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Mobile phone use and risk of brain tumours

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Mobile phone use and risk of brain tumours

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Keywords: Mobile phones, brain tumours, case-control studies, meta-analysis, selection bias

Abstract

Mobile phone use has increased rapidly worldwide since the 1990's. As mobile telephones are used close to the head, the exposure to the radiofrequency radiation emitted by mobile phones has been suggested as a possible risk factor for brain tumours. The effect of mobile phone use on risk of brain tumours, particularly gliomas and meningiomas as well as acoustic neuromas, was evaluated using both a case-control approach and a meta-analysis. In addition, one of the most important sources of error in a case-control study, selection bias due to differential participation, was assessed in a subset of the case-control data.

The risk of glioma and meningioma in relation to mobile phone use was investigated in population-based case-control studies conducted in five North European countries. All these countries used a common protocol and were included in a multinational study on mobile phone use and brain tumours, the INTERPHONE study, coordinated by the International Agency for Research on Cancer (IARC). Cases (1,521 gliomas and 1,209 meningiomas) were identified mostly from hospitals and controls (3,299) from national population registers or general practitioners' patient lists. Detailed history of mobile phone use was obtained in personal interviews. Mobile phone use was assessed using several exposure indicators, such as regular use (phone use at least once a week for at least six months), duration of use as well as cumulative number of hours and calls.

To comprehensively evaluate the effect of mobile phone use on risk of brain tumours, the existing evidence from the epidemiological studies published on the issue was combined using meta-analysis. In the analysis, a pooled estimate was calculated for all brain tumours combined, and also separately for the three most common tumour types, glioma, meningioma and acoustic neuroma using inverse variance-weighted method. Pooled estimate was also obtained for different telephone types (NMT and GSM) and by the location of the tumour (same and opposite side of the head on which the phone was used).

Possible selection bias due to differential participation by exposure status in the Finnish arm of the INTERPHONE study was evaluated by comparing mobile

phone use between study participants and subjects who refused to participate in the study, but were willing to answer a short questionnaire covering only mobile phone use status and educational level. The data included 777 controls and 726 cases with full interview, as well as 321 controls and 103 cases responding only to the short questionnaire. To assess the magnitude of selection bias, the risk for brain tumours was evaluated separately for the participants interviewed and for the combined group consisting of both these subjects and those who only responded to the short questionnaire.

In the case-control studies, mobile phone use was not conclusively related to increased risk of either glioma or meningioma. For both tumour types, the risk was decreased among regular mobile phone users compared to never and non-regular users (OR = 0.78, 95% CI: 0.68–0.91 for gliomas, OR = 0.76, 95% CI: 0.65–0.89 for meningiomas). According to the 12 studies included in the meta-analysis, the pooled estimate for all tumour types combined did not show an association between mobile phone use and brain tumours (OR = 0.98, 95% CI: 0.83–1.16). Nor was much evidence of increased risk found in the analyses by tumour type, telephone type or tumour location. In the Finnish INTERPHONE study, the study participants interviewed were more likely to be mobile phone users than the subjects who refused to give a full interview but responded to the short questionnaire. The risk for brain tumours associated with mobile phone use based on only interviewed participants was below unity, whereas the risk based on the combined group consisting of both full participants and subjects responding the short questionnaire was closer to unity.

The results of neither the case-control studies nor the meta-analysis provide consistent support for an association between mobile phone use and brain tumours. In the case-control studies, a decreased risk was found in relation to regular mobile phone use for both gliomas and meningiomas. As it is not plausible that mobile phone use reduces the risk for brain tumours, there is a possibility that such results are due to selection bias, which tends to distort the results in case-control studies towards the null. In the Finnish INTERPHONE study, an indication of selection bias was detected, as the risk for brain tumours related to mobile phone use was lower among study participants than in the group that also included the subjects who refused to grant a full interview but responded to the short questionnaire. Selection bias may also have distorted the results of the five-country case-control studies.

In conclusion, the present studies do not suggest mobile phone use as a cause of brain tumours. As there was decreased risks in the case-control studies, the possibility that the results are affected by bias, needs to be carefully considered in their interpretation.

LAHKOLA Anna. Matkapuhelinten käyttö ja aivokasvainten vaara. STUK-A246. Helsinki 2010, 73 s. + liitteet 38 s.

Avainsanat: Matkapuhelimet, aivokasvaimet, tapaus-verrokkitutkimukset, meta-analyysi, valikoitumisharha

Tiivistelmä

Matkapuhelimen käyttö on lisääntynyt maailmanlaajuisesti 1990-luvulta alkaen. Koska matkapuhelinta käytetään lähellä päätä, puhelimen lähettämälle radiotaajuiselle sähkömagneettiselle säteilylle altistumisen on ajateltu olevan yhteydessä aivokasvainten vaaraan. Matkapuhelimen käytön vaikutusta aivokasvainten, erityisesti glioomien, meningeoomien ja akustikusneurinoomien, vaaraan arvioitiin sekä tapaus-verrokkiasetelmalla että meta-analyysin keinoin. Tämän lisäksi tapaus-verrokkitutkimuksen erästä keskeisintä virhelähdettä, valikoitumisharhaa, arvioitiin tutkimukseen osallistumisen suhteen tapaus-verrokkitutkimuksen osa-aineistossa.

Matkapuhelimen käyttöön liittyvää gliooman ja meningeooman vaaraa tutkittiin väestöpohjaisissa tapaus-verrokkitutkimuksissa, jotka tehtiin yhteensä viidessä Pohjois-Euroopan maassa. Kaikissa maissa käytettiin yhteistä tutkimusprotokollaa ja ne kuuluivat monikansalliseen matkapuhelimen käytön ja aivokasvainten yhteyttä selvittävään tutkimukseen, INTERPHONEen. INTERPHONE-tutkimusta koordinoi International Agency for Research on Cancer (IARC). Aivokasvaintapaukset (1521 glioomaa ja 1209 meningeoomaa) identifioitiin pääosin sairaaloista ja verrokit (3299) kansallisista väestörekistereistä tai yleislääkäreiden potilasluetteloista. Tutkimushenkilöiden matkapuhelimen käytön historiaa selvitettiin henkilökohtaisin haastatteluin ja matkapuhelimen käyttöä arvioitiin useiden eri altistusindikaattoreiden perusteella. Tällaisia olivat esimerkiksi säännöllinen käyttö (puhelinta oli käytetty vähintään kerran viikossa vähintään 6 kuukauden ajan), käytön kokonaiskesto sekä kumulatiivinen tuntien ja puhelujen määrä.

Jotta voitiin arvioida matkapuhelimen käytön kokonaisvaikutusta aivokasvainten riskiin, käytettiin tutkimusmenetelmänä meta-analyysiä, jossa yhdistettiin tutkimustulokset kaikista tutkimusaihetta käsittelevistä epidemiologisista tutkimuksista. Matkapuhelimen käytön kokonaisvaikutusta kuvaava yhdistetty estimaatti laskettiin analyysissä kaikille aivokasvaimille yhteensä ja erikseen kolmelle yleisimmälle kasvaintyypille, joita ovat gliooma, meningeooma ja akustikusneurinooma. Yhdistetty estimaatti laskettiin myös puhelimen tyypin (NMT ja GSM) ja kasvaimen sijainnin mukaan (samalla

ja eri puolella päätä kuin puhelinta oli käytetty). Yhdistettyjen estimaattien laskemisessa käytettiin käänteisen varianssin painotuksen menetelmää.

Matkapuhelimen käytön yhteyttä tutkimukseen osallistumiseen ja siitä tutkimukseen aiheutuvaa mahdollista valikoitumisharhaa arvioitiin INTERPHONE-tutkimuksen suomalaisessa aineistossa vertaamalla keskenään tutkimushaastatteluun osallistuneita ja sellaisia henkilöitä, jotka kieltäytyivät osallistumasta tutkimukseen, mutta vastasivat matkapuhelimen käyttöä ja koulutusta käsittelevään lyhyeen kyselyyn. Tässä aineistossa oli yhteensä 777 verrokkia ja 726 tapausta, jotka osallistuivat tutkimushaastatteluun sekä 321 verrokkia ja 103 tapausta, jotka vastasivat vain lyhyeen kyselyyn. Valikoitumisharhan suuruutta arvioitiin määrittämällä aivokasvainten vaaraa kuvaava estimaatti erikseen tutkimushaastatteluun osallistuneille henkilöille ja ryhmälle, johon kuuluivat sekä tutkimushaastatteluun osallistuneet että lyhyeen kyselyyn vastanneet henkilöt.

Tapaus-verrokkitutkimuksissa matkapuhelimen käyttöön ei näyttänyt liittyvän suurentunutta gliooman tai meningeooman vaaraa. Molempien kasvaintyyppien vaara oli pienempi säännöllisesti matkapuhelinta käyttävillä kuin niillä, jotka eivät olleet koskaan käyttäneet matkapuhelinta tai käyttivät sitä epäsäännöllisesti (OR = 0.78, 95% CI: 0.68–0.91 glioomille, OR = 0.76, 95% CI: 0.65–0.89 meningeoomille). Myöskään meta-analyysiin sisällytettyjen 12 tutkimuksen perusteella matkapuhelimen käytön kokonaisvaikutukselle laskettu yhdistetty estimaatti ei antanut viitteitä siitä, että matkapuhelimen käytöllä olisi yhteyttä aivokasvainten vaaraan (OR = 0.98, 95% CI: 0.83–1.16). Viitteitä suurentuneesta vaarasta ei juurikaan saatu kasvaimen tyypin, puhelimen tyypin tai kasvaimen sijainnin perusteella tehdyissä analyyseissä. Suomalaisessa INTERPHONE-tutkimuksessa matkapuhelimen käyttö oli yleisempää tutkimushaastatteluun osallistuneiden kuin siitä kieltäytyneiden, mutta lyhyeen kyselyyn vastanneiden henkilöiden joukossa. Matkapuhelimen käyttöön liittyvä aivokasvainten vaara oli pienempi tutkimushaastatteluun osallistuneilla henkilöillä. Yhdistetyllä ryhmällä, johon kuuluivat sekä tutkimushaastatteluun osallistuneet että vain lyhyeen kyselyyn vastanneet henkilöt, aivokasvainten vaara oli hieman edellistä suurempi, mutta ei kuitenkaan suurentunut.

Tapaus-verrokkitutkimusten tai meta-analyysin tulokset eivät tue olettamusta, että matkapuhelimen käytöllä olisi yhteyttä aivokasvainten vaaraan. Tapaus-verrokkitutkimuksissa havaittiin, että säännöllisillä matkapuhelimen käyttäjillä oli pienentynyt vaara sairastua glioomaan tai meningeoomaan. Koska ei ole uskottavaa, että matkapuhelimen käyttö pienentää aivokasvainten vaaraa, on mahdollista, että tällaiset tulokset johtuisivat valikoitumisharhasta. Tapaus-verrokkitutkimuksissa valikoitumisharha voi vääristää tuloksia siten,

että tutkimuksessa havaitaan pienempi vaara kuin mitä se on todellisuudessa. Viite valikoitumisharhan olemassa olosta saatiin suomalaisessa INTERPHONE-tutkimuksessa, jossa matkapuhelimen käyttöön liittyvä aivokasvainten vaara oli pienempi tutkimushaastatteluun osallistuneiden joukossa kuin yhdistetyssä ryhmässä, johon kuuluivat näiden henkilöiden lisäksi myös vain lyhyeen kyselyyn vastanneet. On mahdollista, että valikoitumisharha on vääristänyt myös viidessä Pohjois-Euroopan maassa tehtyjen tapaus-verrokkitutkimusten tuloksia.

Edellä esitettyjen tutkimusten tulosten perusteella voidaan todeta, että matkapuhelimen käyttö ei näyttäisi aiheuttavan aivokasvaimia. Tapaus-verrokkitutkimuksissa matkapuhelimen käyttöön liittyvän aivokasvainten vaaran havaittiin pienentyneen. Tuloksia on tulkittava kuitenkin erityisen varovaisesti, sillä on mahdollista, että ne johtuvat tutkimuksessa olevasta harhasta.

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List of Original Communications

This dissertation is based on the following publications, which will be referred to by their Roman numerals:

I Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M, Johansen C, Klæboe L, Lönn S, Swerdlow AJ, Tynes T and Salminen T (2007): Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 120:1769–1775

II Lahkola A, Salminen T, Raitanen J, Heinävaara S, Schoemaker MJ, Christensen HC, Feychting M, Johansen C, Klæboe L, Lönn S, Swerdlow AJ, Tynes T and Auvinen A (2008). Meningioma and mobile phone use - a collaborative case-control study in five North European countries. Int J Epidemiol 37:1304–13

III Lahkola A, Tokola K and Auvinen A (2006): Meta-analysis of mobile phone use and intracranial tumors. Scand J Work Environ Health 32:171–177

IV Lahkola A, Salminen T and Auvinen A (2005): Selection bias due to differential participation in a case-control study of mobile phone use and brain tumors. Ann Epidemiol 15:321–325

List of Abbreviations

CI	confidence interval
IARC	International Agency for Research on Cancer
GSM	Global System for Mobile Communications
NMT	Nordic Mobile Telephone
OR	odds ratio
RF	radiofrequency
RR	relative risk
SAR	specific absorption rate
SIR	standardized incidence ratio
UMTS	Universal Mobile Telecommunication System
WHO	World Health Organization

Introduction

Mobile phone use has increased rapidly worldwide since the early 1990's. In the North European countries, this technology was adopted especially early and mobile phones have been widely used since the mid-1990's (Gibney 2005). Mobile phones emit a radiofrequency electromagnetic field, which is a part of non-ionizing radiation. Non-ionizing radiation has too low energy to break chemical bonds and thus it cannot directly cause DNA damage (mutations), which is required for cancer initiation (Valberg 1997). It is, however, unknown, whether radiofrequency radiation is capable of affecting cancer development at later stages, such as tumour progression or promotion.

While the role of radiofrequency radiation in carcinogenesis is unclear and no carcinogenic mechanism has been established, considerable public concern has arisen about the possible health effects of mobile phone use. Most of all, the concern is focused on brain tumours since mobile phones are used very close to the head and the energy of the radiofrequency radiation is mostly absorbed in the head and neck region.

To increase the knowledge of the possible effects of mobile phone use, a large multinational case-control study on brain tumours and mobile phone use, the INTERPHONE study, was initiated in 2000. The International Agency for Research on Cancer (IARC) coordinated the study and altogether 13 countries participated in it, Finland being one of them. Within the INTERPHONE study, five-country collaboration between Denmark, Finland, Sweden, Norway and Southeast England was also established shortly after the beginning of the study. The purpose of the five-country collaboration was to perform joint analyses, which was possible since all the study countries used the shared study protocol provided by the IARC (Cardis & Kilkenny 1999). A larger number of study subjects in shared datasets allows more comprehensive analyses and investigation of various aspects of mobile phone use, likewise more precise risk estimates.

The possible effect of mobile phone use on the risk of brain tumours has been investigated in several studies (Hardell *et al.* 1999*;* Dreyer *et al.* 1999*;* Muscat *et al.* 2000*;* Hardell *et al.* 2001*;* Inskip *et al.* 2001*;* Johansen *et al.* 2001*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002a*;* Hardell *et al.* 2002b*;* Muscat *et al.* 2002*;* Hardell *et al.* 2003*;* Lönn *et al.* 2004a*;* Christensen *et al.* 2004*;* Lönn *et al.* 2005*;* Christensen *et al.* 2005*;* Hardell *et al.* 2005a*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2006a*;* Hardell *et al.* 2006b*;* Hardell *et al.* 2006c*;* Schuz *et al.* 2006a*;* Schuz *et al.* 2006b*;* Hepworth *et al.* 2006*;* Takebayashi *et al.* 2006*;* Schlehofer *et al.* 2007*;* Mild *et al.* 2007*;* Klaeboe *et al.* 2007*;* Hours *et al.* 2007*;* Takebayashi *et al.* 2008; Hartikka *et al.* 2009*;*). As the study results are somewhat inconsistent,

a meta-analysis provides a tool for a quantitative synthesis of individual studies and evaluation of the overall effect.

Shortly after the beginning of subject recruitment to the Finnish INTERPHONE study, study participation turned out to be relatively low, especially among controls. Due to the low participation rate, a concern arose whether the study participants represented the target population in terms of exposure. Selection bias may distort the results of a case-control study if study participation is related to the exposure of interest, which in this case was mobile phone use. Because selection bias was deemed possible, its magnitude needed to be investigated.

The studies in this dissertation were performed to investigate the possible relationship between mobile phone use and risk of brain tumours using both case-control design and meta-analysis. In addition, the possibility and magnitude of selection bias due to differential participation by exposure status were evaluated in a subset of the case-control material where information for such evaluation was available.

1. Review of the Literature

1.1. Radiofrequency radiation

1.1.1. Nature and sources of radiofrequency radiation

Electromagnetic radiation is all around us. Numerous devices in everyday life, such as radio, TV, mobile telephones and electric appliances produce electromagnetic radiation of different frequencies in their operation. Radiofrequency (RF) radiation is one type of electromagnetic radiation. In the frequency spectrum of electromagnetic radiation, RF is below optical radiation. There is some variation in the classification of frequency bands within the electromagnetic spectrum, but the RF area can be defined to cover the frequencies from 100 kHz to 300 GHz (Ahlbom *et al.* 2004*;* Jokela 2006).

RF radiation cannot directly break chemical bonds and is therefore defined as non-ionising radiation. In terms of biological effects, this means that RF radiation cannot cause damage to DNA (mutations). In contact with the human body, RF radiation penetrates the tissues where the energy of RF radiation is absorbed and converted into heat. The heating, i.e. the thermal effect, is the only established mechanism for biological effects of RF radiation and it can cause tissue damage if the temperature rises too high (Lang & Jokela 2006b).

On the basis of the scientific evidence available, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) has defined exposure limits, which protect people from the established harmful effects of RF radiation (ICNIRP 1998). The harmful effects are caused by excessive temperature rise in tissues due to absorption of RF radiation. In addition, the restrictions by ICNIRP contain safety margins to avoid any adverse effects, as the public exposure limit with regard to RF caused temperature rise has been set at one tenth or below of the value where harmful effects can occur. In general, it can be said that it is not likely that the exposure to RF sources used in the normal environment can cause temperature rise to the level where human tissues are in danger.

The sources of RF radiation to the general public include mobile telephones and their base stations, radio and TV transmitters and wireless networks. While radio and TV stations emit relatively high power levels (from tens to hundreds of kW) the exposure to the public remains low because the transmitters are located in high masts and the public has no access to the immediate vicinity of the mast (Jokela *et al.* 2006). This is because the level of RF radiation decreases substantially with the distance from the source. The exposure from mobile phone

base stations and wireless networks is also low because of the relatively low output power levels, which are 5–30 W for mobile phone base stations and 100 mW–1 W, for instance, for WLAN, which is commonly used wireless network technology in home and office environments (Jokela *et al.* 2006). In addition, mobile phone base stations are located in such a way that the public cannot be in touch with them and thus expose themselves to high levels, however many people are exposed to low levels as such technology is currently an integral part of our everyday lives.

In contrast to average citizens, the exposures of people working in the maintenance of radio and TV transmitters may be considerable, because the work is usually done while the transmitter is operating and the workers need to be located quite near the RF source. Subjects working with radars (with average power level of 1 kW), as well as dielectric and induction heaters (with power levels up to hundreds kW) are also exposed to RF radiation (Jokela *et al.* 2006). In addition, radio amateurs are exposed to RF due to use of ham radios. For the radiation protection of people exposed to RF radiation in their professions or leisure activities, the exposure limits established by ICNIRP and controlled by the authorities should be followed.

The current model of cancer biology states that DNA damage and further a series of mutations is required for cancer initiation. Due to the non-ionising nature of RF radiation, it is not likely that RF is able to act as a cancer initiator, even though some studies have reported RF-induced DNA damage in rat brain cells (Lai & Singh 1995*;* Lai & Singh 1996). It is also not clear whether RF radiation may affect later stages of carcinogenesis, such as tumour promotion or progression. An animal study reported that RF radiation may increase the number of tumours in mice susceptible to lymphoma (Repacholi *et al.* 1997), but these results could not be replicated elsewhere (Utteridge *et al.* 2002). In general, biological results in this field are contradictory and thus it is impossible to draw final conclusions about potential biological effects, especially as it is not known by which mechanism RF radiation may affect directly at the cell level.

1.1.2. Mobile phone as a source of radiofrequency radiation

Mobile phones, also called cellular phones, are now one of the most important sources of RF radiation in general population. While in the early 1990's mobile phone use was quite rare, it seems that today the people not using a mobile phone are in the minority among Europeans. According to the Official Statistics of Finland, at the end of 2007 there were over six million mobile phone subscriber connections in Finland which equals 115 subscriber connections per 100 inhabitants (Tilastokeskus 2008).

To function, a mobile phone needs to communicate with a mobile phone base station using radio signals. Thus both the mobile phone and the base station emit RF radiation. The mobile phone network is divided into cells from which the mobile phone is in connection to the base station. The shape of the cell depends on the direction of the antenna at the base station and the surrounding geography, while the size of the cell depends on the number of mobile phone users in the area and the output power level of the base station. Since each cell can handle a limited number of concurrent phone calls, the number of base stations has been rapidly increasing to allow effective mobile phone use.

Two major mobile phone network types have been used in Europe, analogue (Nordic Mobile Telephone, NMT) and digital (Global System for Mobile Communications, GSM). NMT operates on 450 or 900 MHz frequencies whereas GSM uses frequencies of 900 and 1800 MHz. Currently, the digital phone network predominates since the analogue telephone system was closed down at the end of 2000. In addition to NMT and GSM telephones, third generation mobile phones have recently been introduced, using a new system called Universal Mobile Telecommunication System (UMTS) or 3G, that operate in 1950 and 2150 MHz bands. However, in this dissertation only exposure from NMT and GSM phones is addressed, due to the timing of the present work.

An NMT 900 MHz phone emits continuously during speech at a constant power level of 1 W, whereas the GSM phones use pulsed signals and adaptive power control. The maximum power of pulse is 2 W for GSM 900 MHz and 1 W for GSM 1800. The duration of pulses is 0.6 milliseconds and interval of 4.6 milliseconds, which results in the phone emitting radiation only 1/8 of the time. Therefore, the maximum average output power level is 0.25 W and 0.125 W for the GSM phones. This maximum power level is used only in the weak field of the base station due to the adaptive power control of GSM phones. The quality of the connection to the base station and the way the phone is used affect the output power level of the mobile phone. When the distance to the base station increases, the phone emits at higher output power level. During a phone call, the phone emits RF radiation only while transmitting (during speech), and the base station constantly moderates the output power level of the mobile phone to achieve the lowest level necessary for efficient operation. The moderation of the power level can reduce the output power level of a GSM phone to below a hundredth of the maximum. When the phone is on standby, the phone sends pulses only at long intervals, typically 1/100 of the time (Jokela *et al.* 2006).

While the output power levels of mobile phones are relatively low, the exposure to RF radiation cannot necessarily be considered minor since the mobile phones are used close to the body. In electromagnetic radiation terms, such exposure is considered to occur in near-field. The exposure from a mobile

phone is confined to the immediate vicinity of the phone i.e. most of the RF energy emitted by a mobile phone affects the parts of the body that are either in contact or few centimetres away from the phone (Balzano 1999). Due to the frequency of mobile phone radiation, an applicable measure for exposure assessment regarding mobile phones is specific energy absorption rate (SAR), which is simplistically a measure for the heating caused by RF. SAR is defined as the energy absorption rate per tissue mass and it is expressed as W/kg. When RF radiation penetrates human tissue, loss of power due to interaction with tissue takes place. The amount of energy absorbed by the tissues depends on RF power level and frequency, distance from the antenna and position of the phone among many other factors (Balzano 1999).

Guidelines for limiting the public's exposure to mobile phone radiation have been based on the SAR from the early 1980's. The guidelines were set on the basis of the energy absorbed and for RF frequencies, the SAR is limited to such a level that the excess temperature rise remains below 1 °C. Such temperature rise equals a whole-body SAR of 4 W/kg and using 50 as a safety factor, the ICNIRP has set the whole-body SAR limit for the population at 0.08 W/kg. However, as mobile phone exposure is highly localised, the SAR of 2 W/kg set as the highest value for localised exposure is applied for mobile phone radiation (ICNIRP 1998). The maximum averaged SAR for mobile phones with an output power level of 0.25 W has been reported to vary from 1.0 to 2.6 W/kg (van de Kamer & Lagendijk 2002). Thus, phones operate close to the guidelines. However, the maximum averaged SAR of 1.6 W/kg caused by 0.25 W power level has been reported to elevate brain temperature by 0.1 °C, which has no physiological significance (Van Leeuwen *et al.* 1999). It cannot, however, be ruled out that RF radiation could have some other interaction mechanisms in biological systems (Lang & Jokela 2006a).

The use of hands-free equipment substantially decreases the exposure caused by mobile phones (IEGMP 2000). Therefore, some authorities have recommended that people who are worried about the possible harmful effects of mobile phones should use hands-free equipment to minimize their exposure, even though using a mobile phone is considered safe (A common approach for the Nordic competent authorities 2004).

1.2. Brain tumours

1.2.1. Definition and incidence of brain tumours

In this dissertation, the term ”brain tumours” is used to cover tumours occurring in the central nervous system, such as gliomas, meningiomas and acoustic neuromas, even though the histological origin of the tumours is not always from brain cells, but from the meninges (meningiomas) or cranial nerves (acoustic neuromas). A similar approach has been common in other studies.

Historically, the classification of brain tumours has varied, but as the WHO classification (Kleihues & Cavenee 2000) has been widely accepted, it was also used as a basis of the classification in this dissertation. In this material, the gliomas comprise several subgroups including astrocytic, oligodendroglial, ependymal and chroroid plexus tumours, as well as mixed gliomas, glial tumours of uncertain origin and ganglioglioma. Meningiomas and acoustic neuromas cover more homogenous tumour types, as the meningiomas comprise tumours of meningothelial cells and acoustic neuromas comprise schwannomas (sometimes called also neurilemomas) of the acoustic nerve (or vestibulo-cochlear nerve i.e. the eighth cranial nerve).

Brain tumours constitute a relatively heterogeneous group of tumours that are among the ten most common cancer types in Finland. The number of new cases with a central nervous system tumour (also includes some other tumours than those of the brain, such as tumours of the spinal cord) is approximately 950 per year (Suomen Syöpärekisteri 2009). The age-specific incidence of brain tumours usually increases until 60–70 years of age, and the incidence rates are relatively similar in developed countries. In the Nordic countries, however, the incidence is somewhat higher than in other countries, which may reflect true risk, diagnostic activity related to high level of health care, or completeness of tumour registration (Inskip *et al.* 1995). Generally, half of brain tumours are gliomas, a quarter are meningiomas, while the rest represent other tumour types such as acoustic neuromas and pituitary adenomas (Stewart & Kleihues 2003). Gliomas are more common among men (male:female incidence ratio 1.5), while meningiomas occur predominantly among women (male:female incidence ratio 0.6) (Inskip *et al.* 1995). Among adult population in the Nordic countries, the incidence of gliomas in 1998 was around 8.5 among men and 5.8 among women per 100, 000 person-years (to the standard population of the Nordic countries in 1985) (Lönn *et al.* 2004b), while the incidence of meningiomas in 1997 was 1.9 among men and 4.5 among women per 100, 000 person-years (to the world standard population) (Klaeboe *et al.* 2005). Both Nordic studies reported an increase in the incidence rates from the 1960’s to the 1990’s but suggest enhanced

diagnostic methods as the most probable explanation for the increase. Acoustic neuroma is a relatively rare tumour type accounting for 8% of all brain tumours and occurring equally frequently in both sexes (Kleihues & Cavenee 2000).

Most gliomas are malignant tumours, whereas most of the meningiomas and all acoustic neuromas are benign. However, a neoplastic process within the limited space of the skull inevitably causes harm by displacing brain tissue even if no invasion of the cerebral tissue is involved. Therefore, even benign tumours can be life-threatening. However, patients with malignant brain tumours have considerably lower survival rates than those with benign tumours. Whereas for all brain tumours in all age-groups the overall survival rate has been reported as 20% at five years, patients with glioblastoma have the poorest prognosis, as only 3% of cases are alive 3 years after diagnosis (Stewart & Kleihues 2003; Berger & Prados 2005). Other gliomas also have relatively poor prognosis, as the proportion of those alive 5 years after diagnosis varies from 44% to 65% depending on the subtype of the tumour (Preston-Martin & Mack 1996). In contrast to gliomas, meningiomas and acoustic neuromas can very often be cured completely (Stewart & Kleihues 2003).

1.2.2. Aetiology of brain tumours

The aetiology of brain tumours is not well understood, as only few risk factors for brain tumours are known. High doses of ionizing radiation have consistently been shown to cause brain tumours. Among the survivors of the atomic bombing of Hiroshima and Nagasaki an increased risk has been detected for all tumours of the central nervous system, particularly for acoustic neuromas (Preston *et al.* 2002). Radiotherapy to the head for scalp ringworm during childhood has been reported to increase the risk of both gliomas and meningiomas (Ron *et al.* 1988). Cranial radiotherapy in the treatment of acute lymphoblastic leukaemia in childhood has also been reported to cause secondary brain tumours (Neglia *et al.* 1991; Relling *et al.* 1999). Unlike high doses, the effect of low doses of ionising radiation, for instance from X-ray examinations, has been investigated but the findings do not support association to brain tumours (Ryan *et al.* 1992; Rodvall *et al.* 1998; Hardell *et al.* 2001; Blettner *et al.* 2007).

In addition to ionising radiation, few other risk factors for brain tumours are known. Increased risk for brain tumours is related to some relatively rare hereditary syndromes, such as neurofibromatosis, tuberous sclerosis and Li-Fraumeni syndrome. Neurofibromatosis type I is associated with gliomas, while neurofibromatosis type II mainly causes acoustic neuromas and meningiomas. Both tuberous sclerosis and Li-Fraumeni syndrome increase the risk of gliomas (astrocytomas, glioblastomas) (Stewart & Kleihues 2003).

Social class may affect the risk of brain tumours. For all brain tumours and separately for gliomas, an increased risk has been reported in higher social classes, while meningiomas have been slightly more common in lower social classes (Preston-Martin *et al.* 2006). The association of all brain tumours with high socioeconomic status has been suggested to be explained by diagnostic bias caused by more active use of health care services pronounced in the higher social classes (Preston-Martin *et al.* 1993*;* Pukkala 1995). Recently, it has also been suggested that various tumour types have different social class patterns, probably reflecting a heterogeneous aetiology of the tumours (Inskip *et al.* 2003). It is possible that the more aggressive tumours are detected regardless of the patient's social class, while the diagnostics of benign tumours may be more dependent on social class.

The effect of dietary intake (mainly N-nitroso compounds), head trauma, infections, occupational exposures and exposure to low frequency electromagnetic radiation on the risk of brain tumours has been investigated, but no consistent evidence of these factors as a cause of brain tumours has been reported (Preston-Martin *et al.* 2006). A decreased glioma risk has been reported in several studies among subjects with allergic conditions (Brenner *et al.* 2002*;* Linos *et al.* 2007*;* Wigertz *et al.* 2007).

1.3. Radiofrequency radiation and health

1.3.1. Mobile phones and brain tumours

There are several publications on the possible effect of mobile phone use on brain tumour risk (Hardell *et al.* 1999*;* Dreyer *et al.* 1999*;* Muscat *et al.* 2000*;* Hardell *et al.* 2001*;* Inskip *et al.* 2001*;* Johansen *et al.* 2001*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002a*;* Hardell *et al.* 2002b*;* Muscat *et al.* 2002*;* Hardell *et al.* 2003*;* Lönn *et al.* 2004a*;* Christensen *et al.* 2004*;* Lönn *et al.* 2005*;* Christensen *et al.* 2005*;* Hardell *et al.* 2005a*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2006a*;* Hardell *et al.* 2006b*;* Hardell *et al.* 2006c*;* Schuz *et al.* 2006a*;* Schuz *et al.* 2006b*;* Hepworth *et al.* 2006*;* Takebayashi *et al.* 2006*;* Schlehofer *et al.* 2007*;* Mild *et al.* 2007*;* Klaeboe *et al.* 2007*;* Hours *et al.* 2007*;* Takebayashi *et al.* 2008*;* Hartikka *et al.* 2009*;* Schoemaker & Swerdlow 2009). Of these, data from the Danish (Christensen *et al.* 2005), Swedish (Lönn *et al.* 2005) and Norwegian studies (Klaeboe *et al.* 2007), as well as a subset of the data in the UK study (Hepworth *et al.* 2006) are also included in the material of this dissertation (in the five country studies on the risk of gliomas and meningiomas).

Most epidemiological studies on mobile phone use and brain tumour risk

have been based on case-control design, while only two incident cohort studies (Johansen *et al.* 2001*;* Schuz *et al.* 2006b) have been published, the latter being an update of the first study. In addition, one case-case analysis (Hartikka *et al.* 2009) and one cohort study addressing the brain cancer mortality of the mobile phone users (Dreyer *et al.* 1999) have been published. Almost all studies have used incident cases (except that by Hardell *et al.* 1999 using prevalent cases) and the most common types of tumours investigated are gliomas, meningiomas and acoustic neuromas. Most of the reports used either personal interview or postal questionnaire in the exposure assessment, while in four studies, the exposure assessment was based on telephone company records (Dreyer *et al.* 1999*;* Johansen *et al.* 2001*;* Auvinen *et al.* 2002*;* Schuz *et al.* 2006b). In some of the studies the use of hands-free equipment has been taken into account, while in the others this was not reported.

Of the studies published on the issue, not all are based on unique datasets, since some original analyses have been pooled with each other or otherwise updated. Concerning the publications by Hardell, who has three different datasets but a greater number of publications, the original reports of each dataset are presented in the following four sections. The first dataset concerns a study performed in 1994–1996 (Hardell *et al.* 1999), the second in 1997–2000 (Hardell *et al.* 2002a) and the third in 2000–2003 (Hardell *et al.* 2005a*;* Hardell *et al.* 2006c). After publishing these original study reports, several other reports based on the same datasets were also published by the same study group (Hardell *et al.* 2001*;* Hardell *et al.* 2002b*;* Hardell *et al.* 2003*;* Hardell *et al.* 2006a*;* Hardell *et al.* 2006b*;* Mild *et al.* 2007). They are not presented since they could not be regarded as original publications. Similarly, the Swedish (Lönn *et al.* 2004a) and Danish (Christensen *et al.* 2004) acoustic neuroma studies will not be discussed, as they are also included in a more comprehensive study on acoustic neuromas presented in Section 1.3.1.3 (Schoemaker *et al.* 2005).

1.3.1.1. Case-control studies of gliomas

The risk for gliomas in relation to mobile phone use has been investigated in 13 case-control studies. Of these, one was conducted in Japan (Takebayashi *et al.* 2008), two in the U.S.A. (Muscat *et al.* 2000*;* Inskip *et al.* 2001) while the others are European (Hardell *et al.* 1999*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002a*;* Christensen *et al.* 2005*;* Lönn *et al.* 2005*;* Hepworth *et al.* 2006*;* Hardell *et al.* 2006c*;* Schuz *et al.* 2006a*;* Klaeboe *et al.* 2007*;* Hours *et al.* 2007).

The studies conducted in the U.S.A. are hospital-based and the European studies are population-based. In hospital-based studies, the controls are usually patients from the same hospitals as the cases, but treated for other medical conditions, whereas in population-based design, the controls are usually enrolled

through population registries. The Japanese study is between these two designs, as the cases were recruited from hospitals and the controls were selected from general population. Together the studies of mobile phone use and risk of gliomas include more than 4,600 glioma cases and 9,300 controls. In half of the studies, the highest exposure category used for mobile phone use was > 10 years (Hardell *et al.* 2002a*;* Lönn *et al.* 2005*;* Christensen *et al.* 2005*;* Hepworth *et al.* 2006*;* Schuz *et al.* 2006a*;* Hardell *et al.* 2006c*;* Takebayashi *et al.* 2008), while in the others the maximal exposure periods were shorter (from > 2 years to > 6 years).

In some studies, there were indications of an association between mobile phone use and risk of glioma, while the majority of results showed no association (Table 1). Increased risks were reported for ever use of mobile phone in a Finnish study (OR = 1.5, 95% CI: 1.0–2.4) (Auvinen *et al.* 2002) and for regular ipsilateral use (phone use on the same side where the tumour occurred, OR = 1.24, 95% CI: 1.02–1.52) in an English study (Hepworth *et al.* 2006). Both the Finnish and English studies also reported several results showing no association between mobile phone use and risk of glioma. In addition, the company records used as a basis of the exposure assessment in the Finnish study are a possible source of error, as the actual user of the mobile phone is not known and did not allow identification of users with subscriptions owned by employers. Further, in the laterality analysis of the English study, a reduced risk was also detected in relation to contralateral use (phone use on the opposite side to that where the tumour occurred) that together with the positive finding for ipsilateral use is consistent with recall bias. It is possible that the patient's recall of the side of phone use is affected by the fact that the patient is aware of the location of the tumour.

In contrast to the results of most studies, the study group of Hardell detected several increased risks in relation to mobile phone use in the study published in 2006, where the risk of gliomas was investigated in various different analyses. The risk of malignant tumours was increased in relation to > 1-year of use of both analogue (OR = 2.60, 95% CI: 1.50–4.30) and digital phones (OR = 1.90, 95% CI: 1.30–2.70) and the risks were also reported to be increased with increasing years of use (Hardell *et al.* 2006c). In addition, the risk of ipsilateral tumours was increased in relation to use of both analogue (OR = 3.10, 95% CI: 1.60–6.20) and digital phones (OR = 2.60, 95% CI: 1.60–4.10). The authors conclude that the study provided evidence of an increased risk of malignant tumours. The study has, however, been criticized for methodological and analytical limitations (SSI Report 2006).

1.3.1.2. Case-control studies of meningiomas

Risk of meningioma in relation to mobile phone use has been investigated in 11 studies (Table 1). Most of these were conducted in Europe (Hardell *et al.* 1999*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002a*;* Christensen *et al.* 2005*;* Lönn *et al.* 2005*;* Hardell *et al.* 2005a*;* Schuz *et al.* 2006a*;* Klaeboe *et al.* 2007*;* Hours *et al.* 2007), while one was performed in the U.S.A. (Inskip *et al.* 2001) and one in Japan (Takebayashi *et al.* 2008). The studies include together more than 2,500 meningioma cases and 7,400 controls.

In six of the studies (Hardell *et al.* 2002a*;* Christensen *et al.* 2005*;* Lönn *et al.* 2005*;* Hardell *et al.* 2005a*;* Schuz *et al.* 2006a*;* Takebayashi *et al.* 2008), the longest duration of mobile phone use was > 10 years, while in the other studies categories from > 2 to > 6 years were used. Of the studies, only the study group of Hardell has consistently reported increased risks for meningiomas in relation to mobile phone use. Increased risk was reported for > 10 years use of analogue phones (OR = 2.10, 95% CI: 1.10–4.30) and for contralateral tumours in relation to ever use of mobile phone (OR = 2.60, 95% CI: 1.10–6.00), while many other results of the study did not indicate an association between mobile phone use and meningioma (Hardell *et al.* 2005a). Both positive findings were based on rather a small number of exposed cases (20 and 14 respectively) and controls (40 and 28 respectively) in the analysis. Due to some methodological issues in the Hardell study it has been suggested that the results should be interpreted with caution (SSI Report 2006).

1.3.1.3. Case-control studies of acoustic neuromas

Acoustic neuromas have been investigated in ten case-control studies, of which one is Japanese (Takebayashi *et al.* 2006), two were performed in the U.S.A. (Inskip *et al.* 2001*;* Muscat *et al.* 2002) and the rest in Europe (Hardell *et al.* 1999*;* Hardell *et al.* 2002a*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2005a*;* Klaeboe *et al.* 2007*;* Schlehofer *et al.* 2007*;* Hours *et al.* 2007). The studies included a total of more than 1,400 cases and 8,500 controls. The largest of these studies, with 678 cases, is a collaborative analysis of five countries in Northern Europe (Schoemaker *et al.* 2005). The highest exposure category including subjects with the longest duration of mobile phone use was > 10 years in the four studies (Hardell *et al.* 2002a*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2005a*;* Schlehofer *et al.* 2007), while in the rest of the studies, the longest exposure durations were from > 3 to > 8 years.

The studies have not provided consistent evidence for the risk of acoustic neuroma in relation to mobile phone use, even though mobile phone use was investigated in several different ways (Table 1). In the five-country joint analysis (Schoemaker *et al.* 2005), increased OR (1.8, 95% CI: 1.1, 3.1) for 10 or more

years of ipsilateral use was found, while the rest of the results did not support any association. The authors suggest that the result may be affected by bias, either due to hearing loss typical for acoustic neuromas leading to the change of the phone side, or to recall bias. Again, the studies by Hardell reported an increase of acoustic neuromas among mobile phone users (Hardell *et al.* 2002a*;* Hardell *et al.* 2005a). An increased risk has been reported for analogue phone use (OR = 3.50, 95% CI: 1.80–6.80) (Hardell *et al.* 2002a) and subsequently to that for > 1-year of use of both analogue (OR = 4.20, 95% CI: 1.80–10.00) and digital phones (OR = 2.00, 95% CI: 1.05–3.80) (Hardell *et al.* 2005a). For 5–10 years of use the risks were again increased in relation to both types of phones, as the ORs were 5.10 (1.90, 14.00) and 2.70 (1.30, 5.70) for analogue and digital phones respectively (Hardell *et al.* 2005a). Also, the risk of ipsilateral acoustic neuromas was increased in relation to the use of both phone types. However, concerns with respect to the methodology and reporting have been expressed regarding both the 2002 study (AGNIR 2003) and the 2005 study (SSI Report 2006).

Table 1. Results of the case-control studies of mobile phones and brain tumours.

Study, year	OR, gliomas (95% CI)	OR, meningiomas (95% CI)	OR, acoustic neuromas (95% CI)	OR, ≥ 10 years of use (95% CI)
Hardell, 1999	0.98 (0.63, 1.50) [a]	1.05 (0.49, 2.27)	0.78 (0.14, 4.20)	1.20 (0.56, 2.59) [b]
Muscat, 2000	0.80 (0.50, 1.20)	–	–	–
Inskip, 2001[c]	0.80 (0.60, 1.20)	0.80 (0.40, 1.30)	1.00 (0.50, 1.90)	–
Hardell 2002a	1.10 (0.90, 1.50) [a, d]	0.80 (0.60, 1.03) [d]	1.20 (0.70, 2.20) [d]	1.80 (1.10, 2.90) [b]
Auvinen, 2002	1.50 (1.00, 1.24)	1.10 (0.50, 2.40)	–	–
Muscat, 2002[c]	–	–	1.70 (0.50, 5.10) [e]	–
Christensen, 2005	0.71 (0.50, 1.01)	0.83 (0.54, 1.28)	–	0.48 (0.19, 1.26) [f]
Lönn, 2005	0.80 (0.60, 1.00)	0.70 (0.50, 0.90)	–	0.90 (0.50, 1.60) [g]
Schoemaker, 2005	–	–	0.90 (0.70, 1.10)	1.10 (0.70, 1.80)
Hardell 2005	–	1.30 (0.90, 1.90) [d]	2.00 (1.05, 3,80) [d]	2.00 (0.90, 4.50) [d, h]
Hepworth, 2006	0.94 (0.78, 1.13)	–	–	1.14 (0.74, 1.73)
Hardell 2006c	1.90 (1.30, 2.70) [a]	–	–	3.60 (1.70, 7.50) [a, d]
Schüz, 2006a	0.98 (0.74, 1.29)	0.84 (0.62, 1.13)	–	2.20 (0.94, 5.11) [g]
Takebayashi, 2007	–	–	0.73 (0.43, 1.23)	–
Schlehofer, 2007	–	–	0.67 (0.38, 1.19)	–
Klaeboe, 2007	0.60 (0.40, 0.90)	0.80 (0.50, 1.10)	0.50 (0.20, 1.00)	–
Hours 2007	1.15 (0.65, 2.05)	0.74 (0.43, 1.28)	0.92 (0.53, 1.59)	–
Takebayashi, 2008	1.22 (0.63, 2.37)	0.70 0.42, 1.16)	–	0.58 (0.09, 3.86) [g]

a) For all malignant tumours (based on the text, these represent tumours that are included in the glioma group in the material of this thesis)
b) For all tumours combined, use of analogue phones
c) The estimates reported in the study were relative risks (RR).
d) Use of digital phones
e) For 3–6 years of use, as the study did not report any risks for overall use.
f) For high-grade glioma
g) For glioma
h) For all benign tumours combined

1.3.1.4. Other studies of mobile phone use and brain tumours

Concerning mobile phone use and brain tumours, two cohort studies have been published to date, the first in 2001 covering years 1982–1995 (Johansen *et al.* 2001) and an update of this study in 2006 with extension of follow-up until 2002 (Schuz *et al.* 2006b). The studies were conducted in Denmark and included 420, 095 subjects with mobile phone subscriptions. The mean follow-up time since the start of the first mobile phone subscription was 8.5 years. The three most common types of brain tumours in the study population were investigated, among several other types of cancer. The number of cases with glioma, meningioma and acoustic neuroma observed during the study period in the study population was 257, 68 and 31 respectively.

The authors of the cohort studies conclude that no evidence of increased brain tumour risk caused by mobile phones was detected in the study. Risk was not associated with all tumours combined (SIR = 0.97) or any single tumour type, as the SIRs for gliomas, meningiomas and nerve sheath tumours comprising most acoustic neuromas were 1.01 (0.89, 1.14), 0.86 (0.67, 1.09) and 0.73 (0.50, 1.03) respectively. The risk was not elevated among long-term mobile phone users as the SIR for > 10 years of use was 0.66 (0.44, 0.95), based on 56, 648 users. The authors consider such a result surprising, as it is not biologically plausible that using a mobile phone would decrease the risk of developing a brain tumour. They conclude that the result can be due to chance, as the result was based on only 28 cases, but also consider the possibility that there is an unknown negative confounding factor affecting the results.

The mortality of mobile phone customers has been investigated in two studies (Rothman *et al.* 1996*;* Dreyer *et al.* 1999) that both used the telephone operators' databases as the exposure source. The first study focused only on the overall mortality that was found to be slightly lower for mobile phone customers than for general population. The latter study also addressed the mortality from brain cancer, which was not increased for mobile phone customers compared to the rest of population. Overall cancer mortality was likewise not elevated among mobile phone customers. The data of the study, however, were quite limited as the follow-up period was only one year and the study included only a few cases of brain cancer deaths, while the cohort included 285, 561 subjects.

Mobile phone use and location of glioma have been investigated in one case-case analysis that included 99 glioma patients (Hartikka *et al.* 2009). In the study, the glioma risk among mobile phone users was evaluated by focusing on the most heavily exposed part of the brain by defining the midpoint of the tumour and the location of the exposure. The risk for glioma among mobile phone users was not statistically significantly increased*;* except for contralateral use the OR was 4.93 (1.13, 21.46). The authors consider the small sample size to be

the main limitation of the study and conclude that a larger study is needed.

The risk of pituitary tumours in relation to mobile phone use was investigated in a recent case-control study (Schoemaker & Swerdlow 2009). The data included 291 cases and 630 controls. The study showed no association between exposure and disease, while mobile phone use was analysed in several different ways. The pituitary adenomas were also included in the Japanese study presented earlier, but no increased risks were detected (Takebayashi *et al.* 2008).

In addition, two meta-analyses, in which the overall effect of mobile phone use on brain tumour risk is evaluated by pooling the original studies, have been published (Kan *et al.* 2008*;* Hardell *et al.* 2008). These meta-analyses will be dealt with in more detail in the discussion.

1.3.2. Effect of mobile phone use on other cancer types

The effect of mobile phone use on other cancer types has been investigated in some studies. The outcomes of the studies have been salivary gland cancers (Auvinen *et al.* 2002*;* Hardell *et al.* 2004*;* Lönn *et al.* 2006*;* Sadetzki *et al.* 2008), lymphoma (Hardell *et al.* 2005b*;* Linet *et al.* 2006), testicular cancer (Hardell *et al.* 2007a), uveal melanoma (Stang *et al.* 2001*;* Stang *et al.* 2009) and facial nerve tumours (Warren *et al.* 2003).

In one study, an indication of an association between salivary gland cancer and mobile phone use was detected (Sadetzki *et al.* 2008), while the other three studies on the issue reported no association (Auvinen *et al.* 2002*;* Hardell *et al.* 2004*;* Lönn *et al.* 2006). Regarding lymphoma, some evidence of an increased risk has been reported, but based on very small number of cases (Hardell *et al.* 2005b*;* Linet *et al.* 2006). The risk for testicular cancer (Hardell *et al.* 2007a) or facial nerve tumours (Warren *et al.* 2003) was not increased in relation to mobile phone use. The risk of uveal melanoma has been investigated by a German study group in two studies, of which the first reported an increased risk (Stang *et al.* 2001) but the second did not detect such an association (Stang *et al.* 2009).

2. Aims of the Study

The general aim of the study was to evaluate the effect of mobile phone use on the risk of brain tumours.

Specific aims of this study were:

1. to assess the possible risk for glioma and meningioma in relation to mobile phone use

2. to summarize the evidence of the published results of the studies on mobile phone use and brain tumours

3. to appraise the impact of selection bias due to non-participation in the Finnish case-control study on mobile phone use and brain tumours

3. Materials and Methods

3.1. Recruitment of subjects to case-control studies

The risk of glioma and meningioma in relation to mobile phone use was investigated in population-based case-control studies conducted in five North European countries, Denmark, Finland, Sweden, Norway and the United Kingdom, between the years 2000 and 2004. The exact study periods differed slightly between countries, but in Finland the study period was from November 2000 to September 2002. As the case-control studies were a part of extensive international research collaboration, the INTERPHONE Study coordinated by WHO, a common research protocol provided by IARC was followed in each country (Cardis & Kilkenny 1999). In the five North European countries, an additional questionnaire focusing on the female reproductive and hormonal factors, birth characteristics, head injuries as well as details of allergic conditions was also used in data collection. The INTERPHONE study concentrated on the most common brain tumours, such as glioma, meningioma and acoustic neuroma.

The case-control studies of glioma and meningioma were carried out in Denmark (nationwide), Finland (excluding Northern Lapland and Åland, representing 98% of the national population), Norway (the southern and central parts, representing 90% of the entire population), Sweden (Umeå, Stockholm, Gothenburg and Lund regions, 65% of the population) and the United Kingdom (Thames region of Southeast England, 23% of the population). The local ethics committees approved the study protocols in each country.

Eligibility criteria for cases included age 20–69 years at diagnosis in the Nordic countries and 18–59 years in Southeast England, residence in the study area and either diagnosis of glioma (International Classification of Diseases for Oncology, Third Edition, codes 9380–9384, 9390–9394, 9400, 9401, 9410, 9411, 9420–9424, 9430, 9440–9444, 9450–9451, 9505) or meningioma (codes 9530–9539). Incident cases during the study period 2000–2004 were identified through neurosurgery, oncology and neurology departments in the study areas. In Finland, the cases were recruited from the five university hospital areas (Helsinki, Turku, Tampere, Kuopio and Oulu). To evaluate and enhance the completeness of coverage, the cases were also checked against the national or regional cancer registries.

In the Nordic countries, national population registers were used for control selection, whereas in the UK in the absence of such a register, the controls were randomly selected from general practitioners' patient lists, which may represent the general population slightly more weakly than the national population

registers. The controls were frequency-matched to the cases by sex, five-year age group and region of residence in all countries. Eligible study subjects were approached either personally at the clinics (cases) or by post (controls). The study was not introduced as focusing on mobile phone use except in Sweden, but most subjects were likely aware of this due to media coverage of the issue. All study subjects received both an invitation letter and written information about the study before being invited to participate. If the subjects contacted by post did not respond, a reminder was sent or the subject was approached by telephone. Informed consent was obtained from all study participants.

3.2. Data collection

3.2.1. Exposure assessment in case-control studies (Studies I and II)

Exposure assessment in the case-control studies on glioma and meningioma was based on a personal interview conducted by trained interviewers and typically performed either at hospital or in some countries at the subject's home. The interview was computer-assisted in all other countries but Finland, where a paper questionnaire with identical wording was used at the time of the interview. Proxy interviews were used for 12% of glioma cases, 1.6% of meningioma cases and 0.06% of controls.

The interview covered use of hand-held mobile phones, medical history, education and family history of brain tumours. Regarding mobile phone use, information on each mobile phone that the subject had regularly used was collected separately. Regular use of mobile phones was defined as making or receiving calls at least once a week for at least six months. For those who had been using a mobile phone regularly, a detailed history of mobile phone use was obtained, including start and end dates, frequency and laterality of use, type of phone, use of hands-free devices, and other factors, such as type of telephone network. Show cards, either on the computer or paper, were used to facilitate recall of the phone models used. Information on the phone models, calendar period of use, operator and network code of the phone number were used to classify phones as analogue or digital.

3.2.2. Retrieval of studies for meta-analysis (Study III)

A meta-analysis was performed to estimate the overall magnitude of the risk for gliomas, meningiomas and acoustic neuromas in relation to mobile phone use. The epidemiological evidence on mobile phone use and brain tumours was searched from the PubMed database (www.ncbi.nlm.nih.gov) using the following search terms either in abstract or title:

1) mobile/cellular phone/telephone and 2) brain tumour/cancer/neoplasm or glioma or meningioma or neuroma/schwannoma. In addition to the PubMed search, the reference lists of the articles retrieved were browsed.

A total of 19 articles (Hardell *et al.* 1999*;* Dreyer *et al.* 1999*;* Muscat *et al.* 2000*;* Hardell *et al.* 2001*;* Inskip *et al.* 2001*;* Johansen *et al.* 2001*;* Hardell *et al.* 2002a*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002b*;* Muscat *et al.* 2002*;* Hardell *et al.* 2003*;* Warren *et al.* 2003*;* Christensen *et al.* 2004*;* Lönn *et al.* 2004a*;* Christensen *et al.* 2005*;* Hardell *et al.* 2005a*;* Schoemaker *et al.* 2005*;* Lönn *et al.* 2005*;* Hardell *et al.* 2006c) were identified from the PubMed database by 1 December 2005. The inclusion criteria required the articles: 1) to be original publications, 2) to use individual exposure data, 3) to be based on case-control or cohort format, 4) to report quantitative measures of association (point estimates expressed either as odds ratios, ORs or as standardised incidence ratios, SIRs) and 5) to report information needed for the estimation of confidence intervals (standard error or confidence interval of effect measure, or number of subjects by exposure and outcome status). As meta-analysis requires that the studies to be pooled have similar aims and end-points, one study was excluded because the end-point was brain tumour mortality rather than incidence (Dreyer *et al.* 1999) and another since it addressed only facial nerve tumours (Warren *et al.* 2003). No unpublished reports were identified. No studies were excluded due to language other than English or due to dissimilar procedures, as both inclusion criteria and exposure assessment methods were similar enough to allow pooling. Grading by quality was not regarded as necessary since the approaches in the studies were relatively uniform.

Of the 17 studies identified fulfilling the criteria, five studies (Hardell *et al.* 2001*;* Hardell *et al.* 2002b*;* Hardell *et al.* 2003*;* Christensen *et al.* 2004*;* Lönn *et al.* 2004a) were excluded from the analysis, because they used study subjects overlapping with the other studies that were already included in the material, leaving finally twelve studies (Hardell *et al.* 1999*;* Muscat *et al.* 2000*;* Inskip *et al.* 2001*;* Johansen *et al.* 2001*;* Auvinen *et al.* 2002*;* Hardell *et al.* 2002a*;* Muscat *et al.* 2002*;* Christensen *et al.* 2005*;* Lönn *et al.* 2005*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2005a*;* Hardell *et al.* 2006c) in the analysis (Table 2). All studies used incident brain tumour cases. One of the studies was a cohort study (Johansen *et al.* 2001), while all others used a case-control design. Half of the studies (Hardell *et al.* 1999*;* Hardell *et al.* 2002a*;* Lönn *et al.* 2005*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2005a*;* Hardell *et al.* 2006c) reported excluding the exposure within one year or less from the index date (diagnosis of cases and corresponding date among controls) in the analysis, while no such restriction of exposure was reported in the other half of the studies. The participation rates were 73%–92% among cases and 51%–91% among controls.

Table 2. Features of the studies included in the meta-analysis (Study III).

First author, year, country	Study base	Included brain tumour types	Cases/ controls [a]	Exposure assessment	Maximum duration of mobile phone use	OR (95% CI) [b]
Hardell 1999, Sweden	Population	Glioma, meningioma	34/69	Postal questionnaire + telephone interview	>5 yrs	0.83 (0.49-1.42)
Muscat 2000, US	Hospital	Glioma	17/22	Interview	>4 yrs	0.70 (0.40-1.40)
Inskip 2001, US	Hospital	Glioma, meningioma, acoustic neuroma	22/31	Interview	>5 yrs	RR = 0.90 (0.50-1.60)
Johansen 2001, Denmark	Population	Glioma, meningioma	82 [c]	Company records	mean follow up 3.1 yrs	SIR = 0.92 (0.74-1.16) [d]
Auvinen 2002, Finland	Population	Glioma, meningioma	18/64	Company records	>2 yrs	1.50 (0.90-2.50)
Hardell 2002a, Sweden	Population	Glioma, meningioma, acoustic neuroma	153/124	Postal questionnaire + telephone interview	>5 yrs	0.92 (0.57-1.47) [e]
Muscat 2002, US	Hospital	Acoustic neuroma	11/6	Interview	3-6 yrs	1.70 (0.50-5.10)
Lönn 2005, Sweden	Population	Glioma, meningioma	136/171	Interview	>5 yrs [f]	0.73 (0.55-0.96) [d]
Christensen 2005, Denmark	Population	Glioma, meningioma	83/193	Interview	≥5 yrs	0.66 (0.46-0.95) [d]
Schoemaker 2005, Nordic countries + UK	Population	Acoustic neuroma	127/646	Interview	>5 yrs [f]	0.95 (0.75-1.18) [d]
Hardell 2005, Sweden	Population	Acoustic neuroma, meningioma	87/129	Postal questionnaire + telephone interview	>5 yrs [f]	1.40 (1.02-1.93) [d]
Hardell 2006c, Sweden	Population	Glioma	98/129	Postal questionnaire + telephone interview	>5 yrs [f]	1.49 (1.10-2.02) [d]

a) The number of cases and controls in the subcategories of the original studies that were included in this meta-analysis. Subcategories were selected to achieve the maximum length of mobile phone use.
b) The overall estimate for brain tumours and mobile phone use used in the meta-analysis
c) A cohort study of 420 095 mobile phone subscribers, with a total of 135 cancer cases of brain and nervous system (no controls).
d) The estimate was calculated by the authors of the meta-analysis by pooling different exposure/ tumour categories reported in the original studies
e) For digital phones
f) The original categories in the articles, 5–9 years (or 5–10) and >10 years, pooled to one category of >5 years

3.2.3. Data collection from refusing study subjects (Study IV)

As the response proportion in the case-control study of brain tumours was not entirely satisfactory in Finland, especially among controls, an additional short questionnaire focusing solely on mobile phone use status and educational attainment was prepared during the first year of the study period. The overall participation rate in the Finnish part of the INTERPHONE study was 46% among primary controls and 84% among cases. The most common reasons for refusal were lack of time, inconvenience and illness in the family.

To evaluate the possible bias due to differential participation in the case-control study of brain tumours in Finland, the short questionnaire was used during the first five months of the study (from April 2001) to collect information from those subjects who refused to grant the full personal interview, both for cases approached personally at the clinics and controls approached by telephone. The short questionnaire contained only two questions, one regarding mobile phone use (regular use or not and start date) and the other elicited the highest educational level attained.

3.3. Statistical methods

3.3.1. Statistical methods in the case-control studies (Studies I and II)

As frequency matching was used throughout the INTERPHONE study, the entire control group recruited for all brain tumours in the matched strata of either the glioma or the meningioma cases, were used in the analyses to increase statistical power. Several features of reported mobile phone use in relation to glioma and meningioma were analysed using both continuous and categorical exposure variables. The cut-points for the categorical exposure variables were defined according to the distribution among controls, so that the never and non-regular users formed the reference category, while the other cut-points were defined by the 50^{th} and 75^{th} percentiles of the exposure distribution among regular mobile phone users. In the analyses of cumulative number of calls and cumulative hours of mobile phone use, the exposure was corrected for the reported use of hands-free devices. The exposure was reduced by 100% if the subject reported use of hands-free devices all the time, by 75% if most of the time, 50% if half of the time and 25% if sometimes but less than half of the time.

For the calculation of exposure indices, a reference date was determined for each subject. The reference date was the date of diagnosis for cases, whereas for controls the reference date was set according to the interview date taking into account the fact that the controls were interviewed on average later than

the cases. Since the prevalence of mobile phone use was likely to increase rapidly over time and it was essential to avoid the effect of the possible interview lag among controls, the reference date for controls was defined using the following formula: $\text{refdate}_{\text{control}} = \text{intdate}_{\text{control}} - [(\text{mean intdate}_{\text{cases}} - \text{mean diagdate}_{\text{cases}}) - (\text{mean intdate}_{\text{cases}} - \text{mean intdate}_{\text{controls}})]$. The reference date calculations were performed separately for each country. To allow for a minimum latency of one year, all mobile phone use within one year prior to the reference date was excluded from the analysis, except when calculating the years since first use, which was evaluated up to the reference date.

The odds ratios (OR) for glioma and meningioma in relation to mobile phone use were estimated by conditional logistic regression, with strata by sex, five-year age group, region and country. The glioma and meningioma datasets were analysed separately. Based on the literature on the aetiology of glioma and meningioma, highest educational level attained, family history of glioma (in the glioma analysis) or meningioma (in the meningioma analysis), radiotherapy to the head and neck region (at least ten years before the reference date), and past diagnosis of neurofibromatosis or tuberous sclerosis of the subject were regarded as potential confounders. All the analyses were conducted both with and without considering the effects of the potential confounding factors.

The risk of glioma and meningioma was evaluated separately by type of phone (analogue and digital) and by tumour location (laterality). The laterality of the tumour was assessed in relation to the reported predominant side of mobile phone use (more than 50% of the time on the same side), using both a method based on cases only (Inskip *et al.* 2001) and another method also including the controls with more statistical power (Lönn *et al.* 2005). The original laterality method by Lönn was slightly modified as the reference group was set to comprise only never and non-regular users, without those using the phone on the other side, who were regarded as non-exposed by Lönn in the unmodified form of this method. As this modification was also done for the glioma analysis subsequent to the publication of the original report (Study I) where the original version of the method was used, the results reported here are somewhat different from the previously published results regarding glioma. All analyses were conducted using STATA statistical software, version 9 (Statacorp 2005).

3.3.2. Methods used in the meta-analysis (Study III)

The studies selected for the meta-analysis were reviewed independently by two authors (Lahkola & Tokola), and all relevant data (ORs, RRs and SIRs with 95% CIs) were retrieved and entered into evidence tables.

In the absence of heterogeneity between studies, the meta-analysis was

carried out using the inverse variance-weighted method for combining the ORs (Sutton *et al.* 2000). This approach is equivalent to fixed effects analysis, assuming that the effect is constant across studies and all differences between studies are attributable to random variation (Sutton *et al.* 2000). When there was heterogeneity between studies, we used random effects analysis, which allows the true risks to vary between studies and assumes a random distribution of these estimates around a common central value.

The weights were calculated based on the width (subtraction of the upper and lower limit) of the confidence interval, due to problems with the rounding of the original confidence intervals (CI) in some of the studies. Also, to improve accuracy, the overall OR for brain tumours was recalculated for one study (Hardell *et al.* 2002a), because the original CIs in the article were reported with only one decimal. For four studies (Lönn *et al.* 2005*;* Schoemaker *et al.* 2005*;* Hardell *et al.* 2005a*;* Hardell *et al.* 2006c), two exposure categories, 5–9 years (or 5–10 years) and > 10 years into > 5 years, were pooled to achieve uniform exposure classification. Further, for those studies reporting the estimates for different tumour categories only separately (Johansen *et al.* 2001*;* Christensen *et al.* 2005) estimates were pooled to calculate of the overall OR (meta-analysis of all tumours combined). When the estimates were not reported for all mobile phones combined (but only separately for analogue and digital phones), the OR for digital phones was used for calculations of the total OR. This was done because digital phone use was more common in most studies and also, it was very likely that the same individuals had been using both analogue and digital telephones and were thus included in both categories in the original reports (Hardell *et al.* 2002a*;* Hardell *et al.* 2005a*;* Hardell *et al.* 2006c).

The meta-analysis concentrated on the subjects most likely to demonstrate an effect (if such exists), i.e. the mobile phone users with the longest period of use. In most studies, the highest exposure category was defined as five or more years of use, but in four studies, the longest period was shorter than this (4 years, 3–6 years, 2 years and the cohort study with a mean follow-up time of 3.1 years). A pooled OR was calculated for all brain tumours combined and also separately for three tumour types: gliomas (9 studies), meningiomas (8 studies) and acoustic neuromas (6 studies). A pooled estimate was also calculated separately by telephone types (analogue and digital, 7 studies) and for ipsi/contralateral use (reported phone use on the same/opposite side of the head where the tumour occurred, 7/5 studies).

Possible heterogeneity between the studies included in the meta-analysis was assessed using the Q statistic to determine whether the results of various studies were consistent enough to be combined. The sensitivity, i.e. the influence of single studies, was evaluated by repeating the calculations of pooled estimates while excluding each study at a time.

3.3.3. Assessment of selection bias in Finnish case-control study (Study IV)

The possible selection bias due to differential participation in the Finnish case-control study was investigated in relation to both mobile phone use and education. In order to assess the effect of the selection bias, we used the data collected through the personal interviews with the study participants and also that obtained from the short questionnaire addressed to those subjects who refused to grant the full personal interview. Cases and controls were investigated separately and the analyses were based on a total of 829 cases (337 women and 492 men) and 1,098 controls (532 women and 566 men). Of the cases, 726 subjects were full participants with personal interview and 103 incomplete participants with only the short survey, whereas among controls the respective corresponding numbers were 777 and 321.

Both mobile phone use status (regular vs. never/ non-regular user) and educational level of the full study participants was compared to those of the subjects with the short questionnaire only (incomplete participants). In addition to this, the effect of sex, education, five-year age group and mobile phone use on study participation was evaluated by logistic regression. Education was classified into three categories in the analyses; low (elementary or comprehensive school), intermediate (upper secondary school, vocational school or college) and high (polytechnic, university). The effect of selection bias was assessed by comparing the OR for brain tumours based on the full study participants with the OR based on the information of both the full study participants and the subjects with only the short questionnaire (incomplete participants). The effect measure used was the Mantel-Haenszel estimate of odds ratio (OR) obtained from analysis stratified by sex, five-year age group, region (university hospital area) and education.

In addition to the full study participants and incomplete participants, there were a total of 65 cases and 519 controls who refused to participate in both the full interview and the short questionnaire. To evaluate mobile phone use among these subjects, we searched a public telephone number database for the possible mobile phone numbers of two sub-groups of controls: randomly selected 50 study participants and 50 total refusers. The number search from the database was performed based on the name and home address of the subject and those for whom a matching entry (in terms of both criteria) was found were classified as mobile phone users.

4. Results

4.1. Risk of glioma and meningioma in relation to mobile phone use (Studies I and II)

A total of 2,530 eligible glioma cases, 1,629 meningioma cases and 6,581 controls were identified in the studies. Of the glioma cases, 60% (1,521 subjects, range 37–81% between countries) and of meningioma cases, 74% (1,209 subjects, range 55–90%) participated to the study. The corresponding figure for controls was 50% (3,301 subjects, range 42–69%) (Table 3). The main reasons for non-participation were refusal (8% of glioma cases, 9% of meningioma cases and 33% of controls), illness or death (18% of glioma cases, 3% of meningioma cases and 0.5% of controls) and failure to contact the subject (7% of glioma cases, 8% of meningioma cases and 15% of controls). Since both datasets (glioma and meningioma) contained strata either without cases or controls, the number of subjects included in the analyses was somewhat smaller than the number of participating subjects (the number of excluded subjects was 170 for glioma and 349 for meningioma analysis). Demographic characteristics of the study subjects are shown in Table 4.

Table 3. Country-specific details of the subjects included in the case-control study on brain tumours and mobile phone use (Studies I and II).

	Number of subjects			Participation rate (%)			Number of telephone interviews		
	Gliomas	Meningiomas	Controls	Gliomas	Meningiomas	Controls	Gliomas	Meningiomas	Controls
Denmark	247	173	819	71	73	52	0	–	–
Finland	266	334	870	81	90	42	3	3	7
Norway	284	206	353	77	71	69	145	99	159
Sweden	363	271	629	74	84	66	18	12	40
UK	361	225	630	37	55	43	0	–	2
Total	1521	1209	3301	60	74	50	166	114	208

Table 4. Demographic characteristics of the study subjects of the case-control study on brain tumours and mobile phone use (Studies I and II).

	Gliomas (n = 1521)		Meningiomas (n = 1209)		Controls (n = 3301)	
	n	%	n	%	n	%
Sex						
Male	893	58.7	301	24.9	1530	46.4
Female	628	41.3	908	75.1	1771	53.7
Age at interview						
18–29	134	8.8	22	1.8	219	6.6
30–39	252	16.6	119	9.8	467	14.2
40–49	329	21.6	279	23.1	742	22.5
50–59	480	31.6	485	40.1	1116	33.8
60–69	326	21.4	304	25.1	757	22.9
Highest educational level						
Comprehensive school	429	28.2	399	33.0	933	28.3
Secondary/ vocational school	367	24.1	285	23.6	789	23.9
Upper secondary school	336	22.1	236	19.5	832	25.2
University	380	25.0	284	23.5	740	22.4
Not known	9	0.6	5	0.4	7	0.2
Mobile phone use						
Regular use, yes/no	867/629	58/42	573/631	48/52	1853/1281	59/41
Years since first use, mean/ max	3.7/ 16.5	–	2.8/ 14.9	–	3.5/ 15.4	–
Cumulative hours of use, mean/ max [a)]	596/ 31817	–	408/ 35960	–	375/ 35475	–
Subjects using hands-free devices	194	12.8	85	7.0	331	10.0

Adjustment for family history and socio-economic status in the analyses did not affect the results, nor did the exclusion of subjects with neurofibromatosis, tuberous sclerosis or a previous history of radiotherapy to the head and neck region. Therefore, all results are from analyses taking into account only the stratification variables (sex, five-year age group, region and country).

Regular use of mobile phone was reported by 58% (867) of glioma cases, 48% (573) of meningioma cases and 59% (1,853) of controls. The OR for glioma in relation to regular mobile phone use was 0.78 (0.68, 0.91) and for meningioma it was 0.76 (0.65, 0.89) (Table 5). Years since first mobile phone use resulted in almost identical estimates for glioma and meningioma, as the ORs for the different tumour types were 0.99 (0.97, 1.01) and 0.99 (0.96, 1.01) per year respectively.

Cumulative number of calls was not associated either with the risk of glioma (OR = 1.00 per 10,000 calls, 95% CI: 0.97, 1.04) or meningioma (OR = 1.00 per 10,000 calls, 95% CI: 0.96, 1.05). In the glioma analysis, the OR for cumulative hours of mobile phone use based on analyses of continuous variable was 1.006 per 100 hours (1.002, 1.010) but there was no trend of risk with cumulative hours of use when the data were examined in categories (Table 5). A similar phenomenon was seen in the meningioma analysis, where the OR for continuous variable was 1.005 per 100 hours (1.001, 1.010).

Since the analyses of continuous and categorical variables for cumulative hours of use gave inconsistent results for both glioma and meningioma, the data were further explored and it emerged that the distribution of the continuous variable in both datasets was skewed. The continuous variable of cumulative hours of use included some very high and most likely erroneous values, which, in turn, was reflected in subjects with implausibly high reported mean daily hours of use over long periods, leading to an untrue relationship between exposure and disease. When the subjects with more than 2 hours daily use through entire exposure history were excluded (in the glioma analysis: 49 controls and 49 cases, 2.1% of observations, in the meningioma analysis: 44 controls and 27 cases, 1.7% of observations), no relation was detected either for gliomas or meningiomas.

Table 5. Odds ratios for glioma and meningioma in relation to various characteristics of mobile phone use, with numbers of glioma and meningioma cases with their controls included in the analyses (Studies I and II).

	Gliomas [a]	Controls [a]	OR (95% CI)	Meningiomas [a]	Controls [a]	OR (95% CI)
Frequency of use						
Never/ non-regular use [b]	629	1281	1.0	631	1249	1.0
Regular use	867	1853	0.78 (0.68, 0.91)	573	1696	0.76 (0.65, 0.89)
Years since first use [c]						
1.5–4	383	895	0.77 (0.65, 0.91)	286	808	0.72 (0.60, 0.86)
5–9	341	738	0.75 (0.62, 0.90)	214	676	0.78 (0.64, 0.96)
≥10	143	220	0.95 (0.74, 1.23)	73	212	0.91 (0.67, 1.25)
Cumulative hours of use [d])						
< median	368	895	0.75 (0.64, 0.89)	278	850	0.68 (0.57, 0.82)
median- 3rd quartile	193	446	0.69 (0.55, 0.85)	125	376	0.79 (0.62, 1.02)
>3rd quartile	262	455	0.90 (0.73, 1.10)	140	411	0.88 (0.68, 1.13)
Analogue phones						
Regular use	232	471	0.85 (0.68, 1.06)	125	437	0.76 (0.58, 0.98)
Years since first use [c])						
1.5–4	26	55	1.22 (0.72, 2.08)	9	49	0.40 (0.18, 0.86)
5–9	99	230	0.71 (0.53, 0.96)	62	212	0.76 (0.54, 1.07)
≥10	107	186	0.93 (0.69, 1.24)	54	176	0.88 (0.61, 1.27)

a) The numbers do not exactly match the total numbers of glioma and meningioma cases (1521 and 1209) and controls (3301) since there were strata without cases and strata without controls in the data (the number of excluded subjects was 170 for glioma and 349 for meningioma analysis). The number of controls is different in glioma and meningioma analyses for this same reason.

b) Reference category used in all analyses

c) Lower limit 1.5 years since phone use was defined as regular when phone was used at least six months at least one year prior to reference date.

d) Estimates adjusted for use of hands-free devices. The cut-points are defined by 50th and 75th percentiles of the exposure distribution among controls who were regular mobile phone users. Data are divided, according to the distribution in controls, into <125, 125–503 and >503 in the glioma analysis, and <125, 125–514 and >514 in the meningioma analysis.

Table 5. Continued.

	Gliomas [a)]	Controls [a)]	OR (95% CI)	Meningiomas [a)]	Controls [a)]	OR (95% CI)
Digital phones						
Regular use	788	1750	0.75 (0.65, 0.87)	533	1598	0.74 (0.63, 0.87)
Years since first use [c)]						
1.5–4	458	1090	0.72 (0.61, 0.85)	342	992	0.72 (0.61, 0.86)
5–9	326	648	0.80 (0.66, 0.96)	183	593	0.77 (0.62, 0.95)
≥10	4	12	0.53 (0.16, 1.72)	8	13	1.85 (0.70, 4.90)

a) The numbers do not exactly match the total numbers of glioma and meningioma cases (1521 and 1209) and controls (3301) since there were strata without cases and strata without controls in the data (the number of excluded subjects was 170 for glioma and 349 for meningioma analysis). The number of controls is different in glioma and meningioma analyses for this same reason.
b) Reference category used in all analyses
c) Lower limit 1.5 years since phone use was defined as regular when phone was used at least six months at least one year prior to reference date.
d) Estimates adjusted for use of hands-free devices. The cut-points are defined by 50th and 75th percentiles of the exposure distribution among controls who were regular mobile phone users. Data are divided, according to the distribution in controls, into <125, 125–503 and >503 in the glioma analysis, and <125, 125–514 and >514 in the meningioma analysis.

The analyses based on different telephone types did not show an association between mobile phone use and gliomas or meningiomas (Table 5). Neither did the laterality analysis based on the method of Lönn (Lönn *et al.* 2005) yield evidence that mobile phone use on the same side of the head as the tumour were associated with each other. The estimates were mostly below 1.0 and the results were fairly similar for both tumour types (Table 6). Mobile phone use on the opposite side of the head from the tumour site yielded even smaller estimates of risk, for both gliomas and meningiomas (Table 6). The updated analyses of glioma showed less association than the original results presented in the publication, where the ORs for year since first ipsilateral use were 1.08 (0.88, 1.31), 1.10 (0.89, 1.35) and 1.39 (1.01, 1.92) in categories of 1.5–4, 5–9 and >10 years respectively (Study I).

When the location of gliomas was investigated using the case-only method (Inskip *et al.* 2001) the relative risk (RR) for ipsilateral mobile phone use of 1.24 (Fisher's exact test: $p<0.001$, two-sided) was obtained on the basis of 674 (394 exposed, 278 unexposed) glioma cases. For meningiomas, the RR obtained in the similar analysis was 1.09 ($p = 0.10$) on the basis of 212 exposed and 184 unexposed meningioma cases.

Table 6. Odds ratios for glioma and meningioma in relation to laterality of tumours and reported side of mobile phone use (Studies I and II).

	Gliomas [a]	Controls [a]	OR (95% CI)	Meningiomas [a]	Controls [a]	OR (95% CI)
Ipsilateral phone use [b]						
Frequency of use						
Never/ non-regular use [c]	532	1281	1.0	486	1249	1.0
Regular	471	1002	0.93 (0.78, 1.11)	250	918	0.81 (0.66, 0.99)
Years since first use						
1.5-4 [d]	205	485	0.86 (0.70, 1.09)	128	442	0.77 (0.60, 0.99)
5-9	189	400	0.92 (0.73, 1.16)	89	363	0.78 (0.56, 1.04)
≥10	77	117	1.14 (0.82, 1.60)	33	113	1.05 (0.67, 1.65)
Cumulative hours of use [e]						
< median	202	492	0.88 (0.71, 1.09)	127	469	0.75 (0.59, 0.97)
median-3rd quartile	113	251	0.86 (0.65, 1.13)	59	208	0.82 (0.57, 1.15)
>3rd quartile	136	247	1.02 (0.78, 1.33)	58	225	0.89 (0.62, 1.27)

a) The numbers do not exactly match the total numbers of glioma and meningioma cases (1521 and 1209) and controls (3301) since there were strata without cases and strata without controls in the data (the number of excluded subjects was 170 for glioma and 349 for meningioma analysis). The number of controls is different in glioma and meningioma analyses for this same reason). Also, this analysis includes only subjects with both side of tumour and use known.

b) Ipsilateral phone use = mobile phone use on the same side of the head as the tumour, contralateral phone use = mobile phone use on the opposite side of the head as the tumour.

c) Reference category used in all analyses. The number of cases in the reference group in the glioma analysis is different to the main analysis (629) since there were 97 cases for whom the side of the tumour was not defined (80 with a central tumour and 17 with a missing value). In the meningioma analysis the numbers differ with the main analysis (631) for the same reason (115 central tumours and 30 missing values).

d) Lower limit 1.5 years since phone use was defined as regular when phone was used for at least six months during a period at least one year prior to reference date.

e) Estimates adjusted for use of hands-free devices. For ipsilateral phone use data are divided, according to the distribution in controls, into <136, 136-567 and >567 in the glioma analysis, and <136, 136-573 and >573 in the meningioma analysis. For contralateral phone use, data are divided into <132, 132-553 and >553 in the glioma analysis, and <133, 133-566 and >566 in the meningioma analysis.

Table 6. Continued.

	Gliomas [a]	Controls [a]	OR (95% CI)	Meningiomas [a]	Controls [a]	OR (95% CI)
Contralateral phone use [b]						
Frequency of use						
Never/ non-regular use [c]	532	1281	1.0	486	1249	1.0
Regular	354	986	0.73 (0.61, 0.88)	224	905	0.67 (0.54, 0.83)
Years since first use						
1.5-4 [b]	150	474	0.68 (0.54, 0.86)	105	424	0.62 (0.47, 0.80)
5-9	137	391	0.71 (0.55, 0.91)	95	364	0.78 (0.58, 1.05)
≥10	67	121	0.97 (0.68, 1.38)	24	117	0.62 (0.38, 1.03)
Cumulative hours of use [e]						
< median	140	485	0.63 (0.50, 0.80)	111	456	0.62 (0.48, 0.80)
median-3rd quartile	97	249	0.77 (0.58, 1.03)	50	220	0.65 (0.45, 0.94)
>3rd quartile	106	240	0.86 (0.64, 1.15)	58	216	0.81 (0.56, 1.17)

a) The numbers do not exactly match the total numbers of glioma and meningioma cases (1521 and 1209) and controls (3301) since there were strata without cases and strata without controls in the data (the number of excluded subjects was 170 for glioma and 349 for meningioma analysis). The number of controls is different in glioma and meningioma analyses for this same reason). Also, this analysis includes only subjects with both side of tumour and use known.

b) Ipsilateral phone use = mobile phone use on the same side of the head as the tumour, contralateral phone use = mobile phone use on the opposite side of the head as the tumour.

c) Reference category used in all analyses. The number of cases in the reference group in the glioma analysis is different to the main analysis (629) since there were 97 cases for whom the side of the tumour was not defined (80 with a central tumour and 17 with a missing value). In the meningioma analysis the numbers differ with the main analysis (631) for the same reason (115 central tumours and 30 missing values).

d) Lower limit 1.5 years since phone use was defined as regular when phone was used for at least six months during a period at least one year prior to reference date.

e) Estimates adjusted for use of hands-free devices. For ipsilateral phone use data are divided, according to the distribution in controls, into <136, 136-567 and >567 in the glioma analysis, and <136, 136-573 and >573 in the meningioma analysis. For contralateral phone use, data are divided into <132, 132-553 and >553 in the glioma analysis, and <133, 133-566 and >566 in the meningioma analysis.

4.2. Meta-analysis of brain tumours and mobile phone use (Study III)

The main result of the meta-analysis, the pooled estimate for all tumour types combined, based on the twelve studies on brain tumours and mobile phone use, did not show an association between exposure and disease (OR = 0.98, 95% CI: 0.83–1.16, Figure 1). As there was evidence for heterogeneity between the pooled studies, a random effects model was used for the calculation of the main result. According to the sensitivity analysis, the OR was not found to be strongly influenced by any single study (Table 7).

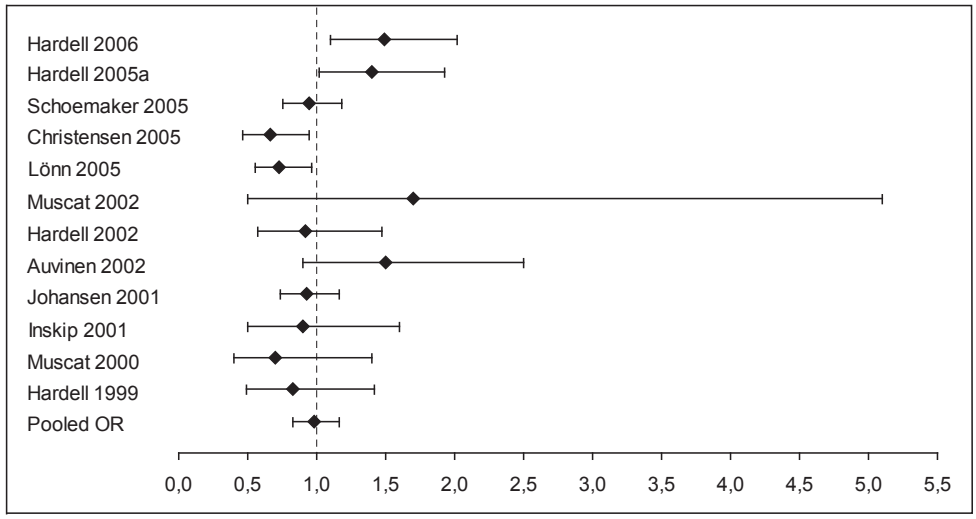

Figure 1. Results of the studies (ORs with 95% CIs) included in the meta-analysis and the pooled OR (0.98, 95% CI 0.83–1.16) for the risk of brain tumours in relation to mobile phone use (on log scale).

Table 7. The Sensitivity analysis (effect of single studies) of the pooled OR (0.98, 95% CI 0.83–1.16, *p* for heterogeneity 0.454, for all brain tumours) (Study III).

Study excluded from the analysis	OR [a)]	95% CI	*p* for heterogeneity [a)]
Hardell 1999	0.99	0.83–1.19	0.429
Muscat 2000	1.00	0.83–1.19	0.448
Inskip 2001	0.99	0.82–1.18	0.419
Johansen 2001	0.99	0.81–1.21	0.511
Auvinen 2002	0.95	0.80–1.13	0.476
Hardell 2002a	0.99	0.82–1.19	0.428
Muscat 2002	0.97	0.84–1.15	0.440
Lönn 2005	1.02	0.85–1.21	0.442
Christensen 2005	1.02	0.86–1.21	0.473
Schoemaker 2005	0.99	0.81–1.20	0.516
Hardell 2005	0.94	0.79–1.11	0.442
Hardell 2006c	0.93	0.79–1.09	0.418

a) After exclusion of the study indicated on each particular row

The pooled estimates calculated for different histological types of tumours were similar both to each other and to the main result. The pooled estimate for gliomas and meningiomas were slightly below one, whereas for acoustic neuromas the OR was slightly above one. Moreover, no major differences in the results were detected in the analysis by telephone type (analogue/ digital), while the estimate for analogue phones was slightly higher than that for digital phones. For ipsilateral tumours (i.e. those occurring on the same side as that on which the mobile phone was used) the OR was above one, with borderline non-significance, whereas the OR for contralateral tumors was very close to one. (Table 8).

Table 8. Pooled estimates from the meta-analysis of mobile phone use and risk of brain tumours, with measures of heterogeneity (Study III).

Tumour or telephone types investigated	Studies included in the meta-analysis	Model used	Heterogeneity in the used model	Pooled OR (95% CI)
All brain tumours [a]	Hardell 1999, Muscat 2000, Inskip 2001, Johansen 2001, Auvinen 2002, Hardell 2002a, Muscat 2002, Christensen 2005, Lönn 2005, Schoemaker 2005, Hardell 2005, Hardell 2006c	Random effects	$\chi^2 = 10.88$, $p = 0.454$	0.98 (0.83–1.16)
Gliomas [b]	Hardell 1999, Muscat 2000, Inskip 2001, Johansen 2001, Auvinen 2002, Hardell 2002a, Christensen 2005, Lönn 2005, Hardell 2006c	Random effects	$\chi^2 = 8.64$, $p = 0.373$	0.96 (0.78–1.18)
Meningiomas [b]	Hardell 1999, Inskip 2001, Johansen 2001, Auvinen 2002, Christensen 2005, Lönn 2005, Hardell 2005	Fixed effects	$\chi^2 = 7.28$, $p = 0.401$	0.87 (0.72–1.05)
Acoustic neuromas [b]	Hardell 1999, Inskip 2001, Hardell 2002a, Muscat 2002, Schoemaker 2005, Hardell 2005	Fixed effects	$\chi^2 = 5.69$, $p = 0.337$	1.07 (0.89–1.30)
Analogue phones [c]	Hardell 1999, Auvinen 2002, Hardell 2002a, Lönn 2005, Schoemaker 2005, Hardell 2005, Hardell 2006c	Random effects	$\chi^2 = 6.11$, $p = 0.411$	1.17 (0.91–1.49)
Digital phones [c]	Hardell 1999, Auvinen 2002, Hardell 2002a, Lönn 2005, Schoemaker 2005, Hardell 2005, Hardell 2006c	Random effects	$\chi^2 = 5.57$, $p = 0.473$	1.04 (0.80– 1.35)
Ipsilateral tumours [d, e]	Hardell 1999, Inskip 2001, Hardell 2002a, Muscat 2002, Lönn 2005, Schoemaker 2005, Hardell 2005, Hardell 2006c	Random effects	$\chi^2 = 10.70$, $p = 0.152$	1.36 (0.99–1.87)
Contralateral tumours [d, f]	Hardell 2002a, Lönn 2005, Schoemaker 2005, Hardell 2005, Hardell 2006c	Random effects	$\chi^2 = 4.30$, $p = 0.367$	1.02 (0.78–1.35)

a) The longest duration of exposure was >5 years in all other reports except in studies by Muscat 2000 & 2002 reporting >4 & 3-6 years, Johansen 2001 with mean follow-up time of 3.1 years and Auvinen 2002 reporting >2 years

b) The duration of the exposure was >5 years in all other reports, except in studies by Hardell 1999 & 2002 reporting >1 years, Muscat 2000 reporting >4 years, Johansen 2001 reporting "ever use", Auvinen 2002 reporting >2 years and Muscat 2002 reporting 3-6 years

c) The duration of the exposure was >5 years in all other reports except in study by Auvinen 2002 reporting >2 years

d) Ipsilateral = tumour located on the same side of the head on which the mobile phone was used, contralateral = tumour located on the opposite side of the head on which the mobile phone was used

e) The duration of the exposure was >1 years in all other reports, except in studies by Inskip 2001 reporting >0.5 years and Lönn 2005 & Schoemaker 2005 reporting >5 years

f) The duration of the exposure was >1 years in all other reports except in studies by Lönn 2005 & Schoemaker 2005 reporting >5 years

4.3. Selection bias in the Finnish case-control study on mobile phone use and brain tumours (Study IV)

Among the controls in the Finnish study of brain tumours, regular use of mobile phone was more common among full study participants (83%, 95% CI: 81, 86) than among the incomplete participants with only the short survey (73%, 95% CI: 68, 76). Among cases too, the full study participants reported mobile phone use more frequently than the incomplete participants (76%, 95% CI: 73, 80, versus 64%, 95% CI: 55, 74) (Table 9).

Control full participants were more highly educated than those controls only completing the short questionnaire. The prevalence of high, intermediate and low level of education among full study participants was 16%, 54% and 29%, whereas for the incomplete participants the corresponding figures were 9, 44 and 48% respectively ($p<0.001$). For cases too, the educational level seemed to be in relation to full participation, as the proportion of subjects with high educational level was greater among the full study participants than incomplete participants (22% and 6% respectively) (Table 9).

Table 9. Mobile phone use and educational level by study participation in the Finnish case-control study on brain tumours (Study IV).

	Cases (n = 829) n (%)		**Controls (n = 1098) n (%)**	
	Study participants (n = 726)	Incomplete participants (n = 103)	Study participants (n = 777)	Incomplete participants (n = 321)
Regular mobile phone use				
Yes	554 (76%)	65 (64%)	646 (83%)	230 (72%)
No	172 (24%)	36 (36%)	131 (17%)	87 (27%)
Highest educational level				
Low	257 (35%)	51 (50%)	228 (29%)	150 (47%)
Intermediate	313 (43%)	46 (46%)	422 (54%)	138 (43%)
High	156 (21%)	6 (6%)	127 (16%)	28 (9%)

In the multivariate logistic regression, there was an association between mobile phone use and full study participation both among cases and controls even after controlling for age, sex and education. The crude and adjusted ORs for full participation were 1.9 (1.4, 2.5) and 1.9 (1.4, 2.8) for controls respectively, whereas for cases the figures were 1.8 (1.1, 2.8) and 1.5 (0.9, 1.4) respectively. The odds ratio for regular mobile phone use based on the full study participants, was 0.55 (0.39, 0.77), whereas the OR based on the incomplete participants was 0.62 (0.26, 1.51). The OR based on both full study participants and incomplete participants was 0.73 (0.56, 0.96).

Of the 50 randomly selected controls who participated fully in the study, 64% had a listed mobile phone number, whereas among those 50 controls who refused to participate both in the study and in the short questionnaire, only for 42% was a mobile phone number found ($p = 0.03$). This finding indicates that mobile phone use may have played a role in study participation.

5. Discussion

5.1. General discussion of the results

In light of the findings of the work presented in this dissertation, mobile phone use is not likely to have a major impact on the risk of brain tumours. In the five-country case-control studies on mobile phone use, the risk for either gliomas or meningiomas was not generally elevated despite the numerous analyses investigating several different measures of mobile phone use. The only indication of a possible positive association between mobile phone use and brain tumours was detected in the case-case analysis of laterality, where the risk for ipsilateral gliomas was slightly increased, based on a substantially smaller number of cases than in the main analysis. The reported side of the head where the cases had mainly used the phone may be affected by the fact that they were aware of the side of their tumour (recall bias). Therefore, this result needs careful interpretation due to the possibility of bias in the reporting of the side of phone use, and also because of the smaller number of subjects included in the analysis than in the data in total. However, the finding is also consistent with a local effect of the RF radiation emitted by a mobile phone.

The analyses of cumulative hours of mobile phone use yielded inconsistent results for both gliomas and meningiomas. In the analyses based on a continuous exposure indicator, a slightly increased risk for gliomas and meningiomas was detected, while no such association was found when the data were examined in categories. The analyses of continuous variables in both datasets were, however, driven by a small number of influential extreme values. Some of them may be erroneous, as they included implausibly high daily hours of use, up to 17 hours per day. When the subjects with the highest daily phone use (> 2 hours throughout the entire usage history) were excluded, no association was detected for either gliomas or meningiomas. In the validation studies, where the self-reported data collected within the INTERPHONE study was compared to the data provided by the telephone operators, duration of calls was not the most adequate indicator of mobile phone use, since the consistency between the two sources of information is low (Samkange-Zeeb *et al.* 2004*;* Berg *et al.* 2005*;* Vrijheid *et al.* 2008).

As cumulative hours of use in the present data were initially computed from two separate measures of exposure, the number and duration of calls per day taking into account the duration of entire exposure history, it may be imprecise and therefore it should probably not be regarded as the principal tool for exposure assessment regarding mobile phone use. During the planning phase

of the analyses and fully unaware of such imprecision of the estimate, cumulative hours of use was, however, considered an important measure reflecting the lifetime cumulative exposure to RF radiation emitted by mobile phones.

In the meta-analysis, where the results of 12 epidemiological studies focusing on the possible brain tumour risk of mobile phones were combined, little association between the exposure and disease was detected within five years from the start of use. There was no association for all brain tumours combined, or for tumours of different histological origin analysed in separate groups. A weak non-significant association was detected in relation to use of analogue telephones. An increased risk for ipsilateral tumours with borderline significance was detected but the result needs to be interpreted with caution, as the original studies included in the meta-analysis may have been subject to recall bias in the reporting of the side of phone use among brain tumour cases.

The overall findings of this dissertation concur with the majority of original studies performed by other study groups, also the studies within the INTERPHONE collaboration (presented in the Section 1.3.1). The publication of the INTERPHONE study results based on the whole 13-country analysis have now been expected for several years, but it seems that they will finally be published in the near future. The 13-country results are of great value, as the data includes the most cases published in any study so far.

Subsequent to the meta-analysis of this dissertation, another two meta-analyses also including the most recent original studies on mobile phone use and brain tumours were published (Kan *et al.* 2008*;* Hardell *et al.* 2008). The results of the first work regarding the overall effect of mobile phone use were fairly similar to those detected in the meta-analysis of this dissertation, while some evidence of increased risk for brain tumours was detected in relation to long-term (≥ 10 years) use (OR = 1.25, 95% CI 1.01–1.54) based on five studies. The authors, however, concluded that this result should be confirmed by additional data from future studies. For some reason, the meta-analysis did not include all studies available at the time when the work was accomplished.

The authors of the latter meta-analysis again reported similar results regarding the overall effect but suggest that there is a consistent pattern of an association between mobile phone use and ipsilateral glioma (OR = 2.0, 95% CI 1.2–3.4) and acoustic neuroma (OR = 2.4, 95% CI 1.1–5.3) using ≥ 10 years latency period (Hardell *et al.* 2008). Those results, however were based on only those studies that reported estimates for more than 10 years of mobile phone use, leaving in the analysis a total of 6 studies for glioma and 4 studies for acoustic neuroma. In the main analysis for overall effect of mobile phone use, there were altogether 10 glioma studies (OR = 0.9, 95% CI 0.8–1.1) and 9 acoustic neuroma studies (OR = 0.9, 95% CI 0.7–1.1). The risk of meningioma was not elevated in

any analysis. Prior to the Swedish meta-analysis, the same authors published a review with a narrow meta-analysis where they also reported elevated risks for gliomas and acoustic neuromas (Hardell *et al.* 2007b). Interestingly, most of the studies included in that report are the same as those included in the meta-analysis in the material of this dissertation that did not find such an association.

For criticism, one needs to emphasize that not all studies included in the two Swedish meta-analyses are based on individual datasets, as both the individual studies published separately and the five-country joint analyses within the INTERPHONE collaboration are included in the material. As the data from both Sweden and Denmark are also included in the five-country case-control studies on glioma and acoustic neuroma, there is overlap in material between the studies included in the Swedish meta-analyses. Finally, the majority of the evidence supporting an association between mobile phone use and brain tumours is from the author's own scientific work that has already been questioned in the scientific field due to methodological limitations. Hardell's study group seems to find positive associations in almost all studies but it has not, however, been possible to find such sources of error in their reports that would explain the positive results. In the latter Swedish meta-analysis, the authors, however, report that if they excluded their own two studies from the analysis the ORs for ≥ 10 years of ipsilateral use would be 1.5 (1.1, 1.9) and 2.1 (0.7, 6.1) for glioma and acoustic neuroma, respectively.

In addition to the previous two meta-analyses, one review reporting combined risk estimates for mobile phone use and brain tumours has also recently been published (Kundi 2009). The authors suggest that there is evidence of an increased risk (OR for gliomas = 1.5, 95% CI 1.2–1.8) but point out that there was no evidence-based exposure metric available and the duration of mobile phone use was still too low in the published studies. They also suggest that several biases may have distorted the results of the original studies.

In contrast to the studies presented above, several reviews and committee reports on the health effects of mobile phone use have previously concluded that there is no convincing evidence that mobile phone use can cause brain tumours (Valberg 1997*;* IEGMP 2000*;* AGNIR 2003*;* Ahlbom *et al.* 2004*;* Feychting *et al.* 2005*;* SCENIHR 2007*;* SSI Report 2007*;* Kan *et al.* 2008*;* SSI Report 2008*;* SCENIHR 2009). The most recent summaries suggest that mobile phone use of less than 10 years does not increase the risk for brain tumours but on long-term use the data are still sparse and conclusions tentative (SSI Report 2008*;* SCENIHR 2009). Therefore, a common recommendation of the committee reports is to carry on further research particularly on long-term exposures and to use cohort design to avoid the sources of error commonly present in case-control studies.

5.2. Strengths and weaknesses of the present studies

There are several strengths in the studies presented in this dissertation. The case-control studies on brain tumours included a larger number of cases, both for gliomas and meningiomas, compared to studies published earlier on the issue. The number of subjects allowed detailed analyses of various aspects of mobile phone use and increased precision of risk estimates. On the other hand, the weaknesses of the case-control studies were the low participation rate among controls and the fact that the exposure assessment was based on self-reports of past exposure. The number of long-term users in these studies was still low compared to the total number of subjects included. If mobile phone use had an effect on brain tumour development, it might have needed longer duration of exposure than what it was possible to achieve in these studies. The effect of confounding seemed unlikely in the studies, since controlling for the known factors, particular hereditary syndromes and previous exposure to ionising radiation, did not alter the results in any analysis. In addition, adjustment for possible interview lag among controls was likely to minimise the role of confounding in relation to the timing of exposure before the interview.

Meta-analysis serves as a powerful tool to estimate the overall effect of particular exposure and disease. Also, despite some inconsistencies regarding classification of exposures, the studies included in the meta-analysis were similar enough, allowing the comprehensive pooling and effective assessment of the overall magnitude of the possible effect of mobile phone use on the risk for brain tumours. Nevertheless, combining published results in a meta-analysis does not allow equally flexible exploration of material as use of primary data. For instance, cross-classification of laterality and amount of use was not possible. As the majority of the original studies did not show an association between mobile phone use and risk of brain tumours, the presence of publication bias in the meta-analysis is unlikely. Usually publication bias is introduced when studies with positive results are both submitted and accepted for publication more easily than those with results indicating no effect (Gail & Benichou 2000). On the other hand, the longest exposure history achieved in the meta-analysis, due to the limitations of the studies included, was five years, which is a relatively short period for tumour induction. Therefore, as the meta-analysis failed to investigate long-term exposures, further research is needed before firm conclusions can be drawn.

Differences in study participation by exposure status may induce selection bias. For instance, if unexposed controls are under-represented among the study subjects, it will lead to the underestimation of the overall effect. The study on selection bias showed that the controls who were not mobile phone users were less likely to participate in the Finnish part of the INTERPHONE study.

However, a similar phenomenon was also detected among cases. Based on these observations, the presence of selection bias in the Finnish study was possible, which was seen when the risk for brain tumours in relation to mobile phone use was evaluated. The OR for brain tumours based on study participants was below unity and showed an apparent protective effect. However, when the incomplete participants were included in the analysis, the protective effect was substantially reduced. Although there was evidence that mobile phone use had played a role in study participation, it resulted in only a slight distortion of the outcome measure away from the null. Thus, the effect of selection bias was not deemed considerable in the Finnish study.

Even though the results regarding selection bias concerned only the Finnish part of the INTERPHONE study, it is likely that the five country studies of glioma and meningioma may also have been affected by selection bias. The risk estimates almost throughout the glioma and meningioma studies were below unity and thus showed a protective effect similar to that detected in the Finnish selection bias study. Decreased risks have also been reported elsewhere, both for glioma and meningioma (Table 1). The Swedish INTERPHONE study group has also reported an indication of the presence of selection bias in the Swedish study (Lönn *et al.* 2005), where the controls were more likely to participate if they were mobile phone users possibly leading to the decreased risk estimates detected in the study.

The recent results from the INTERPHONE study based on most participating study centres also suggest that study participation is related to mobile phone use, even the study was not introduced in all countries as a "mobile phone study" but as a "study focusing on brain tumour aetiology". The effect of such selection is reported to result in a downward bias of around 10% in odds ratios for regular mobile phone use (Vrijheid *et al.* 2009). Prior to that study, a simulation of the impact of possible selection bias within the INTERPHONE study was also performed (Vrijheid *et al.* 2006b). When unexposed study subjects were assumed to be under-represented in the study population, the simulations resulted in reduced risk estimates for mobile phone use and risk of brain tumours. Selection bias had, however, less impact on the estimates than random error. In light of these findings regarding selection bias, it is more likely that the low risk estimates in glioma and meningioma studies are caused by selection bias than that mobile phone use actually protects against brain tumours.

In addition to selection bias, several other sources of errors may also have affected the results regarding the case-control studies. As mobile phone use is nowadays an unremarkable part of everyday activities, the accurate recall of past usage patterns may be problematic. Also, the amount of use has tended to increase, which may result in reporting exposures reflecting more closely current

than past behaviour. Reports of past mobile phone use are subject to random error, as recall, even in the short term, has been shown to be inaccurate (Parslow *et al.* 2003*;* Samkange-Zeeb *et al.* 2004*;* Berg *et al.* 2005). In a recent study on INTERPHONE material (Vrijheid *et al.* 2006b), the recall errors possibly affecting the results were investigated by simulations, which were partly based on the data received from the previous validation studies performed among group of volunteer subjects in eight INTERPHONE countries (Vrijheid *et al.* 2006a). In the validation studies, the self-reported mobile phone use figures were compared with the data received from telephone operators, and it was found that over-reporting of the duration of calls by 50–100% was common among the study subjects. In a Finnish study based on a small sample of volunteers, an average overestimation by 46% of the duration of calls was also detected (Tokola *et al.* 2008).

According to the simulations of the INTERPHONE data (Vrijheid *et al.* 2006b), non-differential random recall error (affecting cases and controls similarly) in exposure measurement is likely to bias the risk estimates towards the null. In a scenario with differential random error in exposure measurement, the random recall error was supposed to affect cases more than controls resulting in bias towards the null, even though the magnitude of error was large and it varied among cases. The authors concluded that the magnitude of systematic errors was considerably smaller than the random errors. Non-differential systematic error increased the risk estimates when the exposure (duration of calls or number of calls) was underestimated, while overestimation of exposure (duration of calls) led to decreased risks. In case of differential systematic recall error, the cases were subject to either underestimation (due to their state of health affecting the recall) or overestimation (case subjects attributing their disease to the exposure) of exposure, while controls were not prone to systematic recall error. The simulations showed that either underestimation or overestimation of exposure (duration of calls or number of calls) among cases had a relatively minor effect on the estimates, however if there was any effect, it was towards the null. The simulation was, however, based on a simplistic scenario, with only one type of error occurring at a time, while in reality a variety of errors are likely to occur concurrently.

In conclusion, random errors in the recall of mobile phone use can lead to substantial underestimation of brain tumour risk, when the true risk estimate is above unity. Also, the effect of random error exceeded the effect of systematic error in the INTERPHONE study, and differences in recall between cases and controls did not have a substantial additional effect on the results. Therefore, in addition to the aforementioned selection bias, random errors may be one explanation for the decreased risk estimates detected in the dose-response analyses in the

case-control studies on glioma and meningioma. In the future, several sources of random errors probably present in the studies of this dissertation can be avoided by a prospective study, where exposure data is collected from both the study subjects and telephone records. To obtain valid information on brain tumour risk, such a study should, however, have possibly a long, perhaps as much as 20-year follow-up. At the time of writing, a large prospective cohort study called COSMOS has been launched in Europe. In all, it is important to improve risk estimation for RF exposure from mobile phones primarily for brain tumours but also other potential health effects. The public health significance of the issue is vast, as wireless technology is present in people's everyday lives throughout the world. The rapidly changing technology, however, presents a challenge for epidemiological studies, which always lag behind the latest technological developments.

6. Conclusions

In this dissertation, the association between mobile phone use and the risk of brain tumours was investigated.

1. The possible risk for glioma and meningioma in relation to mobile phone use was investigated using data from case-control studies performed in five North European countries. These studies (I and II) did not provide consistent evidence for an increased risk of either glioma or meningioma in relation to mobile phone use. Some indication of an association was detected in the analyses of cumulative number of calls using a continuous exposure indicator. The studies may, however, be affected by errors and biases. However, the studies contained a larger number of subjects than previously published studies on the issue. As large-scale mobile phone use was adopted early in the five North European countries, the estimation of the effects of long-term exposure was also possible in the studies.

2. The published results of the studies on mobile phone use and brain tumours were summarized by means of a meta-analysis (Study III), where a pooled estimate of the risk was obtained. The results of the meta-analysis showed that mobile phone use was not clearly associated with a substantially increased risk of brain tumours according to the twelve studies published between 1999 and 2006. The main limitations were a relatively short latency and failure to combine different exposure measures.

3. The magnitude of selection bias due to non-participation was assessed in the Finnish case-control study on mobile phone use and brain tumours. According to the study (IV), an indication of selection bias in the Finnish data was detected, as mobile phone users were slighly more willing to participate in the study. The effect of selection bias on the results was not, however, regarded as substantial.

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Mobile phone use and risk of glioma in 5 North European countries

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Public concern has been expressed about the possible adverse health effects of mobile telephones, mainly related to intracranial tumors. We conducted a population-based case–control study to investigate the relationship between mobile phone use and risk of glioma among 1,521 glioma patients and 3,301 controls. We found no evidence of increased risk of glioma related to regular mobile phone use (odds ratio, OR = 0.78, 95% confidence interval, CI: 0.68, 0.91). No significant association was found across categories with duration of use, years since first use, cumulative number of calls or cumulative hours of use. When the linear trend was examined, the OR for cumulative hours of mobile phone use was 1.006 (1.002, 1.010) per 100 hr, but no such relationship was found for the years of use or the number of calls. We found no increased risks when analogue and digital phones were analyzed separately. For more than 10 years of mobile phone use reported on the side of the head where the tumor was located, an increased OR of borderline statistical significance (OR = 1.39, 95% CI 1.01, 1.92, *p* trend 0.04) was found, whereas similar use on the opposite side of the head resulted in an OR of 0.98 (95% CI 0.71, 1.37). Although our results overall do not indicate an increased risk of glioma in relation to mobile phone use, the possible risk in the most heavily exposed part of the brain with long-term use needs to be explored further before firm conclusions can be drawn.

Key words: mobile phones; brain tumors; case–control studies

Mobile phone use has increased rapidly worldwide since the early 1990s. Mobile phones emit radiofrequency electromagnetic fields that are non-ionizing radiation, *i.e.* have too low energy to break chemical bonds. Hence, such fields cannot cause DNA damage (mutations), which is required for cancer initiation.[1] However, radiofrequency fields might be involved in cancer development at later stages, including tumor progression or promotion. Despite the fact that no carcinogenic mechanism for radiofrequency radiation has been established,[2] there is public concern about the possible health effects of mobile phone use. This is mainly related to intracranial tumors, as mobile phones are used close to the head and the radiofrequency field is absorbed mostly in the head and neck region. The studies published on the issue have covered a relatively small number of study subjects with long-term exposure, and so far the epidemiological evidence does not suggest any clear increase of intracranial tumors related to mobile phone use, although some positive findings have been reported.[3–19]

We conducted a collaborative population-based case–control study on the association of mobile phone use with intracranial tumors in 5 Northern European countries, using a shared protocol of the INTERPHONE study coordinated by the International Agency for Research on Cancer.[20] We report here the results concerning glioma, based on the combined data from Denmark, Finland, Norway, Sweden and Southeast England, where mobile phones have been widely used for at least a decade.[21]

Materials and methods

Study design and population

This population-based case–control study on mobile phone use and risk of gliomas was conducted in Denmark (nationwide), Finland (98% of the population, excluding Northern Lapland and Åland), Norway (the Southern and Middle parts), Sweden (geographical areas covered by the regional Cancer Registries in Umeå, Stockholm, Gothenburg and Lund regions) and the United Kingdom (Thames region of Southeast England). Of these, the Swedish, Danish and British studies have been reported previously.[11,12,15] We recently reported also a collaborative analysis of acoustic neuromas based on these studies.[13]

Eligible cases were subjects resident in the study areas and diagnosed with glioma (International Classification of Diseases for Oncology, Third Edition, codes 9380–9384, 9390–9394, 9400, 9401, 9410, 9411, 9420–9424, 9430, 9440–9444, 9450–9451, 9505) between September 2000 and February 2004 (the study periods were different between countries) at ages 20–69 years in the Nordic countries and 18–59 years in Southeast England. The material reported here is based on a wider age range than that in the INTERPHONE Study[20] to increase the number of study subjects and to cover the young age groups with intensive mobile phone use. Incident cases were identified through neurosurgery, oncology and neurology departments in the study areas. Cases were also checked against the national or regional cancer registries to evaluate and enhance completeness of coverage.

In the Nordic countries, controls were selected from national population registers with frequency-matching on age, sex and region of residence of cases. In the UK, where no such population register exists, the controls were randomly selected from general practitioners' lists, frequency-matched on the above-mentioned factors. Cases were approached either by mail, or personally at the clinics with written information about the study, and were requested to participate in the study, whereas all controls were approached by mail. If there was no reply from those who were approached by mail, another letter was sent or the subject was approached by telephone. All study subjects received both an invitation letter and written information about the study before asking for participation. The study protocols in each country were approved by the local ethics committees. Informed consent was obtained from all study subjects.

Data collection

Trained interviewers conducted the personal interviews. Typically, the interviews were performed at hospital or at the subject's home; with 11% of interview of cases and 6% for controls conducted over the telephone (mainly in Norway). The interview was computer-

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assisted in all countries, except Finland where a paper questionnaire with identical wording was used. In the interview, information was obtained on the use of handheld mobile phones, medical history, highest level of education attained and family history of brain tumors. The DECT phones or other cordless phones were not enquired about because they were not regarded as potential material exposure sources, since the average power that they transmit is only 0.01 W *vs* 0.25/0.125 W with GSM 900/1800 phones. Regular use of mobile phones (at least once a week for at least 6 months) was assessed. For regular users, the interview covered a detailed history of mobile phone use, including start and end dates of use, types of phones used and the frequency of use, laterality, use of hands-free equipment, and other circumstances of use such as type of telephone network. Show cards either on paper or on the computer were used in all countries to aid participants' recall of the models of phones they had regularly used. Information on the model of phones, calendar period of use, operator and network code of the phone number was used to classify phones as analogue and digital.

Statistical analysis

Three intracranial tumor types (glioma, meningioma and acoustic neuroma) were included in the INTERPHONE study. Since frequency-matching was used throughout the study, we have used the entire control group for all intracranial tumors in the frequency matching strata of the glioma cases, in order to maximize power.

Based on the information obtained in the interview, several characteristics related to mobile phone use were investigated, including ever and regular mobile phone use, the cumulative number of calls, the cumulative hours of mobile phone use, lifetime years of use and years since first use. Continuous exposure variables were classified into categories with the cut-points based on the distribution among controls; the never and non-regular users formed the reference category with the median and third quartile of the exposure variable among regular mobile phone users used as the other cut-points. In addition, the highest exposure group was investigated in some analyses, with the cut-point defined as the highest 10% of controls with regular mobile phone use. The cumulative number of calls and the cumulative hours of mobile phone use were adjusted for the reported use of hands-free devices, using methods described previously.[9,10]

All exposure within 1 year before the reference date was ignored, except when calculating the years since first use of mobile phones (Table III). For cases, the reference date was the date of diagnosis, *i.e.* $\text{refdate}_{\text{case}} = \text{diagdate}_{\text{case}}$. For controls, the reference date was set based on the interview date of the control, with adjustment for the mean interval between the diagnostic and interview date of cases and the difference between the mean interview date of cases and controls, *i.e.* $\text{refdate}_{\text{control}} = \text{intdate}_{\text{control}} - (\text{mean intdate}_{\text{cases}} - \text{mean diagdate}_{\text{cases}}) - (\text{mean intdate}_{\text{cases}} - \text{mean intdate}_{\text{controls}})$. This correction was made to adjust for the fact that the controls were interviewed on average later than the cases, and because the prevalence of mobile phone use increased rapidly with calendar period.

The odds ratios (OR) for glioma risk in relation to mobile phone use were obtained by using conditional logistic regression, with strata defined by country, region, sex and five-year age group at the reference date. Educational level, family history of glioma, previous radiation therapy to the head and neck region (received more than 10 years before the reference date), neurofibromatosis or tuberous sclerosis of the subject were regarded as potential confounders. All the analyses were conducted both with and without taking into account the effects of potential confounding factors (by adjustment for education and family history of glioma, and additionally, excluding subjects with a history of radiotherapy to the head and neck or with hereditary conditions affecting the risk of glioma). The results were not materially affected by taking into account those potential confounding factors, in all instances the effect was less than 2%, and therefore the stratified estimates without adjustment for potential confounders (other than those used for matching) are reported. The statistical significance of trend in risk of glioma in relation to exposure was obtained by using a linear term, which was assigned values corresponding to the ordered exposure categories (*e.g.* 4 exposure classes numbered 1–4). This was done both for the entire study population with subjects not using mobile phones regularly as baseline and also separately with exclusion of the nonexposed subjects.

ORs were obtained by type of phone (analogue and digital) and also separately for glioblastomas (ICD-O-3 codes 9440, 9441, and 9442), representing the largest subgroup of gliomas. The ORs for regular mobile phone use were also calculated separately for men and women and by 5-year age group at the reference date. Laterality analyses, where the location of the tumor was assessed in relation to the reported predominant side of mobile phone use, were also conducted based on 2 previously described methods.[5,10] The reliability of the latter method[10] was also investigated by simulations, repeating the random allocation of index hemisphere (corresponding to tumor laterality) to controls 500 times independently. Further, analyses were conducted both based on the whole dataset and individually by country. Heterogeneity in the results between countries, 5-year age groups and sexes were assessed with a log likelihood ratio test by comparing nested models with one including both main effects and an interaction between the factor, for instance the country, and the exposure and the other including only the main effects. The statistical software STATA (version 9) was used for all the analyses.[22]

Results

A total of 2,530 potential cases and 6,581 potential controls were invited to participate in the study. Of the eligible cases, 60% (1,521 subjects) participated (range 37–81% between countries, Table I). The corresponding figure for controls was 50% (3,301

TABLE I – COUNTRY SPECIFIC DETAILS OF THE CASES AND CONTROLS

	Denmark	Finland	Norway	Sweden	UK-Southeast England	Total
Cases						
Included	247	266	284	363	361	1,521
Participation rate	71%	81%	77%	74%	37%	60%
Number with histopathology	247	262	274	339	344	1,466
Interview lag, median and interquartile range (days)	68 (39–115)	15 (3–31)	452 (192–732)	87 (55–146)	142 (39–244)	92 (39–244)
Interview type						
Hospital	120	264	56	210	12	662
Home	117	0	64	92	329	602
Other/missing	10	2	164	61	20	257
Telephone	0	3	145	18	0	166
Controls						
Included	819	870	353	629	630	3,301
Participation rate	52%	42%	69%	66%	43%	50%
Number of telephone interviews	0	7	159	40	2	208

TABLE II – DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

	Cases (n = 1,521)		Controls (n = 3,301)	
	N	%	*N*	%
Sex				
Male	893	58.7	1,530	46.4
Female	628	41.3	1,771	53.7
Age at reference date (years)				
18–29	145	9.5	245	7.4
30–39	265	17.4	486	14.7
40–49	323	21.2	761	23.1
50–59	484	31.8	1,097	33.2
60–69	304	20.0	712	21.6
Highest educational level				
Compulsory school	429	28.2	933	28.3
Secondary/vocational school	367	24.1	789	23.9
Upper secondary school	336	22.1	832	25.2
University	380	25.0	740	22.4
Not known	9	0.6	7	0.2
Country				
Denmark	247	16.2	819	24.8
Finland	266	17.5	870	26.4
Norway	284	18.7	353	10.7
Sweden	363	23.9	629	19.1
Southeast England	361	23.7	630	19.1

subjects, range 42–69%). The main reasons for nonparticipation were refusal (8% of cases and 33% of controls), illness or death (18% of cases and 0.5% of controls) and inability to contact the subject (7% of cases and 15% of controls). Proxy interviews were used for 12% of cases and <1% of controls. The quality of the information received in the interview was evaluated by the interviewers and 67% of cases and 78% of controls were judged by the interviewer to recall their mobile phone use "well" or "very well." Demographic characteristics of the study subjects are shown in Table II.

Ever use of a mobile phone was reported by 92% (1,389) of cases and 94% (2,945) of controls. The OR for glioma in relation to ever use of a mobile phone was 0.63 (95% confidence interval, CI, 0.48, 0.82). Of the cases, 58% (867) reported using a mobile phone regularly while the figure for regular use by controls was 59% (1,853). For regular mobile phone use, the OR was 0.78 (0.68, 0.91) (Table III). The country-specific results for regular use were 0.70 (0.51, 0.96) for Denmark, 0.80 (0.56, 1.13) for Finland, 0.62 (0.42, 0.91) for Norway, 0.82 (0.61, 1.09) for Sweden and 0.95 (0.70, 1.29) for Southeast England. There was no significant heterogeneity between countries in results for regular use (p = 0.47) or any other indicator of mobile phone use (results not shown).

TABLE III – ODDS RATIOS OF GLIOMA (INCLUDING GLIOBLASTOMA) AND GLIOBLASTOMA SEPARATELY RELATED TO MOBILE PHONE USE, WITH NUMBER OF CASES AND CONTROLS INCLUDED IN THE ANALYSES

	All glioma (n = 1,521)	OR (95% CI)	Glioblastoma (n = 710)	OR (95% CI)	Controls (n = 3,301)
Frequency of use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
Regular use	867	0.78 (0.68, 0.91)	368	0.77 (0.64, 0.93)	1,853
Years since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
1.5–4[2]	384	0.77 (0.65, 0.92)	165	0.82 (0.65, 1.04)	895
5–9	342	0.75 (0.62, 0.90)	141	0.69 (0.54, 0.88)	739
≥10	143	0.95 (0.74, 1.23)	64	0.86 (0.62, 1.21)	220
		p for trend = 0.28		p for trend = 0.08	
		p trend, for users only = 0.29		p trend, for users only = 0.93	
Lifetime years of use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
0.5–4	504	0.75 (0.64, 0.88)	210	0.77 (0.62, 0.96)	1,176
5–9	259	0.78 (0.64, 0.95)	111	0.73 (0.56, 0.96)	529
≥10	88	0.94 (0.69, 1.28)	38	0.77 (0.51, 1.17)	134
		p for trend = 0.67		p for trend = 0.14	
		p trend, for users only = 0.27		p trend, for users only = 0.81	
Cumulative number of calls[1,3]					
Never/nonregular use	626	1.0	327	1.0	1,278
<2,172	352	0.73 (0.62, 0.87)	153	0.71 (0.56, 0.89)	897
2,172–7,792	205	0.74 (0.60, 0.91)	87	0.79 (0.59, 1.05)	444
>7,792	265	0.91 (0.74, 1.12)	104	0.83 (0.63, 1.11)	455
		p for trend = 0.93		p for trend = 0.49	
		p trend, for users only = 0.05		p trend, for users only = 0.24	
Cumulative hours of use [1,3]					
Never/nonregular use	626	1.0	327	1.0	1,278
<125	368	0.75 (0.64, 0.89)	166	0.75 (0.60, 0.95)	895
125–503	193	0.69 (0.55, 0.85)	79	0.66 (0.49, 0.89)	446
>503	262	0.90 (0.73, 1.10)	100	0.85 (0.63, 1.13)	455
		p for trend = 0.98		p for trend = 0.50	
		p trend, for users only = 0.09		p trend, for users only = 0.30	
Cumulative number of calls by time since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
<10 years	724	0.76 (0.65, 0.88)	304	0.75 (0.62, 0.92)	1,633
≥10 years (≤1,512 calls)	49	0.68 (0.47, 0.99)	25	0.67 (0.41, 1.08)	111
≥10 years (>1,512 calls)	83	1.12 (0.81, 1.55)	31	0.89 (0.57, 1.41)	106
Cumulative hours of use by time since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
<10 years	724	0.76 (0.65, 0.88)	304	0.75 (0.61, 0.92)	1,633
≥10 years (≤75 h)	52	0.70 (0.48, 1.01)	25	0.66 (0.41, 1.07)	111
≥10 years (>75 h)	81	1.13 (0.82, 1.57)	32	0.93 (0.59, 1.46)	105

[1]The numbers do not match exactly to the total numbers of cases (1,521) and controls (3,301) since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]Lower limit 1.5 years since phone use was defined as regular when phone was used at least 6 months at least 1-year before reference date.–[3]Estimates adjusted for use of hands-free devices.

TABLE IV – ODDS RATIOS FOR GLIOMA IN RELATION TO ANALOGUE AND DIGITAL MOBILE PHONE USE

	Analogue			Digital		
	Cases[1]	Controls[1]	OR (95% CI)	Cases[1]	Controls[1]	OR (95% CI)
Frequency of use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
Regular use	232	471	0.85 (0.68, 1.06)	788	1,750	0.75 (0.65, 0.87)
Years since first use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
1.5–4[3]	26	55	1.22 (0.72, 2.08)	458	1,091	0.72 (0.61, 0.85)
5–9	99	233	0.70 (0.52, 0.95)	326	648	0.80 (0.66, 0.96)
≥10	108	187	0.93 (0.69, 1.25)	4	12	0.53 (0.16, 1.72)
			p for trend = 0.26			p for trend = 0.04
			p trend, for users only = 0.71			p trend, for users only = 0.37
Lifetime years of use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
0.5–4	156	313	0.90 (0.69, 1.16)	587	1,372	0.72 (0.62, 0.85)
5–9	59	125	0.75 (0.51, 1.08)	198	374	0.83 (0.67, 1.04)
≥10	16	31	0.92 (0.48, 1.77)	0	0	Not available
			p for trend = 0.27			p for trend = 0.64
			p trend, for users only = 0.67			p trend, for users only = 0.20
Cumulative number of calls[4]						
Never/nonregular use[2]	629	1,281	1.0	626	1,278	1.0
<Median	111	231	0.88 (0.67, 1.17)	337	846	0.73 (0.61, 0.87)
Median-3rd quartile	47	117	0.61 (0.41, 0.90)	178	418	0.68 (0.54, 0.85)
>3rd quartile	64	112	1.01 (0.69, 1.46)	237	425	0.86 (0.70, 1.07)
			p for trend = 0.68			p for trend = 0.52
			p trend, for users only = 0.43			p trend, for users only = 0.18
Cumulative hours of use[4]						
Never/nonregular use[2]	629	1,281	1.0	704	1,377	1.0
<Median	114	232	0.92 (0.70, 1.22)	335	843	0.72 (0.60, 0.86)
Median-3rd quartile	45	116	0.51 (0.34, 0.77)	173	419	0.68 (0.54, 0.84)
>3rd quartile	64	114	1.04 (0.71, 1.52)	243	427	0.87 (0.71, 1.08)
			p for trend = 0.82			p for trend = 0.75
			p trend, for users only = 0.72			p trend, for users only = 0.08

[1]The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]The reference category consists of subjects with never/nonregular use of any type of phone.–[3]Lower limit 1.5 years since phone use was defined as regular when the phone was used at least 6 months during the period at least 1-year before the reference date.–[4]Estimates adjusted for use of hands-free devices. For cumulative number of calls the data are divided, based on the distribution in controls, into <2,920, 2,920–8,583 and >8,583 for analogue phones, and <1,829, 1,829–6,019 and >6,019 for digital phones. For cumulative hours of mobile phone use the data are divided into <147, 147–492 and > 492 for analogue phones, and <102, 102–394 and >394 for digital phones.

Years since first use and lifetime years of mobile phone use both gave an OR of 0.99 (0.97, 1.01) per year (p for trend 0.28 for years since first use and 0.67 for lifetime years of use). When we restricted the analysis to regular mobile phone users, the results remained largely similar (trend test p-values 0.29 and 0.27 for years since first use and lifetime years of mobile phone use, respectively). There was no increased risk for greater cumulative number of calls (OR = 1.00 per 10,000 calls, 95% CI: 0.97, 1.04, adjusted for hands-free devices). For cumulative hours of mobile phone use, the OR was 1.006 per 100 hr (1.002, 1.010, adjusted for hands-free devices) when such use was analyzed as a continuous variable, but there was no trend of risk with cumulative hours of use when the data were examined in categories (Table III). The subgroup with the highest cumulative call hours (>1475 hr, the cut-point defined as the highest 10% of controls with regular mobile phone use), had a slightly increased but non-significant OR (1.13, 95% CI: 0.86, 1.48) whereas that with the highest cumulative number of calls (>21,740 calls) showed no increased risk (OR = 0.95, 95% CI 0.72, 1.26). The cumulative number of calls 10 years or more before the reference date was not associated with a significantly increased risk of glioma (OR = 1.09 per 10,000 calls, 95% CI: 0.89, 1.35; p for linear trend 0.14). Further, for cumulative hours of mobile phone use more than 10 years before the reference date, the OR was 1.03 per 100 hr (1.00, 1.05; p for trend 0.16).

When we performed the analyses separately for glioblastoma, we found no statistically significantly increased risk in relation to mobile phone use in any analysis. The results for glioblastoma did not differ substantially from the results for all gliomas (Table III).

There was no evidence of increased risk of glioma related to regular use of analogue or digital telephones (OR for analogue telephones = 0.85, 95% CI: 0.68, 1.06, for digital telephones 0.75, 95% CI: 0.65, 0.87, Table IV). From the analyses of continuous variables, the OR for years since first use for analogue telephones (mean 9.2 years among regular users) was 0.99 (0.97, 1.01) per year, whereas for digital telephones (mean 4.6 years among regular users), the OR was 0.97 (0.95, 1.00) per year.

Similar results were obtained for men and women: the OR for regular use was 0.79 (0.65, 0.96) for men and 0.78 (0.63, 0.96) for women (p for heterogeneity between sexes 0.94). In the analysis of regular use by 5-year age group, no systematic differences were found by age at reference date; the OR was smallest for the second youngest age group (25–29 years) (0.33, 95% CI: 0.16, 0.69; p for heterogeneity between age groups 0.39). No significant heterogeneity between age groups or sexes was found for any other exposure characteristic (*i.e.* ever use, cumulative number of calls, cumulative hours of use and regular ipsilateral use) either. No differences in results were found related to a histopathological confirmation of diagnosis (available versus not) and interview type (hospital/home/telephone).

The OR for regular ipsilateral use of mobile phones (phone use reported to be on the same side of the head as the tumor was located), based on assigning an index hemisphere randomly to controls,[10] was 1.13 (0.97, 1.31), whereas the OR for regular contralateral use (phone use on the opposite side of the head to the tumor) was 0.75 (0.64, 0.88) (Table V). The ORs for first ipsilateral and contralateral use 10 or more years ago were 1.39 (1.01, 1.92, p trend for duration of ipsilateral use 0.04) and 0.98 (0.71, 1.37, p trend for duration of contralateral use 0.11), respectively, based on the same method (Table V). Excluding the subjects who had used mobile phone on both sides of the head from the analyses did not

TABLE V – ODDS RATIOS FOR GLIOMA RELATED TO LATERALITY OF THE TUMOR AND REPORTED SIDE OF MOBILE PHONE USE

	Ipsilateral exposure[1]			Contralateral exposure[1]		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Frequency of use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
Regular	471	1,002	1.13 (0.97, 1.31)	354	986	0.75 (0.64, 0.88)
Years since first use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
1.5–4[3]	205	485	1.08 (0.88, 1.31)	150	474	0.70 (0.57, 0.87)
5–9	189	400	1.10 (0.89, 1.35)	137	391	0.74 (0.59, 0.92)
≥10	77	117	1.39 (1.01, 1.92)	67	121	0.98 (0.71, 1.37)
			p for trend = 0.04			p for trend = 0.11
			p trend, for users only = 0.18			p trend, for users only = 0.20
Lifetime years of use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
0.5–4	275	639	1.07 (0.90, 1.28)	199	625	0.70 (0.58, 0.85)
5–9	144	282	1.18 (0.93, 1.49)	109	280	0.79 (0.61, 1.01)
≥10	43	74	1.14 (0.76, 1.72)	41	71	1.01 (0.67, 1.53)
			p for trend = 0.21			p for trend = 0.45
			p trend, for users only = 0.40			p trend, for users only = 0.21
Cumulative hours of use[4]						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
<Median	202	492	1.05 (0.86, 1.28)	140	485	0.67 (0.54, 0.83)
Median-3rd quartile	114	251	1.03 (0.80, 1.33)	97	249	0.78 (0.60, 1.02)
>3rd quartile	136	247	1.24 (0.97, 1.59)	106	240	0.85 (0.65, 1.10)
			p for trend = 0.69			p for trend= 0.01
			p trend, for users only = 0.36			p trend, for users only = 0.07

[1]Ipsilateral exposure = mobile phone use on the same side of the head as the tumor. Contralateral exposure = mobile phone use on the opposite side of the head to the tumor. The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]Reference category is never/nonregular use of mobile phones, and for ipsilaterality, phone use only on the opposite side of the head, and for contralaterality, phone use only on the same side of the head.–[3]Lower limit 1.5 years since phone use was defined as regular when phone was used for at least 6 months during the period at least 1-year before reference date.–[4]Estimates adjusted for use of hands-free devices. Data are divided, based on the distribution in controls, into <136, 136–567 and >567 for ipsilaterality, and <132, 132–553 and >553 for contralaterality.

substantially affect the results (not shown). When restricting the analysis to subjects with the quality of interview related to mobile phone use rated as good or very good by the interviewers, the OR for first ipsilateral use 10 or more years ago was 1.21 (0.74, 1.96). As the laterality analysis method is sensitive to random allocation of the controls, its reliability was investigated. Based on 500 simulations the method seemed rather stable, as the mean of the OR for regular ipsilateral use was 1.12 (range 1.00–1.24) and for regular contralateral use it was 0.76 (range 0.68–0.86).

A case-only analysis gave an overall relative risk (RR) for ipsilateral mobile phone use of 1.24 (Fisher's exact test: $p < 0.001$, two-sided), based on 674 (44%) cases for whom both the side of the tumor and the side of phone use were defined. For the subjects ($n = 60$) with 10 or more years of exposure history (lifetime years of mobile phone use), the ipsilateral RR was 1.01 ($p = 1.00$) whereas for subjects ($n = 106$) for whom the first use of a mobile phone was more than 10 years ago (years since first use), the RR was 1.09 ($p = 0.53$).

Discussion

The results of our analyses do not provide consistent evidence for increased risk of glioma related to use of mobile phones. We did not find indications of increased risk related to regular mobile phone use overall, or in the majority of the subanalyses based on various exposure characteristics. The most exposed group (the highest 10% based on the exposure distribution among controls) did not show an elevated risk of glioma. Neither did the dose-response analyses reveal a clear trend in relation to the overall duration of mobile phone use, number of calls or hours of use. No differences were found between analogue and digital phones and the results for glioblastoma were similar to those including all gliomas. Data from different countries also gave consistent results. One subset of analyses did, however, indicate a possible association with mobile phone use: reported ipsilateral use 10 or more years ago was associated with significantly increased risk of glioma and there was also an increasing trend with years since first use on the ipsilateral side. Analyses of risk in relation to cumulative hours of mobile phone use yielded mixed results and are of very uncertain interpretation because they depend on the analytical method used and they may be driven by a small number of extreme values that may be biased or erroneous. We also note that the results reported here are to a certain degree sensitive to choice of analytical method, and hence are not always identical with those reported in national publications.[11,12,14]

In previous studies, largely negative results have been published.[23] In the German INTERPHONE study, mobile phone use for at least 10 years was associated with an increased glioma risk of borderline significance.[15] In the UK study, with material partly overlapping that in the present analyses, increased risk of ipsilateral use was found, but with a corresponding decrease on the contralateral side.[14] The Danish and Swedish data were published previously and the results did not indicate significantly increased risk of glioma related to mobile phone use.[11,12] Another Swedish group has found increased risks related to several aspects of mobile phone use,[16–19] but the reason for findings inconsistent with most other reports remains unclear. A meta-analysis also failed to reveal any significant association between long-term mobile phone use and intracranial tumors.[24] Most earlier studies[3–8] did not have sufficient numbers of long-term mobile phone users for meaningful risk assessment, if there is a latency of at least 5–10 years.

Our study covers a large number of cases and controls compared with previously published reports: the largest earlier study included less than 1,000 gliomas.[14] Additionally, the countries included in these analyses are pioneers in mobile phone use and therefore the number of mobile phone users with more than 10 years of exposure (88 cases) is larger than in previous analyses, which allows more reliable estimation of the risk related to such long-term mobile phone use. We adjusted exposure history to

match the reference period between cases and controls to account for later interviewing of the controls, which is crucial to ensure comparability of information for a rapidly changing exposure such as mobile phone use. Few risk factors requiring control of potential confounding are known for glioma. We collected information on high-dose radiation, hereditary risk factors and family history. They were, however reported by only few subjects and exclusion of exposed persons did not affect our results. Therefore, the role of confounding appears minimal.

When a frequently fatal condition, such as glioma, is studied, rapid loss of study subjects is inevitable. In the light of this, the participation in our study is fairly high for cases in general. Yet, participation among potential controls was quite low, which can potentially induce selection bias. Previously, mobile phone users have been found more likely to participate than non-users among both cases and controls in Finland and Sweden.[11,25] This may be related to more common use of mobile phone use among people with high level of education and socio-economic status, who are also more willing to participate in research. However, this finding is based on a relatively small number of non-participants who were willing to report their mobile phone use, and may not therefore be directly applicable to the present results. In the current report, the significantly reduced OR for ever *vs*. never use of mobile phones might be explained by this bias, in which case other ORs in the study might have been similarly affected. On the other hand, arguing against this, the country-specific ORs were not associated with the participation rates.

Overestimation of exposure among controls due to selective participation may underestimate true effects, *i.e*. bias results towards the null. In the present study, we performed the trend analyses for years since first use and lifetime years of use also based only on the regular mobile phone users, as such an analysis would be less prone to selection bias if there is more selection between users and non-users than between subjects with different amount of mobile phone use. In both cases, the trend remained fairly unchanged although the point estimate was increased slightly towards unity. This finding is also consistent with the possibility that selection bias may have produced an apparent protective effect of mobile phone use in this study, reflected in the odds ratio below 1 for regular use.

Mobile phone use is nowadays an unremarkable part of everyday activities. Therefore, accurate recall of past patterns may be problematic. Also, the amount of use has tended to increase which may result in reporting exposures reflecting more closely current than past behavior. Reports of past mobile phone use are subject to random error, as recall even in the short term has been shown to be inaccurate.[26–29] Over-reporting of the amount of mobile phone use by 50–100% has been common. This is likely to attenuate any true relationship between exposure and outcome, and it might distort dose-response. However, information on whether the subject used the phone regularly and on year of first use is likely to be more reliable.

Bias due to differential recall of exposure by cases and controls usually tends to overestimate the true effects. Overall, reported regular use of a mobile phone on the same side as that on which the brain tumor was diagnosed (ipsilateral use) was not associated with a significantly increased risk of glioma, when analyzed with the method used by Lönn and coworkers.[10] The risk estimate for ipsilateral use was slightly above unity, while that for contralateral use was below one. This finding could be attributable to recall bias. Yet, the risk seemed to increase with duration of ipsilateral phone use. The method of Inskip also showed a slight increase for tumors located on the same side as the mobile phone was used, although not significantly so for long-term use, based however only on a fifth of the total number of study subjects. The advantage of the case–case analysis is the avoidance of recall bias. These findings leave open the possibility that long-term mobile phone use may increase the risk of gliomas in the more exposed hemisphere.

However, findings related to reported ipsilateral use of mobile phone are difficult to interpret and lend themselves to both causal and non-causal (artefactual) explanations. On one hand, the radiofrequency field is highly local and any possible effect may be limited to a small segment of the brain. On the other hand, there is considerable potential for uncertainty in reporting the side where the mobile phone is held, particularly for exposures a long time ago. This may induce both random error and bias. Recall bias may affect the reported side of mobile phone use if cases overreport use on the side where the tumor was diagnosed, leading to spuriously elevated risks. This would be most likely to occur if mobile phone use was perceived as a potential cause of cancer. Our studies were not introduced to the participants as focusing on mobile phone use (except in Sweden), but nevertheless, most subjects were likely to be aware of this hypothesis due to media coverage of the issue.

Our finding of decreased risk related to regular use on the contralateral side is consistent with recall bias. The interviewers regarded the quality of information slightly better for controls than cases in our study. Restriction of analysis to subjects with the estimated best quality of information related to mobile phone use gave slightly lower, non-significant risk estimates for ipsilateral use, which may indicate information bias. It appears therefore that exposure assessment based on interview may induce errors in both directions, overestimation and underestimation of effects. The only way to avoid these shortcomings is to use more objective sources of information, such as operator records. They were, however, not available for the purposes of this study.

In conclusion, our results do not support mobile phone use for less than 10 years as a cause of glioma. However, we found an indication of increased risk in relation to reported ipsilateral phone use of more than 10 years duration. This may be due to either chance or causal effect or information bias, *i.e*. overreporting of mobile phone use on the affected side by the cases with brain tumors.

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CANCERS

Meningioma and mobile phone use—a collaborative case-control study in five North European countries

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Background Use of mobile telephones has been suggested as a possible risk factor for intracranial tumours. To evaluate the effect of mobile phones on risk of meningioma, we carried out an international, collaborative case-control study of 1209 meningioma cases and 3299 population-based controls.

Methods Population-based cases were identified, mostly from hospitals, and controls from national population registers and general practitioners' patient lists. Detailed history of mobile phone use was obtained by personal interview. Regular mobile phone use (at least once a week for at least 6 months), duration of use, cumulative number and hours of use, and several other indicators of mobile phone use were assessed in relation to meningioma risk using conditional logistic regression with strata defined by age, sex, country and region.

Results Risk of meningioma among regular users of mobile phones was apparently lower than among never or non-regular users (odds ratio, OR = 0.76, 95% confidence interval, CI 0.65, 0.89). The risk was not increased in relation to years since first use, lifetime years of use, cumulative hours of use or cumulative number of calls. The findings were similar regardless of telephone network type (analogue/digital), age or sex.

Conclusions Our results do not provide support for an association between mobile phone use and risk of meningioma.

Keywords cellular phones, brain neoplasms, case-control studies

Meningiomas are neoplasms originating from the meningeal tissue covering the brain and spinal cord. They are usually benign, with 1–3% exhibiting malignant growth.[1] The incidence of meningiomas varies between populations, being higher among women than men.[2] The aetiology of meningiomas has

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Table 1 Country specific details of the cases and controls

	Denmark	Finland	Norway	Sweden	UK-Southeast England	Total
Cases						
Included (*N*)	173	334	206	271	225	1209
Participation rate (%)	73	90	71	84	55	74
Microscopically confirmed (%)	173	325	179	236	216	1129
Telephone interviewed (*N*)	0	3	99	12	0	114
Controls						
Included (*N*)	819	870	353	627	630	3299
Participation rate (%)	52	42	69	66	43	50
Telephone interviewed (*N*)	0	7	159	40	2	208

remained elusive, with some hereditary syndromes (mainly neurofibromatosis type 2 and tuberous sclerosis) and high doses of ionizing radiation among the few established risk factors.[3] Radiofrequency electromagnetic fields emitted by mobile telephones has been suggested as a possible risk factor for meningiomas, mainly based on the analogy with ionizing radiation and the proximity of the meningeal tissue to the handset, i.e. the source of the radiofrequency field.

Previous studies of meningioma risk in relation to mobile phone use have included a relatively small number of study subjects with long-term exposure. Although some positive findings have been reported, so far the totality of epidemiological evidence does not demonstrate an increase in risk of meningiomas related to mobile phone use.[4–9] We conducted a large international study to assess the possible association between use of mobile phones and risk of intracranial meningioma, using a shared protocol of the INTERPHONE study coordinated by the International Agency for Research on Cancer.[10] The data for this study were collected from five Northern European countries, Denmark, Finland, Norway, Sweden and Southeast England, where mobile phone use has been common for at least a decade.[11] Results from the Danish, Swedish and Norwegian studies have been published earlier.[12–14] Collaborative analyses of acoustic neuroma[15] and glioma[16] risks based on these studies have also been reported previously.

Materials and methods

Selection of study subjects

The study was carried out in Denmark (nationwide), Finland (98% of the national population, excluding Northern Lapland and Åland), Norway (the Southern and Middle parts, representing 90% of population), Sweden (Umeå, Stockholm, Gothenburg and Lund regions, 65% of population) and the United Kingdom (Thames region of Southeast England, 23% of population).

Eligibility criteria for cases included age 20–69 years in the Nordic countries and 18–59 years in Southeast England, residence in the study area and diagnosis of intracranial meningioma (International Classification of Diseases for Oncology, Third Edition, codes 9530–9539) between 2000 and 2004 (the exact study periods were slightly different between countries). Cases were identified through neurosurgery, oncology and neurology departments of several hospitals in the study areas. In addition, the national or regional cancer registries were used to evaluate and enhance completeness of coverage. The inclusion criteria were similar to earlier publications[12–14] and the slightly smaller numbers of cases than in national reports are due to revised diagnosis, date of diagnosis or history of previous brain tumour. The diagnosis was microscopically confirmed in 93% of the cases (Table 1).

Controls were selected through the national population registers in the Nordic countries. As there is no such register in the UK, the matched controls were randomly selected from general practitioners' patient lists. In all countries, the controls were frequency-matched to the cases by sex, 5-year age group (at ascertainment date) and region of residence. Eligible cases were approached either by mail, or personally at the clinics, while the controls were first approached by mail. If the subjects contacted by mail did not respond, another letter was sent or the subject was approached by telephone. Before asking for participation, study subjects received both an invitation letter and written information about the study. Informed consent was obtained from all study participants. The ethical review of the study protocol was carried out by local committees in each country.

Data collection

Exposure assessment was based on personal interview that was typically performed at a hospital or at the subject's home and conducted by trained interviewers. Proxy interviews were used for 1.6% of cases and 0.1% of controls. Telephone interviews were common in Norway, where 48% of cases and 45% of controls were

interviewed over the telephone, but infrequent in the other countries (0–4% among cases and 0–6% controls). The interview covered use of hand-held mobile phones, medical history, education and family history of brain tumours. Regular use of mobile phones was defined as making or receiving calls at least once a week for at least 6 months. For regular mobile phone users, a detailed history of use was obtained, including start and end dates as well as the frequency and laterality of use, type of phone, use of hands-free devices and other factors, such as type of telephone network. Show cards were used to facilitate recall of the phone models used. Information on the model of phones, calendar period of use, operator and network code of the phone number was used to classify phones as analogue or digital. In some of the countries, some information was also collected about Digital Enhanced Cordless Technology (DECT) and other cordless phones but this information was not used in the analyses, because the average power that they transmit is only 0.01 W versus 0.25/0.125 W with GSM 900/1800 phones and 1 W with NMT 900 phones.

Data handling and statistical analysis

Frequency-matching employed throughout the INTERPHONE study allowed us to utilize the entire control group recruited for all intracranial tumours (glioma, meningioma and acoustic neuroma) in the matched strata of the meningioma cases, to increase statistical power. The analysis covered several features of reported mobile phone use that are potentially relevant for exposure to radiofrequency electromagnetic fields. Cumulative hours of use was calculated from average number and duration of calls. The analyses were performed using both continuous and categorical exposure variables. In analyses of categorical exposure variables, the cut-points were chosen based on the distribution among controls. The reference category consisted of the never and non-regular users, with the other cut-points defined by the 50 and 75th percentiles of the exposure distribution among regular mobile phone users. In the analyses of cumulative number of calls and cumulative hours of mobile phone use, the exposure was adjusted for the reported use of hands-free devices. The exposure was reduced by 100% if the subject reported use of hands-free devices all the time, by 75% if most of the time, 50% if half of the time and 25% if sometimes but less than half of the time. An additional analysis of the subgroup with the highest cumulative number of calls and cumulative hours of use was performed with the cut-point defined as the value among the 10% of controls with the heaviest mobile phone use (among regular users).

For calculation of exposure indices, a reference date was determined for each subject. For cases, the reference date was the date of diagnosis. As the controls were interviewed on average later than the cases and as the prevalence of mobile phone use increased rapidly over time, the reference date for controls was corrected for this delay. Thus, the reference date for controls was defined as the interview date adjusted for the mean interval between the diagnostic and interview date of cases, and the difference between the mean interview date of cases and controls (in days) i.e. $\text{refdate}_{\text{control}} = \text{intdate}_{\text{control}} - (\text{mean intdate}_{\text{cases}} - \text{mean diagdate}_{\text{cases}}) - (\text{mean intdate}_{\text{cases}} - \text{mean intdate}_{\text{controls}})$. All mobile phone use within 1 year prior to the reference date was excluded from analysis, except when calculating the years since first use, which was evaluated up to the reference date.

The odds ratios (OR) for meningioma associated with mobile phone use were estimated with conditional logistic regression, with strata defined by sex, 5-year age group, region and country. Based on previous literature on aetiology of meningioma, highest educational level attained, family history of meningioma, radiotherapy to the head and neck region (at least 10 years before the reference date), and past diagnosis of neurofibromatosis or tuberous sclerosis of the subject were regarded as potential confounders. All the analyses were conducted both with and without considering the effects of the potential confounding factors. Adjustment for family history and socio-economic status in the analyses did not affect the results, nor did exclusion of subjects with neurofibromatosis, tuberous sclerosis or a history of radiotherapy to the head and neck region. Therefore, all the results reported are from analyses taking into account only the stratification variables (sex, 5-year age group, region and country).

Analyses were conducted separately by type of phone (analogue and digital). Furthermore, analyses were performed both based on the whole dataset and individually by country, and also by sex and by 10-year age group. Heterogeneity in the results between countries, 10-year age groups and sexes was assessed with the likelihood ratio test by comparing nested models, with one including both main effects and an interaction between the stratification factor and the exposure indicator, and the other including only the main effects.

The tumour location was assessed in relation to the reported predominant side of mobile phone use, using previously described methods.[5,13] The Inskip method[5] is based on case-only design, while the Lönn approach[13] includes also the controls in the analysis. For cases, ipsilateral location was defined as tumour on the same side where the mobile phone was mainly held, whereas contralateral location was defined as tumour on the opposite side of where the phone was primarily held. For subjects reporting bilateral use (similar amount of use on both sides), both hemispheres were regarded as exposed. As controls have no tumour, an index laterality was randomly allocated to each of them in the analyses with the Lönn method. In this study, the method used by Lönn *et al*.[13] was modified so that the reference group comprised only never and non-regular users but not those

using the phone on the other side that were included in the reference group in the original analysis. All the analyses were conducted with the statistical software STATA (version 9).[17]

Results

A total of 1629 eligible cases and 6581 controls were identified. Of the potential cases, 74% participated (1209 subjects, range 55–90% between countries, Table 1) and of the controls, 50% (3299 subjects, range 42–69%). The most frequent reasons for non-participation were refusal (9% of cases and 33% of controls), inability to contact the subject (8% of cases and 15% of controls) and illness or death (3% of cases and 0.5% of controls). Since there were strata with either no cases or no controls, several study subjects were excluded, leaving finally 1204 cases (of the 1209 who participated) and 2945 controls (of the 3299 who participated) in the analysis. The recall of mobile phone use in the interview was judged to be 'good' or 'very good' by the interviewers for 82% of the cases and 85% of the controls. The demographic characteristics of the study subjects are shown in Table 2.

Regular mobile phone use was associated with an apparently reduced risk of meningioma, (OR 0.76, 95% confidence interval, CI: 0.65, 0.89), based on 48% regular users among cases and 58% among controls (Table 3). Years since first use or lifetime years of use were not associated with an increased risk of meningioma, as the OR for both variables was 0.99 (0.96, 1.01) per year. Cumulative number of calls was not associated with the risk of meningioma (OR = 1.00 per 10 000 calls, 95% CI: 0.96, 1.05, adjusted for hands-free devices). Those with the highest number of calls or hours of use (>21 753 calls and >1476 h, as among the highest 10% of controls) did not have an increased risk of meningioma (OR = 0.86, 95% CI: 0.60, 1.24 and 1.13, 95% CI 0.82–1.57, respectively). When only mobile phone use at least 10 years prior to the index date was considered, the results were not materially changed. The OR for cumulative number of calls 10 or more years ago was 1.07 (0.80, 1.41) per 10 000 calls, whereas for cumulative hours of use it was 1.02 (0.99, 1.05) per 100 h.

Table 2 Demographic characteristics of the study population

	Cases		Controls	
	N	%	*N*	%
Sex				
Male	301	24.9	1530	46.4
Female	908	75.1	1769	53.6
Age at reference date (years)				
18–29	22	1.8	244	7.4
30–39	129	10.7	490	14.9
40–49	293	24.2	751	22.8
50–59	481	39.8	1103	33.4
60–69	284	23.5	711	21.6
Highest educational level				
Compulsory school	399	33.0	933	28.3
Secondary/vocational school	285	23.6	789	23.9
Higher secondary school	236	19.5	832	25.2
University	284	23.5	738	22.4
Not known	5	0.4	7	0.2

Even though the distribution of cumulative call hours was skewed among both cases and controls, we also explored the linear relation of the call hours as a continuous variable to meningioma risk. It revealed an apparently positive association (OR 1.005 per 100 h, 95% CI: 1.001, 1.010), but this was driven by a small number of very high values which in turn reflected subjects with implausibly high reported mean daily hours of use. The result for cumulative hours of use was mostly based on subjects with more than 3 h of daily use (the 99th percentile for daily hours of use was 2.4 for controls and 3.5 for cases). When we excluded the subjects with more than 2 h of daily use (44 cases and 27 controls, corresponding to 1.7% of observations), no relation was detected. In the analysis of log-transformed number of call hours, no obvious association was observed (results not shown).

When analogue and digital networks were investigated, the results did not differ substantially from each other, or from the results based on all mobile phones. For analogue telephones, the OR for years since first use was 0.99 per year (0.96, 1.01), whereas for digital telephones, it was 0.97 per year (0.64, 1.00). When cumulative hours of use was analysed as a continuous variable, the OR for analogue phones was 1.003 (0.992, 1.014) and for digital phones 1.008 (1.002, 1.014) per 100 h. In the analyses of categorical variables, only minor differences between the two telephone types emerged, possibly due to relatively small numbers of cases within exposure categories (Table 4).

The country-specific meningioma ORs for regular use were 0.87 (0.60, 1.27) for Denmark, 0.75 (0.56, 1.01) for Finland, 0.85 (0.57, 1.29) for Norway, 0.68 (0.49, 0.94) for Sweden and 0.72 (0.51, 1.01) for Southeast England. No indication of heterogeneity between countries was detected in results for regular use ($P = 0.84$) or any other indicator of mobile phone use (all P-values >0.2). Sex did not modify the relationship between mobile phone use and meningioma risk, as the OR for regular use compared with never or non-regular use was 0.79 (0.59, 1.06) for men and 0.75 (0.62, 0.89) for women. There was no heterogeneity by sex or age in the results for regular use ($P = 0.74$ and 0.70, respectively) or in any other indicator of mobile phone use (results not shown). The possible effect of the interview type (hospital/home/telephone) was also investigated and found out to have only marginal

Table 3 Odds ratios of meningioma related to mobile phone use, with number of cases and controls included in the analyses

	Cases[a]	Controls[a]	OR (95% CI)
Frequency of use			
Never/non-regular use	631	1249	1.0
Regular use	573	1696	0.76 (0.65, 0.89)
Years since first use			
Never/non-regular use	631	1249	1.0
1.5–4[b]	286	808	0.72 (0.60, 0.86)
5–9	214	676	0.78 (0.64, 0.96)
⩾10	73	212	0.91 (0.67, 1.25)
Lifetime years of use			
Never/non-regular use	631	1249	1.0
0.5–4	363	1063	0.72 (0.61, 0.86)
5–9	163	488	0.83 (0.66, 1.05)
⩾10	42	130	0.85 (0.57, 1.26)
Cumulative number of calls[c]			
Never/non-regular use	631	1249	1.0
<2195	285	844	0.68 (0.57, 0.82)
2195–7790	130	375	0.86 (0.67, 1.10)
>7790	128	423	0.83 (0.64, 1.07)
Cumulative hours of use[c]			
Never/non-regular use	631	1249	1.0
<125	278	850	0.68 (0.57, 0.82)
125–514	125	376	0.79 (0.62, 1.02)
>514	140	411	0.88 (0.68, 1.13)
Cumulative number of calls by time since first use			
Never/non-regular use	631	1249	1.0
<10 years	500	1484	0.74 (0.63, 0.87)
⩾10 years (⩽1537 calls)	38	105	0.88 (0.58, 1.33)
⩾10 years (>1537 calls)	31	104	0.83 (0.53, 1.29)
Cumulative hours of use by time since first use			
Never/non-regular use	631	1249	1.0
<10 years	500	1484	0.74 (0.63, 0.87)
⩾10 years (⩽70 h)	33	104	0.77 (0.50, 1.19)
⩾10 years (>70 h)	35	104	0.94 (0.61, 1.44)

All odds ratios obtained from analysis that was stratified by sex, five-year age group, region and country.
[a]The numbers do not match exactly to the total numbers of cases (1209) and controls (3299) since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.
[b]Lower limit 1.5 years since phone use was defined as regular when phone was used at least six months at least one year prior to reference date.
[c]Estimates adjusted for use of hands-free devices. The cut-points are defined by 50th and 75th percentiles of the exposure distribution among controls that were regular mobile phone users.

impact on the results (not shown). Additional analyses were also performed excluding cases without microscopically confirmed diagnosis ($n = 80$), but this did not affect the results (not shown). We also conducted analyses including only those subjects whose recall of mobile phone use was reported by the interviewers to be good or very good but the results were not altered substantially (not shown).

Table 4 Odds ratios for meningioma in relation to analogue and digital mobile phone use

	Analogue			Digital		
	Cases[a]	Controls[a]	OR (95% CI)	Cases[a]	Controls[a]	OR (95% CI)
Frequency of use						
Never/non-regular use[b]	631	1249	1.0	631	1249	1.0
Regular use	125	437	0.76 (0.58, 0.98)	533	1598	0.74 (0.63, 0.87)
Years since first use						
Never/non-regular use[b]	631	1249	1.0	631	1249	1.0
1.5–4[c]	9	49	0.40 (0.18, 0.86)	342	993	0.72 (0.61, 0.86)
5–9	62	215	0.75 (0.53, 1.06)	183	593	0.77 (0.62, 0.95)
⩾10	54	178	0.87 (0.61, 1.26)	8	13	1.87 (0.71, 4.93)
Lifetime years of use						
Never/non-regular use[b]	631	1249	1.0	631	1249	1.0
0.5–4	83	284	0.78 (0.57, 1.06)	421	1249	0.73 (0.62, 0.86)
5–9	37	122	0.81 (0.53, 1.25)	107	344	0.78 (0.60, 1.02)
⩾10	5	29	0.43 (0.15, 1.20)	3	0	Not available
Cumulative number of calls[d]						
Never/non-regular use[b]	631	1249	1.0	631	1249	1.0
<median	68	204	0.81 (0.59, 1.12)	265	795	0.68 (0.56, 0.81)
median-3rd quartile	17	108	0.43 (0.24, 0.76)	125	359	0.86 (0.67, 1.10)
>3rd quartile	35	114	0.89 (0.57, 1.40)	118	390	0.77 (0.59, 1.00)
Cumulative hours of use[d]						
Never/non-regular use[b]	631	1249	1.0	631	1249	1.0
<median	66	207	0.79 (0.57, 1.10)	252	800	0.66 (0.55, 0.80)
median-3rd quartile	19	111	0.43 (0.25, 0.75)	119	367	0.78 (0.61, 1.01)
>3rd quartile	34	110	0.94 (0.60, 1.48)	138	372	0.90 (0.70, 1.16)

All odds ratios obtained from analysis that was stratified by sex, five-year age group, region and country.
[a]The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.
[b]The reference category consists of subjects with never/non-regular use of any type of phone.
[c]Lower limit 1.5 years since phone use was defined as regular when the phone was used at least six months during the period at least one year prior to the reference date.
[d]Estimates adjusted for use of hands-free devices. For cumulative number of calls the data are divided, based on the distribution in controls, into <2907, 2907–8530 and >8530 for analogue phones, and <1857, 1857–6048 and >6048 for digital phones. For cumulative hours of mobile phone use the data are divided into <146, 146–490 and >490 for analogue phones, and <101, 101–398 and >398 for digital phones.

In the laterality analyses, both regular ipsilateral use (OR = 0.81, 95% CI: 0.66, 0.99), and regular contralateral use (OR = 0.67, 0.54, 0.83) were associated with apparently lower meningioma risk than never or non-regular mobile phone use. Years since first or lifetime years of ipsilateral use were not clearly related to meningioma, as the ORs were 1.05 (0.67, 1.65) and 0.99 (0.57, 1.73), respectively, for the subjects with the longest (>10 years) exposure history (Table 5). The laterality analyses were also conducted excluding subjects who had used a mobile phone on both sides of the head, but this had little effect on the results (not shown). When the laterality analyses were conducted using only cases (by the method similar to Inskip *et al.*[5]), an overall relative risk (RR) of 1.09 (Fisher's exact test, $P = 0.10$, two sided) was obtained for meningioma in relation to ipsilateral phone use, based on 212 exposed and 184 unexposed cases. For subjects with exposure duration >10 years ($n = 30$), the RR was 1.61 ($P = 0.11$), and for subjects whose first use was 10 or more years ago ($n = 52$), the RR was 1.26 ($P = 0.17$).

Discussion

We did not find evidence of increased risk of meningioma in relation to mobile phone use, as regular use, years since first use, lifetime years of use or cumulative number of calls, were not associated with an increased risk. Our results are consistent with most previous studies and reviews on the issue.[4–6,8,9,18,19]

Table 5 Odds ratios for meningioma related to laterality of the tumour and reported side of mobile phone use

	Ipsilateral phone use[a]			Contralateral phone use[a]		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Frequency of use						
Never/non-regular use	486	1249	1.0	486	1249	1.0
Regular	250	918	0.81 (0.66, 0.99)	224	905	0.67 (0.54, 0.83)
Years since first use						
Never/non-regular use	486	1249	1.0	486	1249	1.0
1.5–4[b]	128	442	0.77 (0.60, 0.99)	105	424	0.62 (0.47, 0.80)
5–9	89	363	0.78 (0.56, 1.04)	95	364	0.78 (0.58, 1.05)
⩾10	33	113	1.05 (0.67, 1.65)	24	117	0.62 (0.38, 1.03)
Lifetime years of use						
Never/non-regular use	486	1249	1.0	486	1249	1.0
0.5–4	157	580	0.73 (0.58, 0.92)	142	563	0.65 (0.52, 0.83)
5–9	72	258	0.99 (0.72, 1.36)	65	263	0.71 (0.51, 1.01)
⩾10	21	73	0.99 (0.57, 1.73)	13	68	0.64 (0.33, 1.23)
Cumulative hours of use[c]						
Never/non-regular use	486	1249	1.0	486	1249	1.0
<median	127	469	0.75 (0.59, 0.97)	111	456	0.62 (0.48, 0.80)
median-3rd quartile	59	208	0.82 (0.57, 1.15)	50	220	0.65 (0.45, 0.94)
>3rd quartile	58	225	0.89 (0.62, 1.27)	58	216	0.81 (0.56, 1.17)

All odds ratios obtained from analysis that was stratified by sex, five-year age group, region and country.

[a]Ipsilateral phone use = mobile phone use on the same side of the head as the tumour. Contralateral phone use = mobile phone use on the opposite side of the head to the tumour. The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known. Also, in this analysis only subjects with both the side of tumour and use are included. The number of cases in the reference group is different to the main analysis (631) since there were 145 cases to whom the side of the tumour was not defined (115 with a central tumour and 30 with a missing value).

[b]Lower limit 1.5 years since phone use was defined as regular when phone was used for at least six months during the period at least one year prior to reference date.

[c]Estimates adjusted for use of hands-free devices. Data are divided, based on the distribution in controls, into <136, 136–573 and >573 for ipsilateral phone use, and <133, 133–566 and >566 for contralateral phone use.

Cumulative number of hours (and to some extent also cumulative number of calls) and lifetime years of use represent cumulative exposure, ipsilateral use and possibly analogue phones represent higher intensity (magnetic field strength) and years since first use represent induction period. No increased risk was found in relation to duration of use, ipsilateral use or use of analogue phones. In the analysis of cumulative hours of use based on a categorical exposure indicator, there was no increased risk for meningioma, not even in the highest (10%) exposure category. When the continuous variable was used, some indication of an association was found, that was, however, based on small number of extreme and possibly erroneous values. The cumulative hours of use may contain uncertainties as an exposure indicator, as it is derived from the number and the duration of calls multiplied by the duration of mobile phone use. Additionally, both parameters were frequently reported also as ranges from which an average was used for estimating calling time. This may easily result in overestimation of exposure unless number and duration of calls are independent. If daily call-time of 30 min is composed of one 30-min call or thirty 1-min calls, it could be misinterpreted as on average 15 calls of 15-min duration, i.e. 225 min (nearly 4 h) constituting substantial overestimation.

It is also possible that cases over-report their mobile phone use (recall bias). Some evidence of this was observed, as in the distribution of cumulative hours of use the highest values among cases clearly exceeded those among controls and were generally based on implausibly high reported hours of mean daily use over long periods. When we performed an additional analysis of cumulative hours of use and excluded the subjects with more than 2 h of daily use corresponding to only 1.7% of observations, the OR was no longer increased.

The strengths of the study include a larger number of meningioma cases than in any previous report. This allowed us to obtain precise risk estimates and conduct detailed analyses of various aspects of mobile

phone use. Furthermore, the number of subjects with long-term exposure is higher than in the earlier studies, due to the recent study period and study populations where large-scale mobile phone use was adopted early. This is essential, as the induction period may be long for a slowly developing benign tumour such as meningioma. A related aspect is larger cumulative exposure, providing a better opportunity to identify possible effects in a highly exposed group. On the other hand, the weaknesses of our study are the low participation rate among controls and the fact that mobile phone use and other exposures are based on self-reports. These limitations are shared by most other studies on the subject.

An apparently reduced risk was found related to regular use of mobile phones. A likely explanation for at least some of the risk reduction is selection bias. There is some empirical evidence for higher participation among mobile phone users than non-users for both cases and controls in the study.[13,20] When mobile phone users are more willing to participate in epidemiological studies than non-users, exposure in the source population is overestimated, which may result in underestimation of the risk in relation to mobile phone use and may partly explain the decreased risk estimates detected in this study, if the selection was differential between cases and controls. Participation varying with level of use may distort the dose–response relation and lead to a J-shaped pattern, consistent with some of our results. The slightly lower proportion of controls with basic education only may be a related finding, as participation in research is commonly associated with a high educational level.[21]

Latent disease bias, where early symptoms of the disease may make cases less likely to become mobile phone users in the period preceding the diagnosis, may also explain the reduced risk estimate. However, the most common symptoms of meningioma are seizures and headache,[22,23] which are unlikely to affect mobile phone use. Furthermore, we found little indication of such bias since the proportion of cases was similar to that of controls across the start of use categories, and also among those that started mobile phone use within a year before the reference date (20% vs 21%).

There was no evidence for confounding, as the crude results were very similar to those of the analyses accounting for highest educational level, family history of meningiomas, tuberous sclerosis, neurofibromatosis or previous radiotherapy to the head and neck region. Also, when calculating the exposure histories, the fact that controls were interviewed on average later than the cases was taken into account by adjustment, which is crucial when investigating an exposure such as mobile phone use that increases rapidly over time.

Considerable random error has been demonstrated in self-reported amount of mobile phone use.[24–26] That is understandable, as mobile phone use is nowadays an unremarkable aspect of everyday life. As mobile phone use has increased during the years of use, the retrospectively reported amount of use may be influenced by not only past, but also current mobile phone use. In the INTERPHONE study, over-reporting of duration of calls by up to 50–100% was common.[27] Non-differential misclassification of exposure is likely to bias the results towards the null, should there be an effect, particularly when a dichotomous or continuous measure of exposure is used.[28] This is not equally obvious when categorical (multinomial) exposure indicators are used, as in our study. Information about regular vs non-regular use reported by the study subjects is likely to be more reproducible and crude measures might therefore be more robust than detailed, quantitative indices. Yet, the aforementioned selection bias may distort those analyses. Obviously, an objective source of exposure information, independent of the study subject, would provide highly valuable information. Yet, only one small cohort study has been able to use quantitative exposure information from operators, but it had a very short follow-up and inadequate number of events.[29] Another cohort has also obtained information from subscriber lists, but only about ownership of a subscription, without any traffic data.[8]

In conclusion, our study does not provide evidence for an increased risk of meningioma in relation to mobile phone use. An apparent association was detected for cumulative hours of use as a continuous exposure indicator but this was based on a small number of extreme and possibly erroneous values. No such association was detected in the categorical analyses. Thus, the present findings do not suggest mobile phone use is associated with an increased risk of meningioma.

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Commentary: Observational studies may conceal a weakly elevated risk under the appearance of consistently reduced risks

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The paper by Lahkola *et al*.[1] is interesting in two respects. First, the issue of possible health effects, in particular cancers, of mobile phones is of obvious public health importance given the wide extent of the exposure. Second, the paper raises several noteworthy methodological issues of general import.

The study of meningiomas in five countries reported in the paper adds two countries to previous articles covering three countries[2–4] and is an integral part of a larger multinational study on meningiomas, gliomas, acoustic neurinoma and parotid gland tumours in 13 countries ('Interphone')[5] whose findings are as yet unpublished. Multi-centric international studies originate and develop within a variety of contexts and constraints, ranging from the degree of urgency of the question under study to the investigators' research and career interests to conditions posed by funding bodies. Given this spectrum of circumstances, each study will necessarily have its own criteria for the publication of results, and a variety of criteria are justifiable provided they are explicitly agreed upon beforehand by the participating investigators.

From a research viewpoint, however, the rationale for multi-centric studies largely rests on the potential

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Original article

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Meta-analysis of mobile phone use and intracranial tumors

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Lahkola A, Tokola K, Auvinen A. Meta-analysis of mobile phone use and intracranial tumors. *Scand J Work Environ Health* 2006;32(3):171–177.

Objectives A summary of epidemiologic evidence regarding the effect of mobile phone use on intracranial tumor risk was obtained by means of a meta-analysis.

Methods Reports of published studies on mobile phone use and intracranial tumors were sought. Altogether 12 relevant publications were identified from the PubMed database and reference lists of articles. Fixed or random effects analysis was carried out depending on the presence of heterogeneity between studies. Risk estimates were obtained for people who had used mobile phones for the longest periods of time (>5 years in most reports). A pooled estimate was calculated for all intracranial tumors combined and also separately for different histological tumor types. Separate analyses were conducted also based on the tumor location and type of mobile telephone network (NMT or GSM).

Results Twelve studies with 2780 cases gave a pooled odds ratio (OR) of 0.98 [95% confidence interval (95% CI) 0.83–1.16] for all intracranial tumors related to mobile phone use. For gliomas, the pooled OR was 0.96 (95% CI 0.78–1.18), for meningiomas it was 0.87 (95% CI 0.72–1.05), and for acoustic neuromas it was 1.07 (95% CI 0.89–1.30). Little indication was found for increased risks of analogue or digital phone use or temporal or occipital tumors.

Conclusions The totality of evidence does not indicate a substantially increased risk of intracranial tumors from mobile phone use for a period of at least 5 years.

Key terms brain neoplasm; cellular phone; pooled analysis.

The use of mobile phones (also called cellular phones) has increased rapidly worldwide since the early 1990s. This increase has generated concern about the possible adverse health effects of mobile phone use, particularly the risk of intracranial tumors.

The first study concerning the association between intracranial tumors and mobile phone use was published in 1999 (1). After this case-control study, which did not report any significantly increased risks of intracranial tumors among mobile phone users, several studies have appeared in the literature. However, the published results are somewhat inconsistent, and single studies appear inconclusive. Several reviews summarizing the results have been published and most conclude that mobile phones are not likely to cause intracranial tumors (2–6). To complement the qualitative summaries provided by the reviews, a meta-analysis provides a tool for the quantitative synthesis of individual studies. A meta-analysis was used to estimate the overall magnitude of the risk for intracranial tumors, comprised of brain tumors such as gliomas and meningiomas, as well as acoustic neuromas, in relation to mobile phone use.

Material and methods

We searched for the epidemiologic evidence on mobile phone use and intracranial tumors in the PubMed database (www.ncbi.nlm.nih.gov) using the following searching terms (used in the title or abstract): (1) mobile/cellular phone/telephone **and** (2) brain tumor/cancer/neoplasm **or** glioma **or** meningioma **or** neuroma/schwannoma. In addition, we browsed the reference lists of the retrieved articles. We obtained a numerical summary of the published results without a detailed qualitative review of individual studies. Such reviews have been published previously (2–6).

Altogether 19 articles (1, 7–24), published by 1 December 2005, were identified that meet the following

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inclusion criteria: (i) being original publications, (ii) using individual exposure data, (iii) based on a case–control or cohort format, (iv) reporting quantitative measures of association [point estimates expressed either as odds ratios (OR) or as standardized incidence ratios (SIR)], and (v) reporting information needed for the estimation of confidence intervals (the standard error or confidence interval of the effect measure or the number of persons by exposure and outcome status). A meta-analysis requires that the studies to be pooled have similar aims and end points. One study was excluded because the end point was brain tumor mortality rather than incidence, and another was excluded that addressed only facial nerve tumors (7–8). No studies were excluded due to language other than English, and no unpublished reports were identified. No studies were excluded because of dissimilar procedures, as both the inclusion criteria and exposure assessment methods were similar enough to allow pooling. As the approaches were relatively uniform, no grading by quality was regarded as necessary.

We were able to retrieve all of the 17 identified studies fulfilling the criteria. On the basis of the considerations, five articles (9–11, 18–19) were excluded from the analysis because they used overlapping study participants of other articles that were already included in the material. Altogether 12 studies (1, 12–17, 20–24) were finally included in the analysis (table 1). Of these studies, nine were population-based (1, 14–16, 20–24), and three were hospital-based (12–13, 17). All of the hospital-based studies were carried out in the United States, while the population-based studies were European. Eleven were case–control studies (1, 12–13, 15–17, 20–24), and one was a cohort study (14). All of the studies included in the meta-analysis used incident intracranial tumor cases. Exposure assessment was based on interviews or questionnaires in all but two studies that used telephone company records (14–15). Six of the

Table 1. Key features of the studies included in the meta-analysis. (OR = odds ratio, 95% CI = 95% confidence interval, US = United States)

Study	Country	End points	Number [a]	Exposure assessment	Telephone types	Longest duration of mobile phone use	OR [b]	95% CI [b]
Hardell et al, 1999 (1)	Sweden	Intracranial tumors (astrocytic, oligo dendroglial and ependymal tumors, mixed glioma, meningioma)	34 cases, 69 controls	Postal questionnaire + telephone interview	Analogue, digital	>5 years	0.83	0.49–1.42
Muscat et al, 2000 (12)	US	Malign intracranial tumors (astrocytic, oligodendroglial and ependymal tumors, mixed glioma)	17 cases, 22 controls	Interview	Not specified	>4 years	0.7	0.4–1.4
Inskip et al, 2001 (13)	US	Intracranial tumors (glioma, meningioma, acoustic neuroma)	22 cases, 31 controls	Interview	Not specified	>5 years	0.9 [c]	0.5–1.6
Johansen et al, 2001 (14)	Denmark	Cancer (brain and nervous system, gliomas, meningiomas)	66 gliomas, 16 meningiomas [d]	Company records, 420 095 mobile phone subscribers	Not specified	Mean follow-up time 3.1 years	0.92 [e, f]	0.74–1.16
Auvinen et al, 2002 (15)	Finland	Intracranial tumors (glioma, meningioma)	18 cases, 64 controls	Company records	Analogue, digital	>2 years	1.5	0.9–2.5
Hardell et al, 2002 (16)	Sweden	Intracranial tumors (astrocytic, oligodendroglial and ependymal tumors, mixed glioma, meningioma, pituitary tumors, acoustic neuroma)	153 cases, 124 controls	Postal questionnaire + telephone interview	Analogue, digital	>5 years	0.9 [g]	0.6–1.5
Muscat et al, 2002 (17)	US	Acoustic neuroma	11 cases, 6 controls	Interview	Not specified	3–6 years	1.7	0.5–5.1
Lönn et al, 2005 (20)	Sweden	Glioma, meningioma	136 cases, 171 controls	Interview	Analogue, digital	>5 years [h]	0.73 [f]	0.55–0.96
Christensen et al, 2005 (21)	Denmark	Glioma, meningioma	83 cases, 193 controls	Interview	Not specified	>5 years [h]	0.66 [f]	0.46–0.95
Schoemaker et al, 2005 (22)	Nordic countries	Acoustic neuroma	127 cases, 646 controls	Interview	Analogue, digital	>5 years [h]	0.95 [f]	0.75–1.18
Hardell et al, 2005 (23)	Sweden	Acoustic neuroma, meningioma	87 cases, 129 controls	Postal questionnaire + telephone interview	Analogue, digital	>5 years [h]	1.4 [f]	1.02–1.93
Hardell et al, (in press) (24)	Sweden	Malign intracranial tumors	98 cases, 129 controls	Postal questionnaire + telephone interview	Analogue, digital	>5 years [h]	1.49 [f]	1.10–2.02

[a] The number of cases and controls in the subcategories of the original studies that are included in the meta-analysis. The subcategories were selected to achieve the maximum length of mobile phone use.
[b] The overall estimate for the use of mobile phones that was used in the meta-analysis.
[c] Relative risk.
[d] Among mobile phone users (a cohort study with 135 cancer cases of the brain and nervous system).
[e] Standardized incidence ratio.
[f] Calculated by the authors of the meta-analysis through the pooling of different exposure or tumor categories reported in the original studies.
[g] Digital phones.
[h] Calculated by pooling the original categories in the articles, 5–9 years (or 5–10) and >10 years, to one category of >5 years.

studies (1, 16, 20, 22, 23–24) reported excluding the exposure within ≤1 year from the index date (diagnosis of cases and corresponding date among the controls) in the analysis, while such restriction of exposure was not reported in the rest of the studies. The participation rates among the cases varied between 73% and 92%, and among controls it ranged from 51% and 91%.

The articles to be included in the analyses were reviewed independently by two authors (AL & KT), and all of the relevant data (odds ratios, relative risks, and standardized incidence ratios with 95% confidence intervals) were retrieved and entered into evidence tables.

In the absence of heterogeneity, we carried out the meta-analysis using the inverse variance-weighted method for combining the odds ratios (25). This approach is equivalent to a fixed-effects analysis, on the assumption that the effect is constant across studies and all differences between the studies are attributable to random variation (25). Most of the studies used identical factors, such as age and gender, for matching or adjustment. The weights were calculated on the basis of the width (subtraction of the lower and upper limit) of the confidence interval (CI), due to problems with the rounding of the original confidence intervals in some of the studies. When evidence for heterogeneity between studies was found, a random effects analysis was used, which allowed the true risks to vary between studies and assumed a random distribution for these estimates around a common central value.

To improve the accuracy, we recalculated the overall odds ratio for intracranial tumors for one study (16) because the original confidence intervals in the article were reported only with one decimal. For four studies (20, 22–24), we pooled two exposure categories, 5–9 years (or 5–10 years) and >10 years into >5 years, to achieve similar exposure classification as in the other reports. Furthermore, different tumor categories were also pooled prior to the meta-analysis of the total odds ratio (all tumors combined) for the articles that reported them only separately (14, 21). When the estimates were reported only separately for analogue and digital phones (but not for all mobile phones combined), we used the odds ratio for digital phones for the calculations of the total odds ratio since it is possible that the same persons had been using both analogue and digital telephones and thus were included in both categories in the original reports (16, 23–24). In addition, digital phone use was more common in most studies.

Our analysis concentrated on the persons most likely to demonstrate an effect, if such exists (ie, the exposed group was defined as those who had used a mobile phone for the longest time, rather than ever users). In most studies, these persons were those with at least 5 years of use, but, in four studies, the longest period was shorter (4 years, from 3 to 6 years, 2 years and the cohort study with the mean follow-up time of 3.1 years, table 1). A pooled odds ratio was calculated for all intracranial tumors combined, based on both duration (years) and cumulative hours of mobile phone use. The odds ratio was also calculated separately for the following three histological groups of tumors: gliomas (comprising astrocytic, oligodendroglial, and ependymal tumors, as well as mixed gliomas—nine studies), meningiomas (eight studies), and acoustic neuromas (six studies). Furthermore, a pooled estimate was calculated separately for telephone types (analogue and digital, seven studies), laterality (reported phone use on the same and opposite side of the head where the tumor occurred, seven and five studies, respectively), study base (hospital-based versus population-based, 12 studies), as well as tumors of the temporal (excluding acoustic neuromas, eight studies), and occipital lobes (five studies). Finally, we also conducted analyses of ipsilaterality (phone use on the same side that the tumor occurred) by tumor type.

Study heterogeneity was assessed using the Q statistic to determine whether the results of various studies were consistent enough to be combined. Furthermore, we assessed sensitivity (influence of single studies) by calculating pooled estimates while excluding each study at a time. The effect of possible publication bias was investigated by means of a funnel plot. Finally, we performed a regression analysis to assess whether the intracranial tumor risk was related to the duration of mobile phone use. The regression analysis was based on all but the one study that used a cohort design (14). In the analysis, we used the geometric mean of the duration of mobile phone use and weighted odds ratios from each study as in the meta-analysis. From the studies, we included the maximum number of exposure categories available in the published reports. For each exposure category, the duration of use was assigned as the geometric mean of the lower and upper limit of that category. If the authors had not reported an upper limit for the duration of mobile phone use, we estimated the maximal duration by assuming that the use of mobile phones had started in 1987 when the first handheld mobile telephones were introduced. The regression analysis was carried out only for all tumor types combined.

Results

The total number of cases in the published studies was 5799, of which 2424 were among mobile phone users. Our analyses included a total of 2870 cases, including 748 cases with at least 2–5 years of mobile phone use. The largest subgroup was gliomas (total 1352 cases, 339 classified as exposed in this analysis), followed by

meningiomas (527 and 149), and acoustic neuromas (605 and 167). These figures have some uncertainties since the number of persons in different exposure or tumor categories were not reported in some reports (1, 16, 23–24). The proportion of microscopically confirmed cases ranged between 25% and 100% (the lower percentage is related to acoustic neuromas that are usually detected in computer scans).

As there was evidence for heterogeneity between the studies for all tumor types combined on the basis of the duration of mobile phone use, a random effects model was used. The pooled estimate based on the 11 studies was very close to unity, and the upper limit of the confidence interval was below 1.2 (figure 1). The sensitivity analysis showed that the odds ratio was not strongly influenced by any single study (figure 2).

The pooled odds ratio for all tumors combined, on the basis of the cumulative hours of mobile phone use, was very close to unity and was obtained from a random effects model (table 2). The type of study base had little influence on the results, as the pooled odds ratio for the population-based studies (from the random effects model) was only slightly higher than that of the hospital-based studies, obtained from the fixed effects model (table 2).

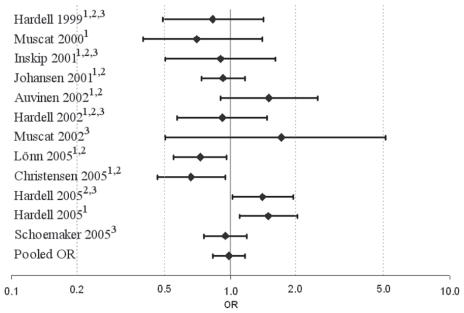

Figure 1. Results of the original studies and meta-analysis (random effects model) of mobile phone use and intracranial tumors. The odds ratios are on a log scale. Pooled odds ratio = 0.98 (95% confidence interval 0.83–1.16). It is indicated which studies included gliomas,[1] meningiomas,[2] and acoustic neuromas.[3]

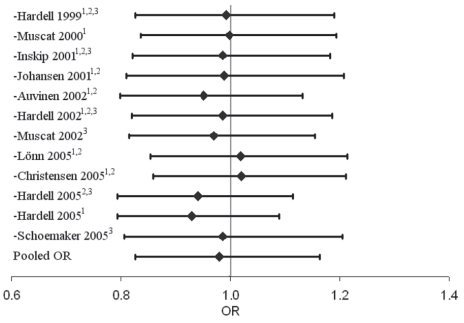

Figure 2. Results of the sensitivity analysis for all types of intracranial tumors combined based on the duration of mobile phone use (years). Each study was excluded at a time from the analysis to assess its influence. The study removed from the analysis is indicated next to the error bar. It is indicated which studies included gliomas,[1] meningiomas,[2] and acoustic neuromas.[3]

The analyses by histological type gave similar results. The pooled odds ratios for gliomas (from the random effects model) and meningiomas (from the fixed effects model) were slightly below one, whereas, for acoustic neuromas (from the fixed effects model), the estimate was slightly above one (table 2). The exclusion of the four studies with a maximal exposure duration shorter than 5 years did not materially affect the results for any tumor type.

The pooled estimates for the use of analogue and digital telephones were obtained with a random effects analysis and were both slightly above one and nonsignificant. The pooled odds ratio for analogue telephones was somewhat higher than for digital telephones. No evidence of increased risks was found for temporal or occipital tumors, on the basis of the random and fixed effects model, respectively. However, for the ipsilateral tumors (ie, those occurring on the same side on which the phone was predominantly used) the odds ratio was above one, with borderline nonsignificance. When the tumor types were analyzed separately by laterality in relation to phone use, a nonsignificantly elevated odds ratio was found for the ipsilateral gliomas, whereas the odds ratios were closer to unity for meningiomas and acoustic neuromas. The odds ratio for the contralateral tumors was very close to one (table 2).

In the regression analysis, we found little evidence of an increasing risk of intracranial tumors with duration of mobile phone use (regression coefficient 0.0072, P=0.41). Finally, a funnel plot was used to assess possible publication bias, but it revealed no indication of such selection (figure 3).

Discussion

Our objective was to pool published risk estimates and thereby assess the influence of random variation and heterogeneity between the study results. This meta-analysis showed little evidence of an association between mobile phone use and the risk of all intracranial tumors combined. Our findings are in line with the previously narrative summaries in which the quality of the studies also included in this meta-analysis has been assessed (5, 26). In the subgroup analyses, no strong or consistent association was found with different subgroups of tumors defined by morphologic type (glioma, meningioma,

Table 2. Pooled estimates of intracranial tumor risk among mobile phone users and measures of heterogeneity between the studies included in the analyses.

Tumor type(s), or other restrictions	Included studies	Model	Pooled OR	95% CI	Heterogeneity	
					Fixed effect analysis	Random effect analysis
All intracranial tumors, duration of mobile phone use (years) [a]	Hardell et al 1999 (1), Muscat et al 2000 (12), Inskip et al 2001 (13), Johansen et al 2001 (14), Auvinen et al 2002 (15), Hardell et al 2002 (16), Muscat et al 2002 (17), Lönn et al 2005 (20), Christensen et al 2005 (21), Schoemaker et al 2005 (22), Hardell et al 2005 (23), Hardell et al 2005 (24)	Random effects	0.98	0.83–1.16	χ^2 = 26.67, P=0.01	χ^2 = 10.88, P=0.45
All intracranial tumors, cumulative hours of mobile phone use [b]	Hardell et al 1999 (1), Muscat et al 2000 (12), Inskip et al 2001 (13), Hardell et al 2002 (16), Muscat et al 2002 (17), Lönn et al 2005 (20), Christensen et al 2005 (21), Schoemaker et al 2005 (22), Hardell et al 2005a (23), Hardell et al 2005 (24)	Random effects	0.98	0.73–1.30	χ^2 = 38.05, P<0.01	χ^2 = 9.27, P=0.41
All intracranial tumors, population based studies [a]	Hardell et al 1999 (1), Johansen et al 2001 (14), Auvinen et al 2002 (15), Hardell et al 2002 (16), Lönn et al 2005 (20), Christensen et al 2005 (21), Schoemaker et al 2005 (22), Hardell et al 2005a (23), Hardell et al 2005b (24)	Random effects	0.99	0.82–1.21	χ^2 = 24.59, P=0.01	χ^2 = 8.48, P=0.39
All intracranial tumors, hospital based studies [a]	Muscat et al 2000 (12), Inskip et al 2001 (13), Muscat et al 2002 (17)	Fixed effects	0.87	0.59–1.30	χ^2 = 1.78, P=0.41	.
Gliomas [c, d]	Hardell et al 1999 (1), Muscat et al 2000 (12), Inskip et al 2001 (13), Johansen et al 2001 (14), Auvinen et al 2002 (15), Hardell et al 2002 (16), Lönn et al 2005 (20), Christensen et al 2005 (21), Hardell et al 2005 (24)	Random effects	0.96	0.78–1.18	χ^2 = 20.01, P=0.01	χ^2 = 8.64, P=0.37
Meningiomas [d]	Hardell et al 1999 (1), Inskip et al 2001 (13), Johansen et al 2001 (14), Auvinen et al 2002 (15), Hardell et al 2002 (16), Lönn et al 2005 (20), Christensen et al 2005 (21), Hardell et al (23)	Fixed effects	0.87	0.72–1.05	χ^2 = 7.28, P=0.40	.
Acoustic neuromas [d]	Hardell et al 1999 (1), Inskip et al 2001 (13), Hardell et al 2002 (16), Muscat et al 2002 (17), Shoemaker et al 2005 (22), Hardell et al 2005 (23)	Fixed effects	1.07	0.89–1.30	χ^2 = 5.69, P=0.34	.
Analogue phone [e]	Hardell et al 1999 (1), Auvinen et al 2002 (15), Hardell et al 2002 (16), Lönn et al 2005 (20), Schoemaker et al 2005 (22), Hardell et al 2005 (23), Hardell et al 2005 (24)	Random effects	1.17	0.91–1.49	χ^2 = 16.28, P=0.01	χ^2 = 6.11, P=0.41
Digital phone [e]	Hardell et al 1999 (1), Auvinen et al 2002 (15), Hardell et al 2002 (16), Lönn et al 2005 (20), Hardell et al 2005 (23), Hardell et al 2005 (24), Shoemaker et al 2005 (22)	Random effects	1.04	0.80–1.35	χ^2 = 14.65, P=0.02	χ^2 = 5.57, P=0.47
Temporal tumors [f]	Hardell et al 1999 (1), Muscat et al 2000 (12), Inskip et al 2001 (13), Johansen et al 2001 (14), Hardell et al 2002 (16), Lönn et al 2005 (20), Hardell et al 2005 (23), Hardell et al 2005 (24)	Random effects	1.02	0.68–1.52	χ^2 = 32.69, P< 0.01	χ^2 = 6.81, P=0.45
Occipital tumors [g]	Muscat et al 2000 (12), Inskip et al 2001 (13), Johansen et al 2001 (14), Hardell et al 2002 (16), Lönn et al 2005 (20)	Fixed effects	0.82	0.54–1.25	χ^2 = 3.29, P=0.52	.
Contralateral tumors [h, i]	Hardell et al 2002 (16), Lönn et al 2005 (20), Schoemaker et al 2005 (22), Hardell et al 2005 (23), Hardell et al 2005 (24)	Random effects	1.02	0.78–1.35	χ^2 = 11.56, P=0.02	χ^2 = 4.30, P=0.37
Ipsilateral tumors [h, j]	Hardell et al 1999 (1), Inskip et al 2001 (13), Hardell et al 2002 (16), Muscat et al 2002 (17), Lönn et al 2005 (20), Schoemaker et al 2005 (22), Hardell et al 2005 (23), Hardell et al 2005 (24)	Random effects	1.36	0.99–1.87	χ^2 = 24.51, P=0.01	χ^2 = 10.70, P=0.15
Ipsilateral gliomas [j]	Hardell et al 1999 (1), Inskip et al 2001 (13), Lönn et al 2005 (20), Hardell et al 2005 (24)	Random effects	1.33	0.78–2.28	χ^2 = 10.34, P=0.02	χ^2 = 2.67, P=0.45
Ipsilateral meningiomas [j]	Hardell et al 1999 (1), Inskip et al 2001 (13), Lönn et al 2005 (20), Hardell et al 2005 (24)	Fixed effects	1.16	0.82–1.63	χ^2 = 1.96, P=0.58	.
Ipsilateral acoustic neuromas [j]	Inskip et al 2001 (13), Muscat et al 2002 (17), Schoemaker et al 2005 (22), Hardell et al 2005 (23)	Random effects	1.05	0.41–2.67	χ^2 = 10.91, P=0.01	χ^2 = 4.62, P=0.20

[a] The longest duration of exposure was >5 years in all other reports, except in that of Muscat et al (12), in which >4 years was used, that of Johansen et al (14) with a mean follow-up time of 3.1 years, that of Auvinen et al (15), in which >2 years was used, and that of Muscat et al (17), which used 3–6 years.

[b] The exposure was defined as ≥424 hours in all other reports, except in that of Hardell et al (16), in which >55 hours was used, in that of Muscat et al (17), in which >60 hours was used, and in those of Hardell et al (23, 24), in which >64 hours was used.

[c] The glioma group consisted of astrocytic, oligodendroglial, and ependymal tumors and mixed gliomas.

[d] The exposure was defined as >5 years in all other reports, except in those of Hardell et al (1, 16), in which >1 years was used, in that of Muscat et al (12), in which >4 years was used, in that of Johansen et al (14), which reported "ever use", in that of Auvinen et al (15), in which >2 years was used, and in that of Muscat et al (17) in which 3–6 years was used.

[e] The exposure was defined as >5 years in all other reports except in that of Auvinen et al (15), in which >2 years was used.

[f] The exposure was defined as >5 years in all other reports, except in that of Hardell et al (1), in which >1 years was used, in that of Muscat et al (12), which reported "ever use", in that of Inskip et al (13), which reported "used more than five times", and in that of Johansen et al (14), in which the exposure duration was undefined.

[g] The exposure was defined as "ever use" in that of Muscat et al 12, "used more than five times" in that of Inskip et al (13), >1 years in that of Hardell et al (16), and >5 years in that of Lönn et al (20), whereas in that of Johansen et al (14) the exposure duration was undefined.

[h] Contralateral = tumor located on the side opposite of that generally used for the mobile phone, ipsilateral = tumor located on the same side generally used for the mobile phone.

[i] The exposure was defined as >1 years in all other reports except in those of Lönn et al (20) and Hardell et al (24), in which >5 years was used.

[j] The exposure was defined as >1 years in all other reports, except in that of Inskip et al (13) in which >0.5 years was used and in those of Lönn et al (20) and Hardell et al (24) in which >5 years was used.

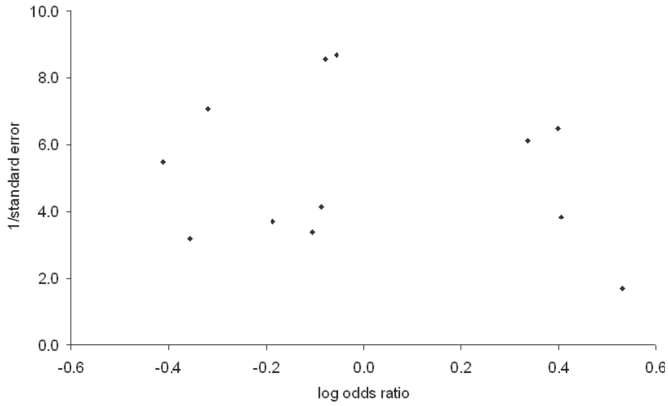

Figure 3. Funnel plot of the studies included in the meta-analysis, showing no evidence of publication bias concerning intracranial tumors and mobile phone use.

acoustic neuroma) or anatomic location (temporal or occipital lobe) of intracranial tumors. The regression analysis showed no clear association between the duration of mobile phone use and the risk of intracranial tumors.

A somewhat increased odds ratio for ipsilateral tumors was found, but the finding was nonsignificant. On the contrary, the pooled odds ratio for contralateral tumors was very close to unity. It is evident that the reported use of a mobile phone is subject to uncertainty due to both random error and information bias (recall bias). Several studies have shown substantial random error already for the short-term recall of mobile phone use (27–29). No studies have been reported with respect to comparing the accuracy of reported mobile phone use between cases and controls to evaluate possible information bias. However, the fact that some studies have shown decreased risks on the contralateral side suggests information bias (16, 20).

Our analysis was based on users with the longest possible duration of mobile phones. In most studies, these were people with at least 5 years of mobile phone use. This approach was chosen a priori, as mobile phones have been introduced relatively recently and therefore a sufficient duration of exposure and latency to allow detection of possible effect was considered a key limitation of the published studies. We felt that the gains of having a well-defined exposed group with the highest achievable duration of exposure outweighed the disadvantage of excluding 50% of the persons in the intermediate exposure category. Five years is still, however, a relatively short time for the induction of intracranial tumors, even if the postulated mechanism, if any, has been thought to be based on promotion rather than on initiation because radiofrequency fields do not have the energy to break the chemical bonds (cause ionization) required for inducing mutations. Hence a limitation of the studies conducted so far is the relatively small number of persons with long-term (eg, more than 10 years) mobile phone use.

Meta-analyses of nonrandomized studies are more prone to bias than those combining experimental studies. One source of uncertainty is different adjustment for confounding between studies. All of the studies in the current meta-analysis used adjustment for age and gender. Other established risk factors for intracranial tumors include hereditary factors and high doses of ionizing radiation. These are, however, relatively rare. In several studies, the influence of these factors was assessed by conducting separate analyses excluding persons with such exposures. As none of the studies reported a substantial effect in such analyses, confounding by these factors appears unlikely. We did not use quality assessment and scoring because the methodology in all of the studies was similar.

We found statistically significant heterogeneity between the results from different studies in the main analysis of all intracranial tumors and additionally in 11 of 16 subgroup analyses. This finding could be due to differences between the studies in procedures or definitions related to end points or exposure assessment. An alternative explanation for inconsistent results is the variability of the true effect between study populations [eg, due to exposure patterns such as the intensity of mobile phone use, field strength (specific absorption rate) or other features].

Furthermore, pooling studies requires that they have been conducted in a comparable fashion, and the published reports contain the essential information to be extracted. We found some inconsistencies in the exposure classification between the studies. Most importantly, the cut-point for the longest exposure duration varied between studies. Furthermore, five studies did not report analogue and digital phones separately, four did not specify the laterality of mobile phone use, and three studies of astrocytomas did not specify tumor lobe.

Due to the incomplete reporting of data in published studies, we were not able to evaluate several factors simultaneously (eg, ipsilateral acoustic neuromas) in relation to use of analogue phones. We chose to exclude a cohort study with brain tumor mortality as the end point because, in such analyses, determinants of survival (case fatality) may also affect the results if correlated with the exposure of interest (7). In this case, the study was so small (2 exposed cases) that its inclusion would not have affected our results.

The number of intracranial tumors among long-term mobile phone users in the current meta-analysis was still only approximately 750. However, results from this meta-analysis indicate that the use of mobile phones for up to 5 years does not increase intracranial tumor risk.

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IV

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ELSEVIER

Selection Bias Due to Differential Participation in a Case–Control Study of Mobile Phone Use and Brain Tumors

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PURPOSE: To evaluate the possible selection bias related to the differential participation of mobile phone users and non-users in a Finnish case–control study on mobile phone use and brain tumors.
METHODS: Mobile phone use was investigated among 777 controls and 726 cases participating in the full personal interview (full participants), and 321 controls and 103 cases giving only a brief phone interview (incomplete participants). To assess selection bias, the Mantel-Haenszel estimate of odds ratio was calculated for three different groups: full study participants, incomplete participants, and a combined group consisting of both full and incomplete participants.
RESULTS: Among controls, 83% of the full participants and 73% of the incomplete participants had regularly used a mobile phone. Among cases, the figures were 76% and 64%, respectively. The odds ratio for brain tumor based on the combined group of full and incomplete participants was slightly closer to unity than that based only on the full participants.
CONCLUSIONS: Selection bias tends to distort the effect estimates below unity, while analyses based on more comprehensive material gave results close to unity.
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KEY WORDS: Brain Neoplasms, Case–Control Studies, Cellular Phones, Selection Bias.

INTRODUCTION

The use of mobile phones has increased rapidly in many countries since the early 1990s. This has generated concern about possible adverse health effects of mobile phone use, particularly risk of brain tumors. Few studies have been published on the issue and the results have been largely negative (1–8).

The largest study so far is an ongoing international collaborative case–control study (INTERPHONE) coordinated by the International Agency for Research on Cancer. In Finland, which is one of the participating countries, participation proportion among controls has been lower than in some earlier Finnish case–control studies. The aim of this study was to evaluate the possible selection bias in mobile phone use in the Finnish part of the INTERPHONE study.

MATERIALS AND METHODS

The National Advisory Board on Health Care and Ethics approved the study protocol. The source population of the Finnish INTERPHONE study consisted of subjects aged 20 to 69 years, resident in Finland (excluding Northern Lapland and Åland with 1.5% of the Finnish population). The cases were recruited prospectively in the five Finnish University hospitals, excluding cases with a previous brain tumor diagnosis. In Finland, practically all neurosurgical treatment is provided by these five hospitals, and the catchment area of these hospitals covers the entire country. The controls were identified from the Population Register Centre with frequency matching on the expected age, sex, and hospital district distribution of the cases. The controls were approached by mail and asked to participate in the study.

Before asking for consent, the subjects were informed of the aims and procedures of the study, with mobile phone use as one of the several exposures of interest. All consenting cases and controls were interviewed by the study personnel. In the interview, information was obtained on mobile phone use, X-ray examinations, medical history, working history, and family history of brain tumors. Regular use of mobile phones (at least once a week for at least six months) was

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Selected Abbreviations and Acronyms

CI = confidence interval
OR = odds ratio

assessed. The interview covered a detailed history of mobile phone use including start of use, types of phones, laterality, hands-free equipment, and other circumstances of use. Those who did not want to participate in the full interview (approximately 1 hour) were asked to give a brief telephone interview (roughly 5 minutes) focusing only on mobile phone use and educational attainment. As detailed information on mobile phone use is not available, the primary analysis of brain tumor risk related to mobile phone use will be based on full participants only.

The study period in the Finnish INTERPHONE study was from November 2000 to September 2002. The overall participation proportion in the Finnish part of the INTERPHONE study was 46% among primary controls and 84% among cases and the most common reasons given by the subjects for refusal were lack of time, inconvenience, and illness in the family. To evaluate the possible bias from differential participation, data collection on mobile phone use and education among subjects unwilling to participate in the full study commenced in April 2001 (five months after start of recruitment).

We evaluated possible selection bias by comparing mobile phone use between full study participants and those refused subjects who gave the brief telephone interview (incomplete participants). The effect of education on study participation and on mobile phone use was also investigated. For the analyses, education was divided into three classes: low (elementary or comprehensive school), intermediate (high school, vocational school or college), and high (vocational high school, university). Study participation was evaluated using logistic regression, with explanatory factors including sex, education, five-year age group and mobile phone use. All the analyses were made separately for cases and controls. A total of 1098 controls (532 women and 566 men) and 829 cases (337 women and 492 men) were included in the analyses. Of the controls, 777 subjects were full participants and 321 incomplete participants, whereas among cases the numbers of full and incomplete participants were 726 and 103, respectively. The number of total refusers was 519 among controls and 65 among cases.

The effect measure used was the Mantel-Haenszel estimate of odds ratio (OR) obtained from analysis adjusted for education, region, sex, and five-year age group. The effect of selection bias was assessed by comparing the OR calculated based on the subjects participating in the full interview (full participants) with the OR calculated using combined information provided by the full participants and the subjects accepting only the brief telephone interview (incomplete participants).

To evaluate mobile phone use among subjects who declined even the telephone interview, we searched a public telephone number database for the possible mobile phone numbers of two sub-groups of controls: randomly selected 50 full participants as well as 50 total refusers. The number search from the database was performed based on the name and home address of the subject and those, for whom a matching entry (in terms of both criteria) was found, were classified as mobile phone users.

RESULTS

Regular use of a mobile phone was reported more frequently by fully participating than incompletely participating controls; 83% (95% confidence interval [CI], 81, 86) versus 73% (95% CI, 68, 76), respectively. The difference in reported mobile phone use between full and incomplete participants was obvious among the female controls; 88% (95% CI, 85, 92) versus 67% (95% CI, 60, 73). Among men, mobile phone use was comparable among the incomplete and full participants; the reported prevalence being 80% (95% CI, 76, 83) and 83% (95% CI, 77, 90), respectively (Table 1).

Among cases, the reported prevalence of mobile phone use was 76% (95% CI, 73, 80) among full participants and 64% (95% CI, 55, 74) among incomplete participants. Again, fully participating female cases reported regular use of mobile phone more frequently (85%, 95% CI, 80, 89) than incompletely participating female cases (57%, 95% CI, 42, 71), whereas for men the figures were similar; 71% (95% CI, 67, 75) and 71% (95% CI, 59, 83), respectively (Table 1).

Controls who participated in the full personal interview were more highly educated than those who gave consent only for the brief telephone interview. Of the full participants, 16% had high, 54% intermediate, and 29% low level of education, whereas those figures for the incomplete participants were 9%, 44%, and 48%, respectively ($p < 0.001$). A similar phenomenon was observed among cases; the proportion of highly educated people was higher among the fully participating than among the incompletely participating cases (22% and 6%, respectively). Education was also related to mobile phone use; among both cases and controls the subjects with the lowest level of education were least likely to have used a mobile phone (Table 2).

In the multivariate logistic regression, mobile phone use was associated with full participation among both cases and controls even after controlling for age, sex, and education. Among controls, the crude OR for participation was 1.9 (95% CI, 1.4, 2.5), whereas the adjusted OR was 1.9 (95%

TABLE 1. Mobile phone use among study subjects by sex and study participation, Finnish case–control study of brain tumors

			Regular use of mobile phone		
			Yes	No	Total
Controls	Women	Full participants*	287 (88%)	39 (12%)	326 (100%)
		Incomplete participants†	135 (67%)	68 (34%)	203 (100%)
		Total	422 (80%)	107 (20%)	529 (100%)
	Men	Full participants	359 (80%)	92 (20%)	451 (100%)
		Incomplete participants	95 (83%)	19 (17%)	114 (100%)
		Total	454 (80%)	111 (20%)	565 (100%)
	All	Full participants	646 (83%)	131 (17%)	777 (100%)
		Incomplete participants	230 (73%)	87 (87%)	317 (100%)
		Total	876 (80%)	218 (20%)	1094 (100%)
Cases	Women	Full participants	245 (85%)	45 (16%)	290 (100%)
		Incomplete participants	26 (57%)	20 (44%)	46 (100%)
		Total	271 (81%)	65 (19%)	336 (100%)
	Men	Full participants	309 (71%)	127 (29%)	436 (100%)
		Incomplete participants	39 (71%)	16 (29%)	55 (100%)
		Total	348 (71%)	143 (29%)	491 (100%)
	All	Full participants	554 (76%)	172 (24%)	726 (100%)
		Incomplete participants	65 (64%)	36 (36%)	101 (100%)
		Total	619 (75%)	208 (25%)	827 (100%)

*Full personal interview.
†Brief telephone interview only.

CI, 1.4, 2.8). Among cases the corresponding ORs were 1.8 (95% CI, 1.1, 2.8) and 1.5 (95% CI, 0.9, 1.4), respectively.

The odds ratio for brain tumor associated with regular use of a mobile phone based on full study participants was 0.55 (95% CI, 0.39, 0.77) whereas the OR based on the incomplete participants (those not willing to give a full personal interview) was 0.62 (95% CI, 0.26, 1.51). The OR based on the full set of subjects (including both the full and incomplete participants) was 0.73 (95% CI, 0.56, 0.96). For female full participants and combined group of full and incomplete participants the ORs were 0.52 (95% CI, 0.28, 0.97) and 0.94 (95% CI, 0.62, 1.42), respectively. For males the figures were 0.56 (95% CI, 0.38, 0.84) and 0.61 (95% CI, 0.43, 0.88), respectively.

Of the 50 randomly selected controls who gave a full interview, 64% had a listed mobile phone number, whereas among the 50 totally refused controls mobile phone number was available only for 42% ($p = 0.03$).

DISCUSSION

Our results demonstrate that mobile phone users are somewhat more likely to participate in a study on brain

TABLE 2. Educational level among study subjects by study participation and mobile phone use, Finnish case–control study of brain tumors

		Educational level			
		Low	Intermediate	High	Total
Controls	Full participants*	228 (29%)	422 (54%)	127 (16%)	777 (100%)
	Incomplete participants†	150 (48%)	138 (44%)	28 (9%)	316 (100%)
	Total	378 (35%)	560 (51%)	155 (14%)	1093 (100%)
Cases	Full participants	257 (35%)	313 (43%)	156 (22%)	726 (100%)
	Incomplete participants	51 (50%)	46 (45%)	6 (6%)	103 (100%)
	Total	308 (37%)	359 (43%)	162 (20%)	829 (100%)
Controls	Phone users‡	260 (30%)	485 (56%)	129 (15%)	874 (100%)
	Non-users	115 (54%)	74 (34%)	26 (12%)	215 (100%)
	Total	375 (34%)	559 (51%)	155 (14%)	1089 (100%)
Cases	Phone users	190 (31%)	288 (47%)	141 (23%)	619 (100%)
	Non-users	117 (56%)	70 (34%)	21 (10%)	208 (100%)
	Total	307 (37%)	358 (43%)	162 (20%)	827 (100%)

*Full personal interview.
†Brief telephone interview only.
‡Mobile phone use at least once a week for at least 6 months.

tumor etiology than non-users. A higher proportion of subjects, who gave a full personal interview, had used a mobile phone regularly than those consenting only to a brief telephone interview, both among cases and controls. This difference was more pronounced among women in both cases and controls.

Differences in participation by exposure status can induce selection bias. Results based only on the full participants showed an apparent protective effect of mobile phone use. However, this effect was substantially reduced when also subjects agreeing only to a brief telephone interview were included in the analysis. If information of total refusers had been available, we assume that the estimate would have been even closer to 1.0 and non-significant. Even minor distortion of results may be of consequence; the results of the earlier studies suggest that the effect of mobile phone use on brain tumor risk is likely to be small, if any.

To evaluate selection bias, i.e., differences between the target population and actual study subjects (full participants), we compared those who fully complied (gave personal interview) with partial compliers (only a short telephone interview). The majority of the subjects refusing the full interview did provide information on education and regular use of mobile phones but we still lacked information from those subjects who declined completely or could not be contacted. However, we obviously had a little information on those people, when we conducted the mobile phone number search and found out that listed mobile phone numbers could be found for fewer total refusers than full participants (42% versus 64%). This difference was even greater than that between incomplete and full participants in reported prevalence of mobile phone use (73% vs. 83%). Yet, this does not include unlisted phone numbers (approximately 6% of all mobile phone numbers) that were not available from the public telephone number database. However, this would affect the comparison only if the proportion of unlisted numbers differed between total refusers and complete participants.

It is likely that a proportion of those who could not be contacted would have agreed to participate in the study. Therefore, this group probably represents both full and incomplete participants and would not differ as much from the full participants as those who refused to take part in the study. Overall, the difference between full participants and other eligible study subjects is probably greater than that observed between full and incomplete participants but less than that between refusers and full participants.

The relationship between willingness to participate and use of mobile phones was partly related to the level of education. However, the differences between full and incomplete participants remained in our study even after adjustment for education.

Selection bias due to non-response is a potential problem in all case–control studies with incomplete enrolment, and evaluation of differential recruitment in terms of exposure of interest is essential (9). However, magnitude of selection bias depends not only on the completeness of response, but also the distribution of exposure between participants and non-participants (10). In our study, there was evidence for higher participation among mobile phone users than non-users, among both cases and controls. This resulted in only slight distortion of the outcome measure away from the null. As selection bias is a particularistic phenomenon, our results pertain to the Finnish study alone and generalization to other studies, even those following the same study protocol, is problematic. Though encouraging, our results give only limited information on the overall validity of the INTERPHONE study, as other biases may also distort the results, including recall bias. Considering the risk estimates corrected for selection bias, it also should be kept in mind that they are based on only a subset of the Finnish INTERPHONE study, combining different types of brain tumors and furthermore, unadjusted for potential confounders. Therefore, the results are not applicable for risk assessment concerning mobile phone use and brain tumors.

In conclusion, substantial distortion of results due to selection bias related to differences in mobile phone use among full study participants and incomplete participants appears unlikely in our study.

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