.59) or with long-term use of mobile phones (OR = 1.09, 95% CI: 0.75–1.59). The highest risk estimate was instead found in the intermediate term use (5-9 years) category (OR = 1.39, 95% CI: 0.97–1.97). Figure 3 shows the associations with time since first use of mobile phones, association with regular use displayed for comparison.

A non-significant increase of the odds ratio was observed in the highest quartile of lifetime cumulative duration of calls (OR = 1.46, 95% CI: 0.98–2.17), while no associations were seen in the three first quartiles (Figure 4). No corresponding increase was observed in the highest quartile of lifetime cumulative number of calls. Odds ratios were approximately the same in the first and fourth quartile (Figure 5).
The result of the separate analysis of cases with and without histological confirmation of the tumor and their respective controls showed that odds ratios consistently were higher for cases without histological confirmation of the tumor than for cases with a histologically confirmed diagnosis (Table 3).

**Figure 3.** Odds ratios with 95% confidence intervals for the association between acoustic neuroma and time since first use of mobile phones, odds ratio for regular use of mobile phones for comparison.

**Figure 4.** Odds ratios with 95% confidence intervals for the association between lifetime cumulative duration of mobile phone calls and acoustic neuroma, cut points chosen approximately at the quartiles of the controls distribution.
Figure 5. Odds ratios with 95% confidence intervals for the association between lifetime cumulative number of mobile phone calls and acoustic neuroma, cut points chosen approximately at the quartiles of the controls distribution.

<table>
<thead>
<tr>
<th>Cumulative number of mobile phone calls</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1100</td>
<td>1.21</td>
</tr>
<tr>
<td>1100-4400</td>
<td>1.07</td>
</tr>
<tr>
<td>4400-13850</td>
<td>1.22</td>
</tr>
<tr>
<td>≥13850</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Table 3. Odds ratios for acoustic neuroma according to different characteristics of mobile phone use stratified on histological confirmation of the tumor

<table>
<thead>
<tr>
<th>Cases histologically confirmed</th>
<th>Cases not histologically confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases Controls OR (95% CI)</td>
<td>Cases Controls OR (95% CI)</td>
</tr>
<tr>
<td>(n=202) (n=296)</td>
<td>(n=220) (n=347)</td>
</tr>
</tbody>
</table>

Frequency of use
- Never or rarely b: 59 (29) 86 (29) 1.00
- Regular use c: 143 (71) 210 (71) 0.99 (0.65–1.52)

Time since first regular use
- < 5 years: 46 (23) 68 (23) 0.94 (0.56–1.57)
- 5 – 9 years: 55 (27) 75 (25) 1.11 (0.66–1.86)
- ≥ 10 years: 42 (21) 67 (23) 0.94 (0.55–1.62)

Cumulative hours of use d,e
- < 38 h: 30 (15) 46 (16) 0.97 (0.55–1.71)
- 38 – 189 h: 39 (20) 59 (20) 0.91 (0.51–1.60)
- 190 – 679 h: 34 (17) 49 (17) 1.03 (0.57–1.87)
- ≥ 680 h: 37 (19) 51 (17) 1.14 (0.63–2.07)

Cumulative no. of calls d,e
- < 1100: 33 (17) 44 (15) 1.07 (0.61–1.86)
- 1100–4400: 35 (18) 54 (19) 0.86 (0.49–1.53)
- 4400–13850: 42 (21) 56 (19) 1.08 (0.62–1.90)
- ≥ 13850: 30 (15) 51 (18) 0.92 (0.50–1.72)

a Two sided P-Values for heterogeneity: likelihood ratio tests were used for testing heterogeneity of effects for each exposure characteristic and Wald tests for different levels of exposure.

b Reference category

c Regular use: ever used a mobile phone on average ≥1 call/week for ≥6 months.

d The total number of exposed does not add up because some regular users entered incomplete data on amount of phone use.

e Cut points approximately at the 25th, 50th and 75th percentiles.
4.2.2 Analyses by laterality of mobile phone use

Lower odds ratios were observed for having used the phone on the same side as the tumor (ipsilateral use) than for use on the opposite side (contralateral use). The odds ratio for ipsilateral regular use was 0.98 (95% CI: 0.68–1.43) and for contralateral regular use 1.33 (95% CI: 0.89–1.99), odds ratios for more than 10 years since first regular use were 1.01 (95% CI: 0.61–1.68) and 1.09 (95% CI: 0.63–1.88), respectively. Associations with lifetime cumulative number and duration of calls followed the same pattern (Table 4).

Table 4. Odds ratios for acoustic neuroma according to laterality of mobile phone use

<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or rarely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>(n=227)</td>
<td></td>
<td></td>
<td>(n=299)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular use</td>
<td>110 (48)</td>
<td>143 (48)</td>
<td>1.00</td>
<td>98 (43)</td>
<td>144 (48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time since first regular use (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>39 (17)</td>
<td>51 (17)</td>
<td>1.05 (0.62–1.78)</td>
<td>35 (15)</td>
<td>41 (14)</td>
<td>1.41 (0.80–2.48)</td>
</tr>
<tr>
<td>5–9</td>
<td>38 (17)</td>
<td>53 (18)</td>
<td>0.95 (0.57–1.58)</td>
<td>57 (25)</td>
<td>57 (19)</td>
<td>1.51 (0.92–2.49)</td>
</tr>
<tr>
<td>≥ 10</td>
<td>40 (18)</td>
<td>51 (17)</td>
<td>1.01 (0.61–1.68)</td>
<td>39 (17)</td>
<td>56 (19)</td>
<td>1.09 (0.63–1.88)</td>
</tr>
<tr>
<td>Cumulative hours of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 38</td>
<td>26 (12)</td>
<td>44 (15)</td>
<td>0.78 (0.45–1.38)</td>
<td>35 (15)</td>
<td>33 (11)</td>
<td>1.69 (0.94–3.05)</td>
</tr>
<tr>
<td>38–189</td>
<td>28 (12)</td>
<td>32 (11)</td>
<td>1.18 (0.63–2.20)</td>
<td>30 (13)</td>
<td>41 (14)</td>
<td>1.05 (0.56–1.95)</td>
</tr>
<tr>
<td>190–679</td>
<td>24 (11)</td>
<td>35 (12)</td>
<td>0.98 (0.52–1.84)</td>
<td>31 (14)</td>
<td>38 (13)</td>
<td>1.31 (0.74–2.32)</td>
</tr>
<tr>
<td>≥ 680</td>
<td>38 (17)</td>
<td>43 (14)</td>
<td>1.20 (0.69–2.08)</td>
<td>33 (15)</td>
<td>39 (13)</td>
<td>1.26 (0.70–2.25)</td>
</tr>
<tr>
<td>Cumulative no. of calls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1100</td>
<td>27 (12)</td>
<td>41 (14)</td>
<td>0.88 (0.50–1.55)</td>
<td>36 (16)</td>
<td>39 (13)</td>
<td>1.42 (0.82–2.47)</td>
</tr>
<tr>
<td>1100–4400</td>
<td>31 (14)</td>
<td>31 (10)</td>
<td>1.44 (0.76–2.74)</td>
<td>27 (12)</td>
<td>31 (11)</td>
<td>1.31 (0.70–2.44)</td>
</tr>
<tr>
<td>4400–13850</td>
<td>28 (12)</td>
<td>42 (14)</td>
<td>0.86 (0.48–1.51)</td>
<td>35 (15)</td>
<td>43 (15)</td>
<td>1.26 (0.73–2.18)</td>
</tr>
<tr>
<td>≥13850</td>
<td>29 (13)</td>
<td>39 (13)</td>
<td>1.06 (0.60–1.90)</td>
<td>31 (14)</td>
<td>38 (13)</td>
<td>1.30 (0.70–2.41)</td>
</tr>
</tbody>
</table>

*Participants reporting that they held the phone on both sides, or changed side of use between first regular use and start of the induction period are considered exposed on both sides except if the participant changed side because of hearing loss within 5 years before reference date. In that case, only the side prior to the change is considered exposed. Controls are assigned the same tumor laterality as their matched case. Participants that were exposed only on the contralateral side were not included in the ipsilateral analyses and the other way around for participants exposed only on the ipsilateral side.

Ipsilateral use: holding the phone on the same side as the tumor or on both sides.

Contralateral use: holding the phone on the opposite side as the tumor or on both sides.

Frequencies only include participants in complete matched strata, i.e. including one case and at least one control with information about exposure. Information about the laterality of mobile phone use was missing for 2 cases and 7 controls.

Reference category: never regular users of mobile phones.

Regular use: ever used a mobile phone on average ≥1 call/week for ≥6 months.

Cut points approximately at the 25th, 50th and 75th percentiles.
Changes of preferred side of mobile phone use were much more common among cases than controls; the proportion of cases that reported having changed their preferred side of use was 52% compared to 8% among controls. The most common reason for changing side of use was hearing loss, reported by 91% of the cases and 27% of the controls, followed by practical reasons, reported by 6% of the cases and 40% of the controls (Table 5).

Table 5. Reasons for changing side of mobile phone use among regular user cases and controls. All changes up to questionnaire date are included.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Cases No. (%)</th>
<th>Controls No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>169</td>
<td>40</td>
</tr>
<tr>
<td>Practical reason</td>
<td>6 (4)</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Hearing problem</td>
<td>154 (91)</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (1)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Other/No particular reason</td>
<td>9 (5)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>No reason entered</td>
<td>1 (1)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

*Numbers do not add up because four participants gave two reasons for changing side.

As might be expected considering the frequent hearing dependent side changes among the cases, laterality specific odds ratios were strongly influenced by the point in time for which the laterality of mobile phone use was determined. Figure 6 shows how the odds ratios for ipsilateral and contralateral regular use of mobile phones varies depending on the time point for which the laterality is determined; at interview, at reference date, one year before, five years before, and ten years before the reference date.
4.2.3 Cordless phones and acoustic neuroma

Regular use of cordless phones was associated with acoustic neuroma (OR = 1.41, 95% CI: 1.07–1.86). As was the case with mobile phone use, the risk estimate was higher for intermediate term use (5-9 years) (OR = 1.72, 95% CI: 1.21–2.45) than for long term use (≥10 years) (OR = 1.22, 95% CI: 0.82–1.80). Figure 7 shows the associations with time since first use of cordless phones (association with regular use displayed for comparison).
Also resembling the patterns seen for mobile phone use, the odds ratio in the highest quartile of lifetime cumulative duration of cordless phone calls was increased (OR = 1.67, 95% CI: 1.13–2.49), while only a modest increase of the odds ratio (with wide confidence intervals) was seen in the highest quartile of cumulative number of calls (OR = 1.32, 95% CI: 0.89–1.95). The figures 8 and 9 show the associations with cumulative duration and cumulative calls, respectively.

As for mobile phones, odds ratios were higher when including only non-histologically confirmed cases and their controls in the analyses. The pattern was observed for all exposure indices of cordless phones. Table 6 shows odds ratios for different indices of cordless phone use for strata with histologically confirmed cases and non-histologically confirmed cases separately.

![Figure 8](image1.png)

**Figure 8.** Odds ratios with 95% confidence intervals for the association between lifetime cumulative duration of cordless phone calls and acoustic neuroma, cut points chosen approximately at the quartiles of the controls distribution.

![Figure 9](image2.png)

**Figure 9.** Odds ratios with 95% confidence intervals for the association between lifetime cumulative number of cordless phone calls and acoustic neuroma, cut points chosen approximately at the quartiles of the controls distribution.
Table 6. Odds ratios for acoustic neuroma according to different characteristics of cordless phone use stratified on histological confirmation of the tumor

<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>Cases histologically confirmed</th>
<th>Cases not histologically confirmed</th>
<th>P_{(diff)}^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%); OR (95% CI)</td>
<td>No. (%); OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or rarely^b</td>
<td>62 (31); 104 (35) 1.00</td>
<td>62 (29); 128 (38) 1.00</td>
<td>0.397</td>
</tr>
<tr>
<td>Regular use^c</td>
<td>138 (69); 190 (65) 1.24 (0.83–1.86)</td>
<td>155 (71); 213 (62) 1.58 (1.07–2.33)</td>
<td>0.398</td>
</tr>
<tr>
<td>Time since first regular use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>47 (24); 78 (27) 1.04 (0.63–1.71)</td>
<td>63 (29); 87 (26) 1.56 (0.98–2.48)</td>
<td>0.289</td>
</tr>
<tr>
<td>5–9 years</td>
<td>64 (32); 60 (20) 1.80 (1.09–2.99)</td>
<td>53 (24); 69 (20) 1.63 (1.00–2.66)</td>
<td>0.245</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>27 (14); 52 (18) 0.90 (0.50–1.62)</td>
<td>39 (18); 57 (17) 1.55 (0.91–2.65)</td>
<td>0.176</td>
</tr>
<tr>
<td>Cumulative hours of use^d,e</td>
<td></td>
<td></td>
<td>0.391</td>
</tr>
<tr>
<td>&lt; 38 h</td>
<td>30 (15); 41 (15) 1.20 (0.67–2.15)</td>
<td>34 (16); 55 (17) 1.26 (0.73–2.17)</td>
<td>0.910</td>
</tr>
<tr>
<td>38–189 h</td>
<td>31 (16); 41 (15) 1.29 (0.70–2.38)</td>
<td>33 (16); 54 (16) 1.30 (0.76–2.23)</td>
<td>0.977</td>
</tr>
<tr>
<td>190–679 h</td>
<td>28 (14); 50 (18) 0.97 (0.55–1.70)</td>
<td>42 (20); 47 (14) 2.05 (1.18–3.58)</td>
<td>0.062</td>
</tr>
<tr>
<td>≥ 680 h</td>
<td>44 (23); 49 (17) 1.52 (0.87–2.66)</td>
<td>40 (19); 48 (15) 1.86 (1.05–3.28)</td>
<td>0.621</td>
</tr>
<tr>
<td>Cumulative no. of calls^d,e</td>
<td></td>
<td></td>
<td>0.817</td>
</tr>
<tr>
<td>&lt; 1100</td>
<td>26 (13); 48 (17) 0.88 (0.48–1.58)</td>
<td>30 (14); 50 (15) 1.27 (0.72–2.22)</td>
<td>0.373</td>
</tr>
<tr>
<td>1100–4400</td>
<td>24 (12); 40 (14) 1.08 (0.58–2.00)</td>
<td>32 (15); 57 (17) 1.15 (0.67–1.99)</td>
<td>0.875</td>
</tr>
<tr>
<td>4400–13850</td>
<td>51 (26); 47 (16) 1.75 (1.05–2.94)</td>
<td>52 (24); 50 (15) 2.50 (1.47–4.24)</td>
<td>0.349</td>
</tr>
<tr>
<td>≥ 13850</td>
<td>32 (16); 48 (17) 1.11 (0.63–1.95)</td>
<td>36 (17); 49 (15) 1.56 (0.90–2.70)</td>
<td>0.397</td>
</tr>
</tbody>
</table>

^aTwo sided P-Values for heterogeneity: likelihood ratio tests were used for testing heterogeneity of effects for each exposure characteristic and Wald tests for different levels of exposure.

^bReference category

^cRegular use: ever used a mobile phone on average ≥1 call/week for ≥6 months.

^dThe total number of exposed does not add up because some regular users entered incomplete data on amount of phone use.

^eCut points approximately at the 25th, 50th and 75th percentiles.

4.3 VALIDATION OF SELF-REPORTED MOBILE PHONE HISTORY (STUDY II)

Successful linkage of subscriptions to match self-reported and operator recorded start year could be performed for 96 cases and 111 controls, representing 29% (n=326) and 22% (n=505) of the regular mobile phone users among cases and controls, respectively. The difference in proportions between cases and controls is statistically significant. The cases did more often than controls give permission to contact network operators (87% compared to 77%) and fill out the mobile phone calendar (97% compared to 93%). Furthermore, the cases who filled out the mobile phone calendar also reported information such as network operator and phone numbers of their subscriptions more completely. The larger proportion of successfully matched start years among cases reflects these differences.
The agreement between time since first use calculated with self-reported and operator recorded data was moderate. The concordance between self-reported and operator recorded data categorized in < 5 year, 5–9 years, and ≥ 10 years since first use was 63% and the Cohen’s kappa statistic 0.42 (95% CI 0.32 - 0.52). Table 7 shows a cross tabulation of the data. Noticeable, 55% of the participants falls in the intermediate term (5–9 years) category of time since first use when determined with operator data, while only 44% self-report themselves in that category. This net flow was seen for both cases and controls although somewhat more pronounced among the controls. The proportions of controls classified in the intermediate term category by operator data and self-reported data were 56% and 41%, respectively; the corresponding proportions among the cases were 54% and 48%.

Table 7. Cross tabulation of self-reported by operator recorded time since first regular mobile phone use

<table>
<thead>
<tr>
<th>Self-reported data</th>
<th>Operator data</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5 years</td>
<td>5–9 years</td>
<td>≥ 10 years</td>
<td>Total</td>
<td>%</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>33</td>
<td>23</td>
<td>2</td>
<td>58</td>
<td>28%</td>
</tr>
<tr>
<td>5–9 years</td>
<td>11</td>
<td>70</td>
<td>10</td>
<td>91</td>
<td>44%</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>9</td>
<td>21</td>
<td>28</td>
<td>58</td>
<td>28%</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>114</td>
<td>40</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>26%</td>
<td>55%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cohen’s kappa coefficient: 0.42 (95% CI 0.32 - 0.52)
Concordance: 131/207 = 63%

The systematic difference between self-reported and operator recorded start year was small; the average difference between self-reported and operator recorded start year was −0.62, 95% CI: −1.42, 0.17 among cases and −0.71, 95% CI: −1.50, 0.07 among controls. The non-systematic errors, however, were substantial; standard deviation of the error expressed as the difference between self-reported and operator recorded start year was 3.92 (95% CI: 3.43–4.57) years for the cases and 4.17 (95% CI: 3.68–4.80) years for the controls. Median and interquartile range of the error were 0, −2 to 2 for cases and 0, −3 to 1 for the controls. No significant differences between cases and controls were detected. There were no obvious differences in results when looking at information linked by personal identification number or subscription phone number.

Variation in self-reported data explained about 20% of the variation in operator data in a linear regression model. The least square regression line differed considerably from the identity line, which represents how data is used in exposure assessment. Figure 10 shows a scatter plot of operator recorded against self-reported start of mobile phone use. The correlation was slightly higher among cases ($R^2 = 0.22$) compared to controls ($R^2 = 0.18$), but the difference was not statistically significant.
The error, expressed as the difference between self-reported and operator recorded start year, was strongly correlated to self-reported start year but not to the operator recorded; Pearson’s correlation coefficients 0.785 and -0.208, respectively.

Figure 10. Operator start plotted against self-reported start year. The solid and dashed lines depict the least squares line and the identity line, respectively. The least squares regression coefficient $\beta = 0.28$. The squared Pearson correlation coefficient $R^2 = 0.20$.

4.4 NOISE EXPOSURE AND ACOUSTIC NEUROMA (STUDY III)

No associations were found between acoustic neuroma and occupational exposure to loud noise for any of the exposure indices used. The odds ratios for the associations with job-exposure derived exposure to noise levels $\geq 85$ dB without hearing protection were 1.02 (95% CI: 0.58–1.82), 0.69 (95% CI: 0.32–1.47), 0.39 (95% CI: 0.13–1.16), and 0.12 (95% CI: 0.01–1.02) for ever exposure, and at least 5, 10 and 15 years of exposure, respectively. The odds ratio for self-reported workplace noise exposure without hearing protection was 1.09 (95% CI: 0.79–1.49).

Associations were found between leisure time noise and acoustic neuroma. The odds ratio for the association with leisure time noise exposure without hearing protection was 1.47 (95% CI: 1.06–2.03). Figure 11 shows odds ratios and 95% confidence intervals for the association between leisure noise and acoustic neuroma. An
exposure-response gradient was observed for the association with lifetime cumulative number of leisure noise exposures with an odds ratio of 1.82 (95% CI: 1.19–2.76) in the highest tertile (≥ 870 exposures) (Figure 12).

We found a stronger association with leisure time noise for women than for men, odds ratios for exposure without hearing protection were 1.74 (95% CI: 1.07–2.81) and 1.23 (95% CI: 0.78–1.93), respectively. Odds ratios in the highest tertile of cumulative number of leisure exposures without hearing protection was 2.68 (95% CI: 1.34–5.37) for women and 1.32 (95% CI: 0.76–2.27) for men.

**Figure 11.** Odds ratios with 95% confidence intervals for the association between acoustic neuroma and exposure to leisure time noise in the categories with hearing protection, without protection and mixed use of protection.

**Figure 12.** Odds ratios with 95% confidence intervals for the association between lifetime cumulative number of leisure time noise exposures without hearing protection and acoustic neuroma, cut points chosen approximately at the tertiles of the controls distribution.
4.5 OCCUPATIONAL EXPOSURE AND ACOUSTIC NEUROMA (STUDY IV)

An occupational history starting before the 5-year induction period was reported by 426 (94%) cases and 640 (90%) controls, leaving 371 cases and 553 controls in complete matched strata that worked before the induction period. Associations were found between acoustic neuroma and job-exposure matrix derived ever exposure to benzene, diesel engine exhaust, gasoline, methylene chloride, and toluene. Table 8 shows associations between acoustic neuroma and job-exposure matrix derived exposure to the evaluated agents. The exposure response pattern seen for toluene was not suggestive of an effect. The association was seen for low rather than for high exposure levels. Table 9 and 10 show the associations with lifetime cumulative exposure, and probability and duration of exposure to selected agents. The association with asbestos reported in an earlier study could not be corroborated in this study (Table 9 and 10).

Table 8. Odds ratios for the associations between acoustic neuroma and JEM derived ever exposure to different occupational agents

<table>
<thead>
<tr>
<th>Exposure agent</th>
<th>Cases (n=365)</th>
<th>Controls (n=542)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal dust</td>
<td>10 (3)</td>
<td>19 (4)</td>
<td>0.75 (0.34–1.66)</td>
</tr>
<tr>
<td>Asbestos</td>
<td>78 (21)</td>
<td>104 (19)</td>
<td>1.18 (0.80–1.75)</td>
</tr>
<tr>
<td>Benzene</td>
<td>46 (13)</td>
<td>49 (9)</td>
<td>1.63 (1.03–2.59)</td>
</tr>
<tr>
<td>Benzo[A]pyrene</td>
<td>56 (15)</td>
<td>71 (13)</td>
<td>1.34 (0.88–2.04)</td>
</tr>
<tr>
<td>Bitumen fumes</td>
<td>6 (2)</td>
<td>8 (1)</td>
<td>1.15 (0.38–3.43)</td>
</tr>
<tr>
<td>Chromium</td>
<td>64 (18)</td>
<td>100 (18)</td>
<td>0.99 (0.67–1.46)</td>
</tr>
<tr>
<td>Diesel engine exhaust</td>
<td>81 (22)</td>
<td>82 (15)</td>
<td>1.89 (1.28–2.79)</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>41 (11)</td>
<td>67 (12)</td>
<td>0.83 (0.52–1.31)</td>
</tr>
<tr>
<td>Gasoline</td>
<td>36 (10)</td>
<td>31 (6)</td>
<td>2.09 (1.21–3.62)</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>1 (0)</td>
<td>3 (1)</td>
<td>0.48 (0.05–4.75)</td>
</tr>
<tr>
<td>Iron</td>
<td>60 (16)</td>
<td>86 (16)</td>
<td>1.12 (0.75–1.65)</td>
</tr>
<tr>
<td>Lead</td>
<td>83 (23)</td>
<td>120 (22)</td>
<td>1.06 (0.73–1.53)</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>45 (12)</td>
<td>49 (9)</td>
<td>1.58 (0.97–2.58)</td>
</tr>
<tr>
<td>Nickel</td>
<td>60 (16)</td>
<td>89 (16)</td>
<td>1.07 (0.72–1.58)</td>
</tr>
<tr>
<td>Perchloroethylene</td>
<td>16 (4)</td>
<td>18 (3)</td>
<td>1.35 (0.64–2.86)</td>
</tr>
<tr>
<td>Quartz dust</td>
<td>25 (7)</td>
<td>34 (6)</td>
<td>0.96 (0.53–1.74)</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>7 (2)</td>
<td>8 (1)</td>
<td>1.17 (0.41–3.35)</td>
</tr>
<tr>
<td>Toluene</td>
<td>46 (13)</td>
<td>47 (9)</td>
<td>1.68 (1.03–2.74)</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>63 (17)</td>
<td>82 (15)</td>
<td>1.22 (0.82–1.82)</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>37 (10)</td>
<td>60 (11)</td>
<td>0.88 (0.55–1.42)</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>60 (16)</td>
<td>86 (16)</td>
<td>1.12 (0.75–1.65)</td>
</tr>
<tr>
<td>Wood dust</td>
<td>22 (6)</td>
<td>28 (5)</td>
<td>1.08 (0.59–2.00)</td>
</tr>
</tbody>
</table>

aOdds ratios from conditional regression models matched on age, sex and residential area and adjusted for smoking and education, 5 years latency; the reference category includes people working, but not exposed to the specific agent, before the 5-year latency period.

bMore than 5% probability of exposure before the 5-year latency period.
Table 9. Odds ratios\(^a\) for the associations between acoustic neuroma and JEM derived exposure to selected agents, by ever exposure\(^b\) and cumulative exposure\(^c\)

<table>
<thead>
<tr>
<th>Exposure agent</th>
<th>Cases (n=365)</th>
<th>Controls (n=542)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed No. (%)</td>
<td>Exposed No. (%)</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>78 (21)</td>
<td>104 (19)</td>
<td>1.18 (0.80–1.75)</td>
</tr>
<tr>
<td>Low</td>
<td>49 (13)</td>
<td>49 (9)</td>
<td>1.52 (0.96–2.42)</td>
</tr>
<tr>
<td>High</td>
<td>29 (8)</td>
<td>55 (10)</td>
<td>0.82 (0.47–1.41)</td>
</tr>
<tr>
<td>Benzene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>46 (13)</td>
<td>49 (9)</td>
<td>1.63 (1.03–2.59)</td>
</tr>
<tr>
<td>Low</td>
<td>22 (6)</td>
<td>24 (4)</td>
<td>1.62 (0.85–3.11)</td>
</tr>
<tr>
<td>High</td>
<td>24 (7)</td>
<td>25 (5)</td>
<td>1.64 (0.88–3.05)</td>
</tr>
<tr>
<td>Diesel engine exhaust</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>81 (22)</td>
<td>82 (15)</td>
<td>1.89 (1.28–2.79)</td>
</tr>
<tr>
<td>Low</td>
<td>40 (11)</td>
<td>41 (8)</td>
<td>1.83 (1.10–3.07)</td>
</tr>
<tr>
<td>High</td>
<td>41 (11)</td>
<td>41 (8)</td>
<td>1.95 (1.16–3.28)</td>
</tr>
<tr>
<td>Gasoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>36 (10)</td>
<td>31 (6)</td>
<td>2.09 (1.21–3.62)</td>
</tr>
<tr>
<td>Low</td>
<td>18 (5)</td>
<td>15 (3)</td>
<td>2.04 (0.93–4.49)</td>
</tr>
<tr>
<td>High</td>
<td>18 (5)</td>
<td>16 (3)</td>
<td>2.14 (1.03–4.46)</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>45 (12)</td>
<td>49 (9)</td>
<td>1.58 (0.97–2.58)</td>
</tr>
<tr>
<td>Low</td>
<td>24 (7)</td>
<td>24 (4)</td>
<td>1.61 (0.83–3.11)</td>
</tr>
<tr>
<td>High</td>
<td>21 (6)</td>
<td>25 (5)</td>
<td>1.56 (0.80–3.01)</td>
</tr>
<tr>
<td>Toluene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever exposure</td>
<td>46 (13)</td>
<td>47 (9)</td>
<td>1.68 (1.03–2.74)</td>
</tr>
<tr>
<td>Low</td>
<td>32 (9)</td>
<td>24 (4)</td>
<td>2.22 (1.23–4.00)</td>
</tr>
<tr>
<td>High</td>
<td>14 (4)</td>
<td>23 (4)</td>
<td>1.05 (0.50–2.20)</td>
</tr>
</tbody>
</table>

\(^a\)Odds ratios from conditional regression models matched on age, sex and residential area and adjusted for smoking and education, 5 years latency

\(^b\)More than 5% probability of exposure before the 5-year latency period

\(^c\)The sum over probability×level×years of exposure for each occupation, cut points at the 50\(^{th}\) percentiles of the controls distributions

There was also covariation between the agents associated with acoustic neuroma. The agents benzene, diesel engine exhaust, gasoline, and methylene chloride were common exposures in the occupational group of “machinery fitters, assemblers and mechanics” (occupational code 751 according to the Nordic occupational classification of 1978\(^65\) [NYK 78]). Ever holding a job under this occupational title before the induction period was associated with an odds ratio of 2.20 (95% CI: 1.24–3.8), based on 34 exposed cases and 28 controls. A sensitivity analyses showed that odds ratios were increased for all indices of diesel exhaust exposure also after excluding this group, while the power was limited in the corresponding analyses of benzene, gasoline and methylene chloride.

No associations were found with self-reported workplace exposures.

Results from sensitivity analyses performed with a 10-years induction period differed only marginally from our a priori decided analyses with a 5-year induction period.
Table 10. Odds ratios\textsuperscript{a} for the associations between acoustic neuroma and JEM derived exposure to selected agents, by duration and probability\textsuperscript{b} (P) of exposure

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Ever exposed\textsuperscript{c}</th>
<th>Exposure duration 1-9 years\textsuperscript{d}</th>
<th>Exposure duration ≥ 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=365)</td>
<td>Controls (n=542)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Asbestos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>27 (7)</td>
<td>21 (4)</td>
<td>1.88 (1.01–3.51)</td>
</tr>
<tr>
<td>25% ≤ P &lt; 50%</td>
<td>18 (5)</td>
<td>31 (6)</td>
<td>0.91 (0.46–1.80)</td>
</tr>
<tr>
<td>P ≥ 50%</td>
<td>33 (9)</td>
<td>52 (10)</td>
<td>0.99 (0.59–1.68)</td>
</tr>
<tr>
<td>Benzene\textsuperscript{e}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>46 (13)</td>
<td>49 (9)</td>
<td>1.63 (1.03–2.59)</td>
</tr>
<tr>
<td>Diesel engine exhaust</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>45 (12)</td>
<td>40 (7)</td>
<td>2.16 (1.31–3.57)</td>
</tr>
<tr>
<td>25% ≤ P &lt; 50%</td>
<td>24 (7)</td>
<td>29 (5)</td>
<td>1.63 (0.88–3.01)</td>
</tr>
<tr>
<td>P ≥ 50%</td>
<td>12 (3)</td>
<td>13 (2)</td>
<td>1.64 (0.70–3.84)</td>
</tr>
<tr>
<td>Gasoline\textsuperscript{e}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>36 (10)</td>
<td>31 (6)</td>
<td>2.09 (1.21–3.62)</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>45 (12)</td>
<td>49 (9)</td>
<td>1.58 (0.97–2.58)</td>
</tr>
<tr>
<td>Toluene\textsuperscript{e}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% ≤ P &lt; 25%</td>
<td>36 (10)</td>
<td>31 (6)</td>
<td>2.09 (1.20–3.63)</td>
</tr>
<tr>
<td>P ≥ 25%</td>
<td>10 (3)</td>
<td>16 (3)</td>
<td>0.92 (0.39–2.15)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Odds ratios from conditional regression models matched on age, sex and residential area, adjusted for smoking and education, 5-year latency

\textsuperscript{b}Probability of workplace exposure to the agent

\textsuperscript{c}At least one year in a workplace with the indicated probability of exposure at least 5 years prior to the reference date.

\textsuperscript{d}Participants was categorized according to their highest probability of exposure, and may have additional years with lower probability of exposure

\textsuperscript{e}Notes about categorization. Benzene: Analyses includes two cases and one control with exposure probabilities above 25%; Gasoline: Analyses includes one case and one control with exposure probabilities above 50%; Toluene: Categories 25% ≤ P < 50% and P ≥ 50% are collapsed due to few observations.
5 DISCUSSION

5.1 MAIN FINDINGS

5.1.1 Mobile and cordless phones and acoustic neuroma (Study I)

We did not find evidence of an association between mobile phone use and acoustic neuroma risk. The odds ratios were close to unity for long-term use, regular use, and ipsilateral use of mobile phones. Non-significantly elevated odds ratios were found for the highest quartile of lifetime cumulative duration of calls, but no corresponding increase was seen for cumulative number of calls; the odds ratios for the first and fourth quartile of cumulative number of calls were basically the same. Odds ratios were consistently lower when restricting the analyses to histologically confirmed cases. We found strong indications of reversed causality in the laterality analyses. Laterality specific odds ratios that reflected the preferred side of use at different points in time showed strong protective effects for ipsilateral use and increased risks for contralateral use when using laterality information close to or after diagnosis, while the difference between odds ratios for ipsilateral and contralateral use almost disappeared when information about laterality 5 or 10 years before the reference date was used.

An association was seen between acoustic neuroma and regular use of cordless phones, but without consistent exposure-response pattern according to time since first use; the odds ratio for long-term use was not increased, and lower than the odds ratios for short and intermediate term use. An increased risk estimate was observed in the highest quartile of cumulative hours of cordless phone use but not for cumulative number of calls. Also for cordless phone use the odds ratios were consistently lower when restricting the analyses to histologically confirmed cases.

5.1.2 Validation of self-reported mobile phone use (Study II)

A lower proportion of controls than cases could be included in the validation of self-reported start year, reflecting a more thorough reporting among cases of details about past mobile phone subscriptions that were needed to link self-reported information to operator recorded data. The random errors in self-reported start year when compared to operator recorded data were considerable, while the systematic errors were modest. Kappa statistics showed a fair to moderate agreement between self-reported and operator recorded time since first mobile phone use when categorized into < 5, 5–9 and ≥10 years. There was a strong correlation between the error and self-reported start year but not between the error and operator recorded start year. Unfortunately we were able to match only a very limited number of questionnaire answers about duration and number of calls to operator data. The proportion of answers that could be validated was judged too small for valid results, and further analysis was not undertaken.
5.1.3 Noise and acoustic neuroma (Study III)

No association was found between acoustic neuroma and occupational exposure to loud noise; either for job-exposure matrix derived or self-reported exposure. For leisure time loud noise, an association was seen with participation in loud noise leisure activities without hearing protection, and a positive exposure-response gradient was observed for the lifetime cumulative number of such exposures. The association with leisure time noise exposure was considerably stronger for women than for men.

5.1.4 Workplace chemical exposure and acoustic neuroma (Study IV)

Associations were found between acoustic neuroma and job-exposure matrix derived exposure to benzene, diesel engine exhaust, gasoline, and methylene chloride. There was considerable covariation between these exposures, which were all common exposures in the occupational group “machinery fitters, assemblers and mechanics”, a group for which a more than doubled risk of acoustic neuroma was found.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Validation of self-reported start year (Study II)

A relatively small proportion of the participants’ answers about mobile phone start year could be validated, partly because some participants did not allow operator contact and because only two of the four major network operators that had been active on the Swedish market were able to provide data to the study, but also because many participants failed to provide enough information about their past mobile phone subscriptions to enable linkage with operator data. Correct information regarding details like network operator, subscription ownership and phone number is needed to make a reliable linkage between self-reported subscriptions and subscriptions found in the operators’ records. The probability of having the self-reported information validated is thus dependent on the participant’s ability to recall this information. A selection of good reporters is therefore likely, which would reduce the level of error observed in the validated group compared to the whole population of respondents. Because the cases were more thorough in reporting details about old subscriptions, a larger proportion of among them could be validated than among the controls. Another potential source of bias is possible erroneous linking of subscriptions, which would on average increase the observed errors.

5.2.2 Misclassification of disease (Study I, III and IV)

5.2.2.1 Clinical diagnosis of acoustic neuroma

Acoustic neuromas constitute about 80% of the cerebellopontine angle tumors. Other common tumors of the cerebellopontine angle are meningiomas and epidermoid
tumors, comprising about 10% and 6% of cerebellopontine angle tumors, respectively.\textsuperscript{67} Although an acoustic neuroma diagnosis based on magnetic resonance imaging techniques is considered very accurate,\textsuperscript{68} differential diagnosis may on occasion be difficult.\textsuperscript{67, 69} However, the proportion of non-acoustic neuroma lesions that may be present among the 53% of the cases with non-histologically confirmed tumors is expected to be very low, and cannot be considered a potential source of bias in this study.

5.2.2.2 Detection bias

A larger problem occurs if detection of the tumor is dependent on the exposure status. The majority of small acoustic neuromas do not grow after clinical diagnosis,\textsuperscript{1} meaning that many acoustic neuromas only grow for a limited period. For people who experience more subtle symptoms from the tumor, it cannot be excluded that tumor detection is dependent on variables such as age, socioeconomy, health care seeking behavior, or general health awareness. Expectations of health may also be important. For example, a history of loud noise exposure, especially in combination with older age, may give people an explanation for a progressive unilateral hearing loss and keep them from seeking care. On the other hand occupationally exposed could also be more inclined to get a medical examination as they may be entitled to an economic compensation for the hearing disability, and they may be subject to routine screening programs.

In the present study we noticed that odds ratios for the associations between acoustic neuroma and use of mobile and cordless phones were consistently higher for non-histologically confirmed cases and their matched controls than for histologically confirmed cases and their controls. The difference could be a result of random variation, but since the pattern is consistent over all exposure indices for both cordless and mobile phones we propose that mobile and cordless phone use may draw attention to a unilateral hearing loss and thus increase the possibility of tumor detection. Mobile and cordless phones may, because of their wireless features, more often than traditional fixed phones be used in noisy environments and in situations where changing ear may be difficult e.g. when carrying things. All cases with a histological confirmation have gone through surgical removal of the tumor, while the non-histologically confirmed cases either were managed with observation with serial MRI scanning or treated with stereotactic radiotherapy. The two latter groups on average have smaller tumors and a larger proportion of non-growing tumors. They may be expected to have less severe symptoms than the histologically confirmed group and differential detection of the tumor may be more likely.

5.2.3 Misclassification of exposure (Study I, III and IV)

Misclassification of exposure is probably the largest source of bias in the assessment of the associations between acoustic neuroma and the studied exposures.
If true associations between the exposure and the outcome exist, non-differential misclassification, that is, when the probability of misclassification is independent of case-control status, will on average dilute observed associations for analyses with dichotomous exposure categories. Exceptions exist, if the measurement error correlates with the true value spurious associations can occur even if the misclassification is non-differential. For polytomous exposures, dilution is expected between the extreme categories, e.g. the highest exposure level and unexposed, while the effect on intermediate categories may be less predictable, and exposure response patterns may be distorted. The estimates for the intermediate exposure categories may even be biased away from null.

Differential misclassification, i.e. when disease status affects the probability of misclassification, may result in spurious associations even in the absence of true associations between exposure and outcome.

Misclassification of exposure also occurs when exposure is accounted for after the onset of disease or if failing to account for exposure in the etiologically relevant time period. Given that the cases and controls are matched on reference date, the misclassification should be non-differential, but could dilute true associations. We used a 1-year latency period in the assessment of mobile and cordless phone use, mainly for reasons of comparability to earlier studies. A 5-year latency period was used in the assessment of exposure to noise and chemicals, because we consider this to be a more realistic time frame for initiation, growth and detection of this slow growing tumor.

5.2.3.1 Misclassification of mobile and cordless phone use (Study I)

Validation studies, including the validation study presented in this thesis, show large random errors in self-reported exposure information about mobile phone use. The only previous study of adult cases’ and controls’ ability to recall past mobile phone use observed a tendency among cases to increasingly overestimate number and duration of calls the further back in time they recalled, a tendency that was not observed among controls. Recall bias was also indicated in the INTERPHONE analysis of both acoustic neuroma and glioma. Implausible values of calling time were reported and elevated odds ratios was observed in the highest decile ($\geq 1640$ h) of cumulative calling time together with decreased odds ratios in the 4th to 9th deciles. Our study (study II) showed large random errors when self-reported start years were compared with operator recorded start years, and moderate agreement between self-reported and operator derived time since first use categorized into $< 5$, 5–9, and $\geq 10$ years. We observed no evidence of differential recall of mobile phone start year, but tendencies of more accurate reporting among cases than controls. Validating self-reported data with operator information requires that the participant remembers details about old subscriptions. Therefore a selection of good reporters into the validation is likely to have occurred, and recall may still have been differential among the non-validated participants.
Substantial non-differential recall errors in the reporting of past mobile phone use may have diluted associations between mobile phone use and acoustic neuroma if they existed, but it is also possible that spurious associations may have been created by recall bias.

Recall of past use of cordless phones has never been addressed, but there is reason to assume that large non-differential recall errors and risk of recall bias may be present here as well.

5.2.3.2 Misclassification of noise exposure (Study III)

Self-reported exposure to occupational and leisure time noise may be subject to both non-differential and differential reporting errors. Cases may try harder to recall past exposures than controls. Three previous studies have reported associations with self-reported noise exposure data, \(^{55-57}\) while the only study with prospectively collected exposure data failed to find an association between occupational noise and acoustic neuroma.\(^{58}\) One possible explanation for this discrepancy is recall bias in the studies with self-reported noise exposure data. In our study, no association was found with self-reported occupational noise, but with self-reported leisure noise. It cannot be excluded that differential recall has been present in the assessment of leisure but not occupational noise.

When job-exposure matrices are used non-differential misclassification is inevitable because of the ecological approach where people with different work tasks at different workplaces are grouped together under the same occupational titles and assigned an estimated average exposure. Non-differential exposure misclassification may dilute observed associations and increase the risk of making type II errors.

5.2.3.3 Misclassification of workplace chemical exposure (Study IV)

Both a job-exposure matrix and self-reported workplace exposure to chemical agents and work tasks were employed in the assessment of workplace chemical exposure. Non-differential misclassification is expected in job-exposure matrix derived exposure information, while the self-reported exposure data may be suspected to be sensitive to recall bias. However, the self-reported exposures showed no associations with acoustic neuroma.

5.2.4 Confounding (Study I, III and IV)

Although acoustic neuroma have been associated with both smoking\(^{25-27}\) and socio-economic factors,\(^{28,29}\) adjusting for smoking and education generally had little impact on the odds ratios, also in the analyses of occupational exposure where confounding could have been expected. However, there are data implying that confounding seldom is a problem in occupational studies even if the occupational
setting appears to be perfect for this bias to occur.\textsuperscript{71} To control for factors related to employment, only people who had ever worked before the induction period were included in the analyses of occupational exposure to noise and chemicals. Ionizing radiation, the only certain risk factor of acoustic neuroma, is unlikely to be associated to any of the exposures studied. Confounding between different chemical workplace exposures was on the other hand very likely as we observed covariation between all of the agents associated with acoustic neuroma risk. However, adjusting these exposures for each other in a regression model was not feasible as the groups for which the exposures did not overlap were too small. Associations between workplace exposure to noise and chemicals are likely; however no associations were found for occupational exposure to noise.

\textbf{5.2.5 Selection bias (Study I, III and IV)}

Selection bias occurs if the probability of participation is related to both exposure and case-control status. Participation rates were higher among regular mobile phone users among both cases and controls in the INTERPHONE study, but the participation was higher among cases than controls, leading to an estimated 10\% decrease of the odds ratios.\textsuperscript{74} The result of our non-participant survey does not indicate any difference concerning regular mobile phone use between participating controls (70\%) and non-participating controls (67\%). The data on non-participant cases were too limited and could not provide any information about any difference in regular mobile phone use between participant and non-participant cases. If regular mobile phone use were less common among non-participant than participant cases a selection of exposed cases would result and the effect on the estimates would be an upward bias. However, given the large participation among the cases, differential participation between mobile phone users and non-mobile phone users would have limited effect on the estimates.

Participation in an earlier Swedish case-control study on mobile phone use and brain tumor was shown to be associated with income, education, and non-manual employment,\textsuperscript{75} which can be assumed to be inversely associated with workplace exposure to noise and chemicals. Given the lower participation among controls this would bias odds ratios upwards. However, adjusting for education should limit this bias. The effect of adjusting for education and smoking was very modest in our studies, which indicates small effects from selection on these variables. Furthermore, we did not observe any general increase of odds ratios for exposures typical for non-manual employment.

Leisure time noise was associated with educational level in our study and a selection of leisure noise exposed participants may have occurred. Given the higher participation rates among cases, this could have led to an underestimation of the odds ratios, but also here the effect of adjusting for education was very modest.
5.3 RESULTS IN RELATION TO PREVIOUS RESEARCH

5.3.1 Mobile and cordless phones (Study I)

5.3.1.1 Comparison with previous epidemiological studies

Our results are largely similar to the results of the INTERPHONE study,\textsuperscript{35} a large multicenter case-control study that included 1105 acoustic neuroma cases, and the two cohort studies conducted,\textsuperscript{37-39} while it differs from the results of the case-control studies conducted in Sweden by Hardell and colleagues.\textsuperscript{36, 44, 45}

The INTERPHONE case-control study,\textsuperscript{35} which is the largest study conducted on mobile phones and acoustic neuroma risk so far, found an odds ratio of 0.85 (95% CI: 0.69–1.04) for ever regular use of mobile phones and 0.76 (95% CI: 0.52–1.11) for ≥10 years of mobile phone use, which is, although slightly lower, not incompatible with the results in the present study, especially considering that effect estimates in the INTERPHONE study were likely underestimated by approximately 10% from selection bias.\textsuperscript{74} Also similar to our results, a cohort study conducted in Denmark found a relative risk of 0.87 (95% CI: 0.52–1.46) for ≥11 years mobile phone subscribers.\textsuperscript{37} A recently updated UK cohort study found strikingly similar results to ours, with a relative risk for ever use of mobile phones slightly above one (RR = 1.19, 95% CI: 0.81–1.75), a similar estimate for ≥10 years use (RR = 1.17, 95% CI: 0.60–2.27), and the highest risk estimate for 5–9 years of use (RR = 1.46 (95% CI: 0.94–2.27).\textsuperscript{39}

The international INTERPHONE analysis found an elevated odds ratio in the highest decile of cumulative calling time (OR = 1.32, 95% CI: 0.88–1.97), but decreased odds ratios in the 4\textsuperscript{th} to 9\textsuperscript{th} deciles with the lowest odds ratio in the 9\textsuperscript{th} decile (OR = 0.48, 95% CI: 0.30–0.78).\textsuperscript{35} This exposure response pattern, together with implausible reports of calling time raised concerns about recall bias. There was no corresponding increase of the odds ratio in the highest decile of cumulative number of calls (OR = 0.93, 95% CI: 0.61–1.41). This general pattern with an increase of the highest category of cumulative calling time but no corresponding increase in the highest category of cumulative number of calls resembles the results in our study. We did however ask about weekly or daily called time in predefined categories (Figure 1) and it is not possible to identify any implausible reports of called time which could have revealed possible tendencies for recall bias.

In a series of Swedish case-control studies, Hardell and colleagues reported significantly increased odds ratios for the association between acoustic neuroma and mobile phones, in particular for use of analogue mobile phones, but also for digital mobile phones. The reported pooled odds ratios for >1 year of analogue mobile phone use was 2.9 (95% CI: 2.0–4.3), and 1.5 (95% CI: 1.1–2.1) for >1 years use of the 2\textsuperscript{nd} generation of digital phones (GSM).\textsuperscript{36} Increased odds ratios were reported after short induction times. In a pooled analyses of their two first studies, the odds
ratio reported for < 5 years of analogue mobile phone use was 2.3 (95% CI: 1.2-4.1), and 1.4 (95% CI: 1.01-2.1) for digital mobile phones. Acoustic neuromas are slow growing tumors and large effects after short induction times is not what would be expected.

Both the INTERPHONE study and the Hardell studies generally found higher odds ratios for ipsilateral use than for contralateral use, while we found higher odds ratios for contralateral use. In our study, we show that cases to a high degree change preferred side of mobile phone use because of hearing loss. We found very strong protective effects for ipsilateral use when information about laterality close to or after the reference date was used (Figure 6). We even found higher odds ratios for contralateral use even when using information about laterality that reflected how the participants held the mobile phone 10 year before the reference date, indicating that many acoustic neuroma cases may already have had a beginning unilateral hearing loss when they started to use mobile phones. (We did not ask about changes of preferred side of phone use before they became regular mobile phone users.)

Only a few studies of the association between cordless phone use and acoustic neuroma are available. Hardell and colleagues have reported a 50% increased risk (OR = 1.5, 95% CI: 1.05-2.1) already after < 5 years of cordless phone use, while no association was found in the Swedish interphone study (OR = 0.7, 95% CI: 0.4–1.2).

5.3.1.2 Consistency with acoustic neuroma incidence trends

If the use of mobile phones would increase acoustic neuroma risk, this would be reflected in acoustic neuroma incidence trends because of the very large penetration of the technology in the population. Figure 13 shows the increase in mobile phone subscriptions in Sweden from 1981 to 2007 based on data available on the International Telecommunication Union’s (ITU) web page. The penetration of mobile phone technology in the Swedish population expressed as the number of mobile phone subscriptions per 100 inhabitants increased from 9 to almost 100 between 1994 and 2004. Considering the slow growth of acoustic neuroma tumors, we would expect a considerable delay in the effect on the acoustic neuroma incidence. Would an effect exist, an increased incidence of acoustic neuroma would be unlikely to noticeable in incidence trends earlier than in the beginning of the last decade. However, the number of acoustic neuroma diagnoses reported yearly to the Swedish cancer register decreased after 2000 for both men and women. In Denmark, where all acoustic neuroma patients are referred to a single tertiary referral center and cases have been prospectively registered since 1976, data show a steady increase in the incidence from around 8 per million per year between 1976 and 1983 to over 20 per million per year in the beginning of the last decade. The incidence seemed to peak in 2004 with an incidence of 23 acoustic neuromas per million population per year and then decrease to around 19 patients per million population per year in 2008. Thus, the temporality of the adoption of the mobile phone
technology by the broad masses and the increased acoustic neuroma incidence is not consistent with an effect of mobile phone use on acoustic neuroma risk.

![Mobile phone subscriptions per 100 inhabitants, Sweden 1981-2007](image)

**Figure 13.** Mobile phone subscriptions per 100 inhabitants in Sweden 1981–2007. Hand held mobile phones were introduced in Sweden 1987. Mobile phone subscriptions before 1987 all concerned larger devices such as bag phones or phones mounted in cars or boats. There is a break in the series between 2004 and 2005 due to a changed definition of active subscriptions.

### 5.3.2 Noise (Study III)

Of the previous studies, four out of five found an association between noise exposure and acoustic neuroma. Of the studies that recorded associations, three were part of the interphone case-control study and used self-reported exposure information about occupational and non-occupational noise and one study used self-reported occupational histories linked to a National Occupational Hazards Survey data base.

Preston-Martin and colleagues found an odds ratio for occupational noise exposure (men only) of 2.2 (95% CI: 1.12–4.67). Edwards et al. found odds ratios of 1.43 (95% CI: 0.96–2.13) and 1.38 (95% CI: 0.80–2.36) for exposure to occupational and non-occupational noise respectively. Schlehofer et al. found an association with persistent occupational noise (OR = 2.31, 95% CI 1.15–4.66) but not with exposure in leisure time only (OR = 0.96, 95% CI 0.35–2.63). Hours and co-workers reported an odds ratio of 2.55 (95% CI: 1.35–4.82) for self-reported ever noise exposure and 2.26 (95% CI: 1.08–4.72) and 4.95 (95% CI: 1.32–18.5) for work only and occupational only exposure respectively. A second study of Edwards et al. using a job-exposure matrix and census register data on occupation for exposure assessment reported an odds ratio of 0.89 (95% CI: 0.64–1.23) for exposure to noise.
levels of $\geq 85$ dB. While our results concerning occupational noise is comparable only with the result of the second study of Edwards et al., our results for leisure time noise are comparable with two if the interphone studies. The reasons for the discrepancy between the occupational studies using self-reported and job-exposure derived exposure information, and the difference between our results for occupational and leisure time noise, are unclear. Obvious explanations would be random variation or differences in vulnerability to recall bias. Self-reports of occupational histories or census information on a job-exposure matrix are likely to be less subjective than direct reports of occupational noise. Difference in vulnerability to recall bias would however not explain the difference between our results for self-reported occupational exposure and the results in 3 earlier studies that investigated this association. The lack of associations found between job-exposure matrix determined loud noise exposure in our study and the study of Edwards and colleagues may be due to non-differential misclassification of exposure produced by the job-exposure matrix in combination with lack of power due to low proportions of subjects exposed to high noise levels in both studies. Edwards et al reported that 14% of men and 3% of women were employed in occupations with noise levels $\geq 85$ dB, which is similar to the data from our study where 16% of men and 4% of women had been employed in an occupation with noise levels $\geq 85$ dB (the higher proportions in our study is probably explained by the fact that complete occupational histories were available in our study, while Edwards et al. used information from censuses). A similarity that may be important is that we used the same job-exposure matrix as Edwards et al. Workers in the noisiest workplaces are likely to comply with the regulations about hearing protection which will reduce the exposure. Misclassification of hearing protection is likely in our study. We only asked for the proportion of the time hearing protection was used and people that reported that they used hearing protection less than 50% of the time may still have used them selectively while doing noisy work tasks. Edwards et al. did not have any information about hearing protection. People may be more inclined to expose themselves to higher noise levels without protection in leisure settings that in occupational settings. Furthermore, our results for leisure noise implied a stronger association with acoustic neuroma for women than for men. Although such a difference is biologically unlikely, it could explain the difference between our results for occupational and leisure time noise, as a very small proportion of the women were exposed to high occupational noise levels and there would be a lack of power to detect any effect among the women.

5.3.3 Chemicals (Study IV)

Acoustic neuroma risks in relation to occupational exposure to specific agents have only been addressed in one previous study by Prochazka and colleagues who found associations for exposure to mercury $< 10$ years prior to the reference date (OR = 2.9, 95% CI: 1.2–6.8), benzene (OR = 1.8, 95% CI: 1.0–3.2), asbestos $\geq 10$ years prior to the reference date (OR = 1.2, 95% CI: 1.0–1.6) and for women, exposure to textile
dust ≥ 10 years prior to the reference date (OR = 2.0, 95% CI: 1.2–3.4). Preston-Martin and co-workers\textsuperscript{54} found an association with self-reported weekly exposure to benzene. Our study could confirm the association with job-exposure matrix determined exposure to benzene but not to asbestos. An increased risk for having worked ≥ 10 years in the occupational group “machinery fitters, assemblers and mechanics” was also reported by Prochazka et al. (OR = 1.6, 95% CI: 1.1–2.4).

5.4 EXPERIMENTAL AND MECHANISTIC DATA

5.4.1 Mobile and cordless phones

Support from cell models, animal models or mechanistic data for an association between acoustic neuroma and radiofrequency fields is lacking. The International Agency for Research on Cancer’s (IARC) recent evaluation of carcinogenicity of radiofrequency electromagnetic fields concludes that there is limited evidence from experimental animals.\textsuperscript{79} The Advisory Group on Non-ionising Radiation (AGNIR) states in a recent evaluation that no biological effect has consistently been shown in cell models for radiofrequency exposure below the guideline limits, and that results from several large scale animal studies of the initiation and development of cancer in relation to radiofrequency fields all have been robustly negative.\textsuperscript{33}

5.4.2 Noise

The hypothesis that noise exposure should cause acoustic neuroma is not derived from knowledge about biological mechanisms, but there findings that speak in favor of a possible link with growth factors expressed in response to noise trauma. Interestingly, vascular endothelial growth factor (VEGF) seems to play an important reparative role after noise induced inner ear trauma and have been shown to be expressed in cochlear and vestibular structures after noise induced trauma.\textsuperscript{80, 81} VEGF also seems to be involved in acoustic neuroma growth.\textsuperscript{82-84} In addition, Bevacizumab, a drug that inhibits angiogenesis by inhibiting VEGF can induce tumor shrinkage and improve hearing in neurofibromatosis type II patients with progressive acoustic neuromas.\textsuperscript{85}

5.4.3 Chemicals

Of the occupational chemical exposures that were associated with acoustic neuroma in our study, benzene and diesel engine exhaust are classified by the Agency for Research on Cancer (IARC) as “carcinogenic to humans” (group 1).\textsuperscript{86, 87} Gasoline and methylene chloride are classified by IARC as “possibly carcinogenic to humans” (group 2b).\textsuperscript{88, 89} Tumorigenic agents may reach the Schwann cells or satellite glial cells in the vestibulocochlear nerve through uptake in the lungs and distribution with the blood to the vestibulocochlear nerve sheet tissue. The blood-nerve barrier is more permeable than the blood-brain barrier, especially in the peripheral nerve ganglia,\textsuperscript{90, 91} where the majority of acoustic neuromas seem to arise.\textsuperscript{8, 12} Permeability to
fluorescein has been demonstrated in the vestibular ganglion of rabbit.\textsuperscript{92} Fluorescein is a water soluble tracer with a molecule weight of 376 u. In addition, the vestibular nerve perineum is very thin and may allow diffusion of tumorigenic substances from the cerebrospinal fluid.\textsuperscript{93}

5.5 SUMMARY REMARKS AND FUTURE RESEARCH

5.5.1 Mobile and cordless phones and acoustic neuroma risk

So far, the evidence from epidemiological studies, incidence trend data, and experimental data all speak in the direction of a lack of an effect of radiofrequency fields emitted from mobile phones on acoustic neuroma risk. The result of our study did not alter this picture.

Results from studies with prospectively collected data show no association between acoustic neuroma and mobile phones. Results of the large multicenter INTERPHONE study only show an elevated odds ratio in the highest decile of cumulative calling time, but decreased odds ratios in the 4\textsuperscript{th} to 9\textsuperscript{th} deciles and decreased odds ratios for regular use of mobile phones and for \(\geq 10\) year since start of use.\textsuperscript{35} The sharp increase in the prevalence of mobile phone use from the mid 1990’s to the beginning of the last decade, reflected by the increase in mobile phone subscriptions shown in figure 13 would, if mobile phone use were associated with acoustic neuroma risk, be followed by an increase in acoustic neuroma incidence. This cannot be seen.\textsuperscript{1, 19, 77} Hardell and colleagues have consistently found associations between mobile and cordless phones and acoustic neuroma, also after less than 5 years of use, which is implausible considering the slow growing nature of acoustic neuroma tumors.\textsuperscript{16} In addition, increased risks after short induction periods are incompatible with acoustic neuroma incidence trends.\textsuperscript{1, 19, 77} Reversed causality was observed in the laterality specific risk estimates in our study, and it is likely that the laterality specific risk estimates in earlier studies are unreliable.

Cordless phones operate with an output power that is only a fraction of the average output power from GSM or NMT phones.\textsuperscript{33} It is therefore unlikely that we would notice effects from cordless phones before we see it for mobile phone use.

Detection bias, indicated in our study, would explain risk increases already after short induction periods; the use of mobile or cordless phones may increases the probability of detection of an already existing tumor by drawing attention to a unilateral hearing loss.

Many studies, including our, have shown that self-reported information about past use of mobile phones is have limited accuracy, and there are reports from both validation studies\textsuperscript{51} and case control studies that suggest recall bias.\textsuperscript{35, 46} Future studies on mobile phones and cordless phones should therefore use prospectively collected data, if possible, including objective data from network operators to reduce
misclassification that could dilute the associations. One thing to consider when doing epidemiological research on fast evolving technologies, is that the results may concern a technology that is already obsolete or in decline.

### 5.5.2 Noise and acoustic neuroma risk

This is the sixth study of acoustic neuroma risk in relation to noise exposure. Two and a half decades after Preston-Martin and colleagues published the first study, we still lack an answer to the question whether loud noise is involved in the etiology of acoustic neuroma. Recall bias is still a plausible reason for the associations seen in the INTERPHONE noise studies and in our analysis of self-reported leisure loud noise, but not for the result in the first study by Preston-Martin et al. Lack of power due to few subjects occupationally exposed to high noise levels without hearing protection may also explain the lack of association in the two last Swedish studies (including this study). Finally, the noise-exposure matrix may have produced too much non-differential misclassification, diluting the associations. Studies with more accurate exposure data would be needed in order to finally answer this question. However, the lifetime risk of getting an acoustic neuroma in Great Britain for a person living to 80 years of age has been estimated to 1 in 1000. From a public health point of view, damaged hearing caused by loud noise exposure is a larger problem, and is good reason to limit exposure to loud noise in the population.

### 5.5.3 Workplace chemical exposures and acoustic neuroma risk

The covariation of exposure to benzene, diesel engine exhaust, gasoline, and methylene chloride made it impossible to determine which (if any) of these exposures that caused the associations. It may also have been caused by another agent, not included in the NOCCA job-exposure matrix. The association with diesel engine exhaust did, however, remain after excluding the “machinery fitters, assemblers and mechanics” group, through which the exposures mainly were associated.

Potential causal relationships between occupational exposure to benzene, diesel engine exhaust, gasoline, and methylene chloride are supported by experimental and mechanistic data about the carcinogenicity of these substances, which in particular for benzene and diesel engine exhaust are very solid. However, our results have to be replicated, also for benzene, even if this association has been reported in previous studies. Prochazka and colleagues also used a job-exposure matrix and may have had the same potential biases, for example, from extensive covariation of exposures. Preston-Martin and colleagues used self-reported exposure information and the analysis may have suffered from recall bias.

Workplace exposures, and therefore occupational cancers, are highly preventable. It is therefore very important to identify potentially carcinogenic, or in this case tumorigenic, agents in the work environment. It is therefore desirable to examine
these associations again in future studies. However, using a job-exposure matrix for estimation of exposure would be likely to again produce similar problems with covariation between exposure variables. Blinded expert reviews of even more detailed occupational histories may be a possible way to get around this problem.
6 CONCLUSIONS

Mobile and cordless phones and acoustic neuroma risk
- We found no evidence for an association between mobile phone use and acoustic neuroma risk
- Laterality specific risk estimates for mobile phones are prone to bias from reversed causality, cases tend to change the preferred side of mobile phone use because of hearing loss on the tumor ear, sometimes many years before diagnosis
- Mobile and cordless phone use may increase the probability of detection of acoustic neuroma tumors
- Self-reported information on start year of mobile phone use is afflicted by large random errors, but only modest systematic errors, and no evidence was found of differences in recall between cases and controls

Noise exposure and acoustic neuroma risk
- We found no evidence for an association between occupational exposure to loud noise and risk of acoustic neuroma
- An association was found with leisure time loud noise and acoustic neuroma, with a positive exposure response gradient for number of leisure time noise exposures without hearing protection. Recall bias may, however, be an alternative explanation for these findings.

Occupational exposure to chemical agents and risk of acoustic neuroma
- Associations were found between acoustic neuroma and job-exposure matrix determined workplace exposure to benzene, diesel engine exhaust, gasoline fumes, and methylene chloride, of which benzene and diesel engine exhaust are classified as carcinogenic to humans by IARC
- There was large covariation between these agents according to the job-exposure matrix as a majority of exposed to benzene, gasoline and methylene chloride were exposed as workers in the occupational group “machinery fitters, assemblers and mechanics.”
7 SAMMANFATTNING [SUMMARY IN SWEDISH]

Avhandlingens syfte var att öka kunskapen om miljöfaktorers inverkan på risken att få akustikusneurinom och att öka förståelsen om de metodproblem som kan uppstå när man studerar denna tumör.


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