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# Occurrence studies of intracranial tumours

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Säteilyturvakeskus
Strålsäkerhetscentralen
Radiation and Nuclear Safety Authority

STUK

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# Academic dissertation

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## Occurrence studies of intracranial tumours


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**Keywords:** brain neoplasms, glioma, meningioma, acoustic neuroma, incidence, registries, cellular phone

# Abstract

Intracranial tumours are a histopathologically heterogeneous group of tumours. This thesis focused on three types of intracranial tumours; gliomas, meningiomas and vestibular schwannomas (VS). The main objectives of the dissertation were to estimate the occurrence of intracranial tumours by different subtypes, and to assess the validity and completeness of the cancer registry data. The specific aims of the publications were to evaluate the validity of reported incidence rates of meningioma cases, to describe the trends of VS incidence in four Nordic countries, and to define the anatomic distribution of gliomas and to investigate their location in relation to mobile phone use.

Completeness of meningioma registration was examined by comparing five separate sources of information, and by defining the frequencies of cases reported to the Finnish Cancer Registry (FCR). Incidence trends of VS were assessed in the four Nordic countries over a twenty-one-year period (1987–2007) using cancer registry data. The anatomic site of gliomas was evaluated using both crude locations in the cerebral lobes and, in more detail, a three-dimensional (3D) distribution in the brain. In addition, a study on specific locations of gliomas in relation to the typical position of mobile phones was conducted using two separate approaches: a case-case and a case-specular analysis.

The thesis was based on four sets of materials. Data from the international Interphone study were used for the studies on gliomas, while the two other studies were register-based. The dataset for meningiomas included meningioma cases from the FCR and four clinical data sources in Tampere University Hospital (neurosurgical clinic, pathology database, hospital discharge register and autopsy register). The data on VS were obtained from the national cancer registries of Denmark, Finland, Norway and Sweden.

The coverage of meningiomas was not comprehensive in any of the data sources. The completeness of FCR was approximately two-thirds (64%; 95% CI, 50–78). The underreporting was more pronounced among the elderly and in those with no histological confirmation of the meningioma diagnosis.

An increasing trend of VS incidence was observed, but with considerable differences between countries. The overall annual increase of VS incidence was 2.8% per year (95% CI, 2.3–3.2) in 1987–2007, when all the four countries and both sexes were combined. However, no statistically significant increase was seen in the rates of VS incidence in Finnish men or Swedish women, and the incidence even showed some decrease in Finnish women (–0.4%, 95% CI, –1.8 to +1.1) during the study period. The overall increase in rates stabilized in the late 1990s, with relatively constant incidence rates and even some decline after 2000.

Gliomas were distributed unevenly in the brain, with substantial variation between the cerebral lobes showing an excess of gliomas in the frontal and temporal lobes (over four-fold relative to occipital lobe, even after accounting for tissue volume). In the detailed spatial 3D-analysis, statistically significant heterogeneity was found with most gliomas in the anterior subcortical part of the brain. There was no excess of gliomas in the parts of the brain nearest to the typical location where mobile phones are held. Gliomas among never-regular mobile phone users and contralateral users (phone held on the opposite side of the head than the side of tumour) were closer to the source of electromagnetic field (EMF) than among regular and ipsilateral (exposure at the same side as the tumour location) users. In the case-specular analysis, the distance from the glioma cases to the mobile phone was shorter than for the speculars (hypothetical controls assigned for each glioma case). However, no such association was found in analyses by amount of phone use. In both models, glioma cases were closer to the source of exposure in long-term users (over ten years of use), but the differences remained non-significant.

The results indicate that even if the cancer registries from the Nordic countries are considered exemplary, benign intracranial tumours are underreported despite the national regulations for mandatory reporting. The FCR had not covered one-third of the meningioma cases diagnosed during the study period. Furthermore, the practices of both classifying and reporting VS cases varied considerably between Nordic countries and over time, which challenged the interpretation of the results. Gliomas were heterogeneously distributed within the brain, but this uneven arrangement in the brain did not correlate with the amount (cumulative call-time) or duration (years of use) of mobile phone use.

*LARJAVAARA Suvi. Kallonsisäisten kasvainten esiintyvyys. STUK-A247. Helsinki 2011, 110 s. + liitteet 53 s.*

**Avainsanat:** aivokasvaimet, gliooma, meningeooma, akustikusneurinooma, ilmaantuvuus, rekisteri, matkapuhelin

# Tiivistelmä

Kallonsisäiset kasvaimet ovat histopatologisesti hyvin epäyhtenäinen kasvainryhmä. Väitöskirja käsitteli kolmea kallonsisäistä kasvaintyyppiä: glioomia, aivokalvonkasvaimia sekä kuulohermonkasvaimia. Väitöskirjan päätavoitteina oli kuvata eri kallonsisäisten kasvainten esiintyvyyttä sekä arvioida syöpärekisteritietojen kattavuutta ja oikeellisuutta. Osajulkaisujen yksityiskohtaisina tavoitteina oli arvioida aivokalvonkasvainten raportoidun ilmaantuvuuden luotettavuutta, kuvata kuulohermonkasvainten ilmaantuvuustrendejä neljässä Pohjoismaassa, määrittää glioomien anatomisen sijainnin jakaumaa sekä arvioida glioomien sijaintia suhteessa matkapuhelimen käyttöön.

Aivokalvonkasvainten rekisteröinnin kattavuutta arvioitiin vertailemalla tapauksia viidestä eri tietolähteestä ja esittämällä näistä Suomen Syöpärekisteriin ilmoitettujen tapausten osuus. Kuulohermonkasvainten ilmaantuvuutta Pohjoismaissa 21 vuoden ajalta (1987–2007) tarkasteltiin käyttämällä syöpärekisteritietoja. Glioomien anatomista sijaintia tutkittiin sekä määrittämällä näiden karkea sijainti aivolohkoissa että yksityiskohtaisemmin käyttämällä kolmiulotteista jakaumaa aivoissa. Lisäksi glioomien tarkkaa sijaintia suhteessa tyypilliseen matkapuhelimen sijaintiin puhelun aikana arvioitiin kahdella analyysillä, tapaus-tapaus (*case-case*) -menetelmällä sekä vertaamalla tapauksia hypoteettisiin verrokkeihin (*case-specular*).

Väitöskirja pohjautui neljään aineistoon. Kaksi glioomia käsittelevää osajulkaisua perustuivat kansainväliseen Interphone-tutkimukseen, ja kaksi muuta julkaisua olivat rekisteripohjaisia. Aivokalvonkasvainten aineistoon kerättiin aivokalvonkasvaimet Suomen Syöpärekisteristä ja neljästä kliinisestä rekisteristä Tampereen yliopistollisesta sairaalasta (neurokirurgisesta klinikasta, patologien ylläpitämästä rekisteristä, sairaalan poistumisrekisteristä ja ruumiinavausrekisteristä). Kuulohermonkasvainten aineisto käsitti kuulohermonkasvaimet kansallisista syöpärekistereistä Norjasta, Ruotsista, Suomesta ja Tanskasta.

Aivokalvonkasvainten rekisteröinti ei ollut kattavaa missään aineistossa. Suomen Syöpärekisterin kattavuus oli noin kaksi kolmasosaa (64 %;

95 % CI, 50–78). Rekisteröinti oli puutteellisinta vanhuksilla ja niillä, joiden kasvaimesta ei ollut histologista varmistusta.

Kuulohermonkasvainten ilmaantuvuus oli kasvussa, mutta maitten välillä oli huomattavia eroja. Vuosittainen kasvu oli keskimäärin 2,8 % (95 % CI, 2,3–3,2) vuosina 1987–2007, kun mukana oli kasvaimet kaikista maista ja molemmilta sukupuolilta. Suomalaisilla miehillä tai ruotsalaisilla naisilla ei kuitenkaan havaittu tilastollisesti merkitsevää kasvua, ja suomalaisilla naisilla oli jopa jonkin verran ilmaantuvuuden laskua tutkimusajanjaksolla (–0,4 %, 95 % CI, –1,8 – +1,1). Kuulohermonkasvainten yleinen ilmaantuvuuden kasvu taittui 1990-luvun loppupuolella, jonka jälkeen ilmaantuvuus pysytteli melko tasaisena, ja jopa laski vuoden 2000 jälkeen.

Glioomien sijainti aivoissa oli epätasaisesti jakautunutta, ja aivolohkojen välillä oli merkittäviä eroja. Glioomia oli eniten otsa- ja ohimolohkoissa (yli nelinkertaisesti verrattuna takaraivolohkoon, suhteutettuna kunkin aivolohkon massaan). Yksityiskohtainen kolmiulotteinen analyysi osoitti tilastollisesti merkitsevää epätasaisuutta – suurin osa glioomista sijaitsi aivojen etuosissa kuorikerroksen alapuolella. Glioomia ei esiintynyt enemmän niissä aivojen osissa, jotka olivat lähinnä tavallisinta matkapuhelimen pitokohtaa. Glioomat olivat lähimpänä sähkömagneettisen kentän lähdettä (eli matkapuhelinta) henkilöillä, jotka eivät olleet koskaan käyttäneet matkapuhelinta säännöllisesti tai olivat käyttäneet puhelinta eri puolella päätä kuin kasvain sijaitsi. *Case-specular*-analyysissä glioomien etäisyys matkapuhelimesta oli lyhyempi kuvitteellisilla verrokeilla. Tulokset eivät kuitenkaan olleet riippuvaisia matkapuhelimen käytön määrästä. Molemmissa malleissa (*case-case, case-specular*) glioomat olivat lähempänä matkapuhelinta puhelimen pitkäaikaisilla käyttäjillä (yli kymmenen vuotta käyttäneillä), mutteivät tilastollisesti merkitsevästi.

Tulokset osoittavat, että vaikka pohjoismaisia syöpärekisterejä pidetään esimerkillisinä maailmanlaajuisesti, hyvänlaatuiset kallonsisäiset kasvaimet olivat alirekisteröityjä lakisääteisestä ilmoitusvelvoitteesta huolimatta. Suomen Syöpärekisterin tiedot eivät kattaneet kolmasosaa tutkimusajanjaksolla diagnosoiduista aivokalvonkasvaimista. Kuulohermonkasvainten histologinen ryhmittely ja raportointi poikkesivat huomattavasti sekä Pohjoismaiden välillä että myös ajanjaksosta riippuen. Aineiston epäyhtenäisyyden vuoksi tulosten tulkitseminen oli haasteellista. Glioomat olivat jakautuneet epätasaisesti aivoissa, mutta sijainti ei ollut yhteydessä matkapuhelimen käytön määrään (kumulatiivinen puheaika) tai kestoon (käyttövuodet).

# Contents

# List of original publications

I Larjavaara S, Haapasalo H, Sankila R, Helén P and Auvinen A (2008): Is the incidence of meningiomas underestimated? A regional survey. Br J Cancer 99:182–184.

II Larjavaara S, Feychting M, Sankila R, Johansen C, Klaeboe L, Schüz J and Auvinen A: Incidence trends of vestibular schwannomas in Denmark, Finland, Norway and Sweden in 1987–2007. (Submitted)

III Larjavaara S, Mäntylä R, Salminen T, Haapasalo H, Raitanen J, Jääskeläinen J and Auvinen A (2007): Incidence of gliomas by anatomic location. Neuro Oncol 9:319–325.

IV Larjavaara S, Schüz J, Swerdlow A, Feychting M, Johansen C, Lagorio S, Tynes T, Klaeboe L, Tonjer SR, Blettner M, Berg-Beckhoff G, Schlehofer B, Schoemaker M, Britton J, Mäntylä R, Lönn S, Ahlbom A, Flodmark O, Lilja A, Martini S, Rastelli E, Vidiri A, Kähärä V, Raitanen J, Heinävaara S and Auvinen A: Location of gliomas in relation to mobile phone use: a case-case and case-specular analysis. Am J Epidemiol (In press)

# Abbreviations

| | |
|---|---|
| CBTRUS | Central Brain Tumor Registry of the United States |
| CI | confidence interval |
| CNS | central nervous system |
| CT | computerized tomography |
| EMF | electromagnetic field |
| FCR | Finnish Cancer Registry |
| GBM | glioblastoma multiforme |
| GSM | Global System for Mobile Communication |
| IARC | International Agency for Research on Cancer |
| ICD | International Classification of Diseases |
| MOTNAC | Manual of Tumor Nomenclature and Coding |
| MR(I) | magnetic resonance (imaging) |
| NMT | Nordic Mobile Telephone system |
| OR | odds ratio |
| PIN | personal identification number |
| RF | radiofrequency |
| SAR | specific absorption rate |
| SNOMED | Systematized Nomenclature of Medicine |
| VS | vestibular schwannoma |
| WHO | World Health Organization |

# 1. Introduction

Central nervous system (CNS) tumours (including benign tumours located in the CNS) account for 3–4% of all cancer cases in Finland and the Nordic countries (Sankila et al. 2007, NORDCAN 2010). At present, little is known on the etiology of intracranial tumours, even if brain cancer is one of the most lethal cancer types. Only certain rare hereditary syndromes and ionizing radiation are proven to predispose for intracranial tumours with consistent evidence (Inskip et al. 1995, Wrensch et al. 2002).

The debate continues on whether incidence rates of intracranial tumours are increasing. From the current literature no conclusion can be derived (Lönn et al. 2004a, Boyle and Levin 2008). If rates are increasing, this would represent important knowledge in neuro-oncological research, suggesting accession of an etiologic factor yet to be acknowledged.

New exposures potentially associated with intracranial tumours are searched. One of these exposures is the use of mobile phones that has increased rapidly worldwide since the beginning of 1990s (Gibney 2005). If the risk of developing an intracranial tumour is greater among mobile phone users, the increase in incidence may be noticed by location (in proximity to mobile phones) and over time (with long-term use). This assumption of preferential location is justified by electromagnetic fields emitted by mobile phones decreasing strongly with distance, to one tenth in five centimetres distance (Cardis et al. 2008). Similarly, the process would require a great amount of time, with an induction period of ionizing radiation-induced solid tumours being probably ten years or more (UNSCEAR 2000).

CNS tumours are a heterogeneous group of tumours with substantial differences in occurrence, location, treatment and prognosis. Therefore, studying incidence rates separately for distinct tumour types should be used as the standard method. In this thesis analyses were conducted for gliomas, meningiomas and vestibular schwannomas (VS).

Anatomic locations of gliomas influence treatment options and prognosis (Wrensch et al. 2002). Prior to this thesis, the specific locations of gliomas have not been studied widely (Duffau and Capelle 2004). In most previous studies crude locations (mostly presented as the distribution of gliomas in the cerebral lobes) are substitutes of specific locations giving relatively little information. However, precise locations based on specific anatomic data give much more detailed information.

This thesis aimed at providing new knowledge on the occurrence of adult intracranial tumours, by particularly focusing on the role of cancer registries in the collecting and sharing of data.

Several errors in occurrence estimates are present in the studies on intracranial tumour incidence trends. In all academic research, a crucial task is to understand the presence of these potential biases. In order to provide good estimates of the true incidence rates, these biases should not only be evaluated, but corrected. In this thesis, the rates of meningiomas and VS reported by the cancer registry were evaluated, and also to some extent rectified. Assessing the undercount and under-registration of the data derived from the Nordic cancer registries provide valuable information on specific problems in the registration. The cancer registry based studies from the Nordic countries are considered exemplary (Lönn et al. 2004a, Klaeboe et al. 2005, Deltour et al. 2009), therefore it can be assumed that the challenges encountered working with the material from the Nordic cancer registries are likely to be highly generalisable internationally.

The aim of this dissertation was to evaluate the occurrence of intracranial tumours by taking varying approaches with different tumour subtypes, in addition to assessing the validity and completeness of the data, and availability of the required data, in cancer registries.

# 2. Review of the literature

## 2.1. Definition and clinical aspects of intracranial tumours

Tumours are defined, and named, based on their histology (morphology) and location (topography). Intracranial tumours consist of a variety of histopathological types within the bony structure of the cranium, including tumours of the brain, cranial nerves, cranial meninges and pituitary and pineal glands. Brain tumours include tumours infiltrating the brain parenchyma, while the term brain cancer excludes benign tumours. The term central nervous system (CNS) tumours include also tumours of the spinal cord and spinal meninges along with intracranial tumours.

For simplicity, the term *intracranial tumour* has been at times replaced by the term *brain tumour* in this thesis to avoid excessive repetition of the rather rigid term *intracranial tumour*, which is not in everyday use by clinicians. In these situations, *brain tumour* is regarded as a general term for intracranial tumours, and cannot be misinterpreted; if particularly only tumours of the brain parenchyma must be covered, this has been clearly indicated.

The histological classifications (based on the cell type of the tumour) of intracranial tumours include over a hundred different types (Louis et al. 2007). In addition, intracranial metastases of other organs are also counted as brain tumours, and are ten times more common than primary intracranial tumours (Buckner et al. 2007, Larson et al. 2005).

Brain tumours differ from other cancer types, as they very rarely metastasize outside the central nervous system (Kumar et al. 2003). Despite their inability to metastasize, intracranial tumours are difficult to treat as they are located commonly in areas which cannot be operated, or if operated, lead to severe complications. Brain cancer is often devastating, as even benign tumours may be lethal (Preston-Martin 1996, Kumar et al. 2003). Malignant intracranial tumours account for approximately 1–2% of all malignant cancer cases (Kleihues et al. 2002, Buckner et al. 2007).

Subgroups of brain tumours vary a great deal in their characteristics. This dissertation focuses on gliomas, meningiomas and vestibular schwannomas (VS) in adults. Other primary intracranial tumours (such as, e.g. pituitary or pineal tumours, lymphomas) and metastases are not included in this thesis.

### 2.1.1. Histological types of intracranial tumours

Intracranial tumours are defined by the cell type they originate from. Histological grading, based on the degree of differentiation of the tumour, predicts the behaviour of the tumour (malignancy increases with the grade). The grade of

the neoplasm influences the choice of operation and treatment, particularly if adjuvant radio- or chemotherapy is needed (Louis et al. 2007). A simplified classification of the CNS tumours is shown in **Table 1**, modified from WHO Classification of Tumours of the Nervous system (Louis et al. 2007). Only groups of tumours relevant to this thesis are shown with further subgrouping.

Gliomas account for one-third of all primary CNS tumours, and for 80% of all malignant primary CNS tumours (Central Brain Tumor Registry of the United States, CBTRUS 2010). Meningiomas account for approximately one-third of all primary CNS tumours and nerve sheath tumours for < 10% (60 – 90% of these nerve sheath tumours are VS) (Matthies and Samii 2004, Propp et al. 2006, CBTRUS 2010). Other primary CNS tumour types include e.g. pituitary tumours (13%), lymphomas (< 3%), craniopharyngiomas (< 1%) (CBTRUS 2010). These are not included in this thesis.

#### 2.1.1.1. Gliomas

Gliomas originate from the supporting glial cells of the brain tissue (astrocytes, oligodendrocytes and ependymal cells).

Gliomas are subdivided into astrocytomas and others (e.g. oligodendrogliomas, mixed gliomas, epedymomas) (**Table 1**). Astrocytomas account for three-fourths of all gliomas. They are further divided into pilocytic astrocytomas

**Table 1.** A simplified classification of the CNS tumours. (Adapted from Louis et al. 2007).

| Tumour | Grade |
|---|---|
| **NEUROEPITHELIAL TUMOURS** | |
| **Astrocytomas *** | |
| Pilocytic astrocytoma * | I |
| Diffuse astrocytoma * | II |
| Anaplastic astrocytoma * | III |
| Glioblastoma * | IV |
| **Oligodendrogliomas *** | |
| Oligodendroglioma * | II |
| Anaplastic oligodendroglioma * | III |
| **Oligoastrocytic tumours, mixed *** | |
| Oligoastrocytoma * | II – III |
| **Ependymal tumours *** | I – III |
| **Choroid plexus tumours** | I – III |
| **Neuronal and mixed neuronal-glial tumours** | I – IV |
| **Pineal tumours** | I – IV |
| **Embryonal tumours** | IV |

| Tumour | Grade |
|---|---|
| **TUMOURS OF THE MENINGES** | |
| **Meningeal tumours** | |
| Meningioma | I |
| Atypical meningioma | II |
| Anaplastic meningioma | III |
| **Non-meningothelial tumours of the meninges** | I – III |
| **TUMOURS OF CRANIAL AND SPINAL NERVES** | |
| Schwannoma | I |
| Neurofibroma | I |
| Malignant peripheral nerve sheath tumour (MPNST) | II – IV |
| **HEMATOPOIETIC TUMOURS** | |
| **GERM CELL TUMOURS** | I – IV |
| **TUMOURS OF THE SELLAR REGION** | I |

* Gliomas

(grade I) (5–6% of all gliomas), diffuse astrocytomas (grade II) (<2%), anaplastic astrocytomas (grade III) (8%) and glioblastomas (grade IV) (45–56%) (Louis et al. 2007, CBTRUS 2010). The second most common glioma type after astrocytoma is oligodendroglioma (grade II–III) (5–7% of all gliomas). Oligodendrogliomas, together with astrocytomas, form oligoastrocytomas (i.e. mixed gliomas) (grade II) (2–9% of all gliomas). Ependymomas (usually grade II–III) originate from the ependymal cells around the ventricles (<6% of all gliomas) (Louis et al. 2007, CBTRUS 2010).

According to CBTRUS, less than two-thirds of gliomas are located in the cortical lobes of which 25% are located in the frontal lobe, 20% in the temporal, 13% in the parietal and 3% in the occipital lobe (cerebral lobes are presented in **Figure 1**).

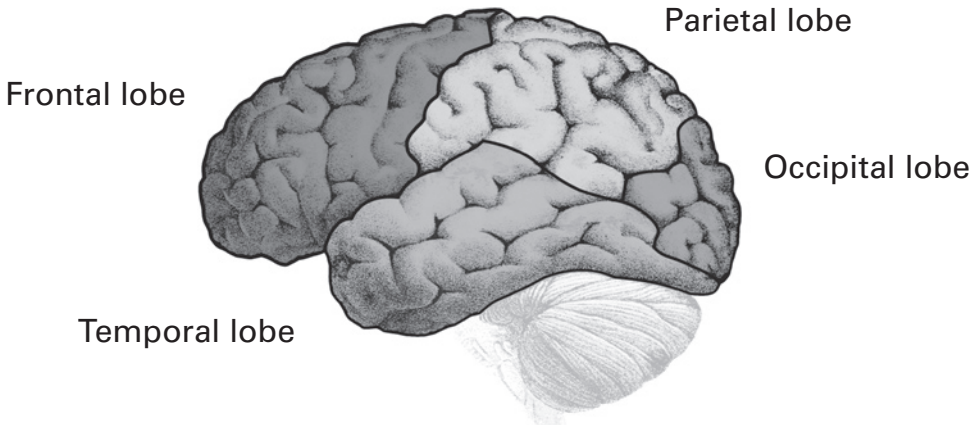



**Figure 1.** Crude representation of the cerebral lobes.

#### 2.1.1.2. Meningiomas

Meningiomas are usually benign tumours (in over 90% of cases) formed from the cells of the meninges (Claus et al. 2005). Meningiomas are mainly located on the surface of the brain at the convexity (often in the falx cerebri, the sulcus between brain hemispheres, or attached to the parasagittal sinus) or by the sphenoidal wing (a bony process of the sphenoid bone at the base of the skull) (Campbell et al. 2009).

#### 2.1.1.3. Schwannomas

Schwannomas are benign tumours that arise from Schwann cells, which form the myelin sheath around nerves. Schwannomas may develop at the spinal nerve

roots, the cranial or the peripheral nerves. Vestibular schwannoma (VS), also called acoustic neurinoma (or neuroma, neurilemmoma), is a schwannoma of the eighth cranial nerve. VS constitute approximately 60% of all schwannomas and roughly 90% of all intracranial schwannomas (Weller and Cervos-Navarro 1977, Propp et al. 2006). The vestibulocochlear nerve (VIII cranial nerve) consists of a cochlear (acoustic) and a vestibular part. The vast majority of VS are located in the vestibular part, which is mainly responsible for balance. The adjacent cochlear division is very rarely the site of origin of VS (Louis et al. 2007).

### 2.1.2. Diagnosis, treatment and prognosis

Symptoms of intracranial tumours are diverse depending on the size and location of the tumour. Focal symptoms, such as epileptic seizures, alteration in personality, problems in memorizing, hemiplegia, aphasia and visual aberrations, are often first symptoms of a brain tumour, both gliomas and meningiomas (van Breemen et al. 2007, Buckner et al. 2007). Symptoms occurring with larger tumours associated with elevated intracranial pressure include severe headache, nausea and vomiting (Buckner et al. 2007). The first symptoms of VS are normally unilateral hearing loss together with tinnitus, often combined with vertigo (Myrseth et al. 2006).

Diagnosis of an intracranial tumour can be suspected after computerized tomography (CT) that reveals an intracranial mass. Magnetic resonance imaging (MRI) is much more accurate in confirming a possible brain tumour. A definite diagnosis can only be made based on histology, even if often the diagnosis is strongly suspected from radiological imaging. In some circumstances the diagnosis can be based on unambiguous imaging solely, particularly with non-symptomatic and benign tumours and especially among the elderly (who cannot undergo heavy diagnostic procedures, e.g. biopsies).

Surgical operation of a brain tumour is important, no matter what the histological subgroup is, if the tumour is causing symptoms. Surgical removal is curative for most benign brain tumours. For malignant tumours, the operative treatment is the initial procedure followed by either postoperative radiotherapy and/or chemotherapy (Wen and Kesari 2008). Radiotherapy is the basis of postoperative treatment for malignant gliomas, yet chemotherapy is becoming increasingly important in the treatment options (Wen and Kesari 2008). In certain cases surgery cannot be undergone, but a stereotactic biopsy for diagnostic purposes can be nearly always taken. Choices for postoperative treatments vary not only depending on the grade and behaviour of the glioma, but also on the performance status of the patient, expected survival

and location of tumour. The effects of operative treatment on survival and prognosis remain controversial especially among low-grade gliomas, but an increasing number of studies (retrospective and uncontrolled studies) suggest that surgery should be a standard treatment for all gliomas (Norden and Wen 2006). Investigation continues to identify the best treatment option for gliomas.

The primary treatment of meningiomas is surgical. Only in some cases this is followed by radiotherapy (high-grade, unresectable or recurrent meningiomas) (Campbell et al. 2009). Chemotherapy is not yet established for meningiomas, and has shown only modest benefit in the treatment of anaplastic or atypical meningiomas (Lusis et al. 2004, Campbell et al. 2009). Expectant management (i.e. conservative, non-operative), both radiologically and clinically, is a reasonable choice for treatment for incidental and asymptomatic meningiomas (Nakamura et al. 2003, Campbell et al. 2009).

There is no standard treatment for VS (Nikolopoulos et al. 2002). The four most used treatment options for VS are watchful waiting, microsurgery, radiosurgery and radiotherapy.

Survival from an intracranial tumour is strongly associated with patient's age and histological type of the tumour (Wrensch et al. 2002). Survival rates are poor in all glioma types (except children's pilocytic astrocytomas), as unfortunately even low-grade gliomas may eventually progress into high-grade tumours. With the standard treatment, patients with glioblastoma multiforme (GBM) have a median survival of only 7–15 months and a 5-year survival rate of 3% (Hess et al. 2004, Norden and Wen 2006, Wen and Kesari 2008). For less malignant gliomas the 5-year survival rates for anaplastic tumours (grade III) are 40% for oligodendroglioma and 30% for astrocytoma, and 70% for oligodendroglioma and 50% for diffuse astrocytoma (grade II) (Norden and Wen 2006). Patients undergoing complete resection of meningioma are cured of their tumour (Bulsara et al. 2004). However, in a clinical study, the median survival rate for anaplastic meningiomas was approximately only 1.5 years (Perry et al. 1999). VS is almost always curable, thus VS do not influence survival rates of a patient (Matthies and Samii 2004).

## 2.2. Etiology of intracranial tumours

Etiology of all subtypes of brain tumours is poorly understood. A methodological limitation hindering etiologic studies is that few studies are based on detailed histological grouping of intracranial tumours. Development and behaviour of different types of intracranial tumours differ considerably, thus it is conceivable that also etiological factors of brain tumours may differ by subtype.

### 2.2.1. Hereditary and environmental factors

The only well-established etiological factors for all types of brain neoplasms are high-dose ionizing radiation and some inherited syndromes (Inskip et al. 1995, Preston-Martin and Mack 1996, Wrensch et al. 2002). Ionizing radiation is associated with all intracranial tumours, but there is stronger association with meningiomas and schwannomas than with gliomas (Ron et al. 1988, Preston-Martin and Mack 1996, Preston et al. 2002, Wrensch et al. 2002). There is also one causal factor specific to a certain brain cancer type, i.e. immune suppression increasing brain lymphomas (Wrensch et al. 2002). However, these known causes account for a very small proportion of all brain cancer cases.

Today, more and more interest is turned on potential genetic risk factors for intracranial tumours rather than studying behavioural and environmental risk factors. This is partly due to increasing understanding of the molecular pathology of brain tumours (particularly gliomas). Also, studies investigating possible environmental exposures have remained inconclusive. Potential risk factors for intracranial cancer are discussed in the following parts.

#### 2.2.1.1. Heredity and genes

Certain hereditary syndromes are documented to predispose to brain cancer. These rare mutations in highly penetrant genes include neurofibromatosis 1 and 2 (NF1, NF2), von Hippel-Lindau disease and tuberosis sclerosis, and less commonly Li-Fraumeni syndrome, Cowden's disease and Turcot's and Gorlin's syndromes (Farrell et al. 2007). The incidence of these syndromes is estimated to be at most one case in 3,000 live births (for NF1) to one in 200,000 live births (for Cowden's disease) (Farrell et al. 2007). In addition, these syndromes account for only a few percentages (1–5%) of the intracranial tumour cases (at the most 5%, when the broadest definition of a predisposing familial syndrome is applied) (Inskip et al. 1995, Preston-Martin and Mack 1996, Batchelor et al. 2001, Wrensch et al. 2002). However, no conclusive studies on the lifetime risk of brain tumour for carriers of these syndromes have been conducted, but based on earlier reports approximately 5–10% of those with the trait for NF1 develop a CNS tumour, and up to 50% of those with NF2 develop an intracranial meningioma (Preston-Martin and Mack 1996, Farrell et al. 2007). The brain tumour types associated with these syndromes include gliomas (mainly NF1, NF2, Li-Fraumeni), neuromas (mainly NF2) and meningiomas (mainly NF2).

Some persons are more sensitive to gamma radiation than others, based on heredity. However, it is not known whether this is due to a problem with the repair capacity alone of the individuals or whether there is interaction present. At present, too few studies are conducted on lymphocytes' sensitivity

to gammaradiation (sensitive patients being more susceptible to environmental radiation) to give sufficient evidence (Bondy et al. 2001).

Familial aggregation of intracranial cancers has been shown, but with inconsistent results. It is challenging to distinguish genetic characteristics from a shared environment by family members. A twin study focusing on all cancer types found no increased risk of brain neoplasms in twins, however, the brain cancer cases were few (Lichtenstein et al. 2000). Some studies have shown a significant, approximately two-fold, increase in brain tumours among first degree relatives of glioma or other CNS tumour patients (Hemminki and Li 2003, Malmer et al. 2003, Scheurer et al. 2007). However, other studies have shown no significant excess risk of intracranial tumour with any malignancy in relatives (Hill et al. 2003, Hill et al. 2004).

The first molecular genetic evidence for familial aggregation of gliomas was shown in Finnish families with the presence of a mutation locus at 15q23-q26.3 in association with familial glioma (Paunu et al. 2002). Since then, at least five other loci for glioma have been identified by genome-wide association studies (Shete et al. 2009).

Genetic polymorphisms of common genes might influence a person's susceptibility to brain cancer together with environmental exposures. These polymorphisms are believed to affect detoxification processes, cell cycle regulation and DNA stability and repair (Ohgaki and Kleihues 2005, Wrensch et al. 2005, Schwartzbaum et al. 2006, Fisher et al. 2007). This potential association of specific polymorphisms and brain tumours is currently of great interest to researchers.

#### 2.2.1.2. Immunological agents: allergy and microbes

Allergy, or rather absence of allergy, has appeared as a new interesting etiological hypothesis. Allergies seem to have an inverse association with risk of glioma, with a significantly reduced risk by 30–60% (Schlehofer et al. 1999, Wigertz et al. 2007, Scheurer et al. 2008). Glioma cases also show significantly lower immunoglobulin E-levels (in concordance with lower allergy levels) (Wiemels et al. 2004, Wiemels et al. 2007). However, a large study combining several cohorts found insufficient evidence either for the hypothesis of allergy decreasing rates of gliomas (or meningiomas), or against it (Schwartzbaum et al. 2003).

On the contrary, there is some evidence that certain microbes (e.g. polyomaviruses, *Toxoplasma gondii*) have a positive association with intracranial cancer, but the results are inconsistent (Davis et al. 2000, Wrensch et al. 2002, Shaw et al. 2006). There are also several examples of microbes with no increased risk shown (e.g. polio, chicken pox and mother's exposure to influenza during pregnancy) (Wrensch et al. 2002).

#### 2.2.1.3. Seizures and head injury

Epilepsy and convulsions are suggested to be associated with increased risk of brain tumours (brain tumours meaning here 'tumours of the brain', excluding other intracranial tumours), but as epilepsy often presents as the first symptom of brain tumour, finding evidence is difficult. However, in a study with epilepsy existing at least two years prior to diagnosis, a significant, more than six-fold risk of glioma was found (Schlehofer et al. 1999). Antiepileptic drug users had an increased risk of a CNS tumour of over four-fold. However, the risk decreased strongly after the first year the drug use began, suggesting that epilepsy was an early symptom of a brain tumour and yielded to its better detection (Lamminpää et al. 2002).

Similarly to epilepsy, proving the relation of brain cancer and head injury is challenging, as strong recall bias tends to be present. No statistically significant association with any brain tumour type other than vascular tumours (e.g. hemangioblastomas) was found in a large cohort study (Inskip et al. 1998).

#### 2.2.1.4. Diet, smoking, alcohol and medications

No specific components of diet are suspected of being associated with brain cancer, apart from N-nitroso compounds found in food products. A review study by Preston-Martin and Mack (1996) listed twelve case-control studies with N-nitroso compounds, of which most suggested at least a weak association with intracranial tumours. Again, studying the association of N-nitroso compounds and brain cancer is difficult, as they are common in everyday food.

In some studies a reduced risk of glioma seems to be associated with coffee and tea intake, i.e. consumption of caffeinated beverages (Holick et al. 2010, Michaud et al. 2010).

No association between smoking or alcohol consumption and increased risk of intracranial tumours has been reported (Preston-Martin and Mack 1996). Maternal smoking is not believed to increase the risk of childhood brain cancer (Boffetta et al. 2000, Filippini et al. 2002).

The association of medications with brain tumours has not been studied much. So far, no strong associations have been published. In a study from Texas, the risk of glioma was reduced by one third using non-steroidal anti-inflammatory drugs (NSAIDs) (Scheurer et al. 2008), and GBM risk was reduced to half when a self-reported use of NSAIDs was present (Sivak-Sears et al. 2004). Risk reduction among antihistamine users has been reported (Schlehofer et al. 1999, Wigertz et al. 2007), but also a non-significant increase (Scheurer et al. 2008). Similarly to antiepileptic drug users, with only epileptics using those drugs, it is impossible to separate the component of allergy from antihistamine use (confounding by indication).

#### 2.2.1.5. Electromagnetic radiation

Electromagnetic radiation consists of a variety of different types of radiation, both ionizing and non-ionizing (see a simplified model in **Figure 2**). Ionizing radiation is known to be potent in causing mutations (DNA damage), by breaking chemical bonds in molecules followed by a potential cancer (Valberg 1997). However, no consistent evidence has been shown that non-ionizing radiation had an association with brain cancer (Ahlbom et al. 2009). Mobile phones, emitting a non-ionizing electromagnetic field (EMF), are discussed later (**2.2.1.9.**).

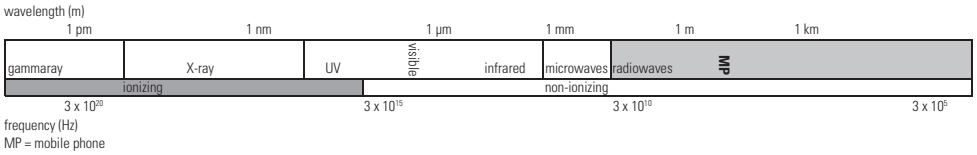



**Figure 2.** Representation of the electromagnetic spectrum. (Adapted from MAOL 1991).

Childhood radiotherapy given for malignant disease, and historically also for non-malignant conditions, increases the rates of CNS tumours. Studies with radiotherapy applied to the head for treating leukemia (Neglia et al. 1991, Relling et al. 1999, Loning et al. 2000) or other types of primary cancers (Neglia et al. 2006), enlarged tonsils (Shore-Freedman et al. 1983), *tinea capitis* (ringworm of the scalp) (Ron et al. 1988, Shore et al. 2003), skin hemangioma (Karlsson et al. 1998) and thymic enlargement (Hildreth et al. 1985), show a manifold increase in risk of brain tumours.

Survivors from atomic bomb explosions are believed to have an excess of CNS tumours. However, the results are not consistent and studies are still ongoing (Inskip et al. 1995, Preston-Martin and Mack 1996, Preston et al. 2002, Yonehara et al. 2004). Nevertheless, in a large cohort study on atomic bomb survivors a clear suggestion of a dose-response for schwannoma was seen, but also the crude rates for other intracranial tumour types suggested an increasing dose-response relationship (Preston et al. 2002).

Radiotherapy is used in treatment for brain tumours. In a register-based study, a two-fold increased risk of a second CNS cancer after plain surgery of brain cancer was observed, but a five-fold risk for those treated with radiotherapy (alone or combined with surgery and/or chemotherapy) (Salminen et al. 1999). A clear increase in new primary neoplasms of the CNS has been shown among childhood cancer patients having received radiation therapy in the brain (Neglia et al. 2006, Hijiya et al. 2007).

Residential EMF (i.e. living close to power lines, depending on electrical wiring configurations) with radiation of low energy is not believed to increase intracranial tumour incidence (Kheifets 2001).

#### 2.2.1.6. Occupation and industry

Occupational and industrial exposures include chemicals and other hazards, but occupational exposure may also include EMFs. A recent study with an occupational exposure to extremely low frequency EMFs found no statistically significantly elevated risk for meningioma or glioma (Coble et al. 2009). Studies with workers with X-rays and nuclear power have shown inconsistent results (Alexander et al. 2001, Wang et al. 2002). The largest epidemiological study to date with radiation exposed workers in the nuclear industry showed no association of increased risk for CNS tumour in relation to radiation dose (Cardis et al. 2007a).

Apart from EMFs, in the comprehensive review by Wrensch et al. (2002), the authors concluded that despite numerous studies done, the results in all occupational exposures remain inconclusive. An academic dissertation with over 100,000 Finnish workers found for all nervous system tumours the highest occupation-specific incidence rates among male distillers and female cigarette makers (Pukkala 1995). Medical workers and people working in nursing showed standardized incidence ratios typically above one, in addition to men working in the military and the police force and women in the food industry and in beauty and hygiene services (Pukkala 1995).

#### 2.2.1.7. Hormones and other factors

Estrogen, progesterone and androgen receptors are frequently present in both meningiomas and gliomas (Carroll et al. 1995, Batistatou et al. 2004, Korhonen et al. 2006). Endogenous and exogenous sex hormones may play a role in the development of meningiomas (Wahab and Al-Azzawi 2003, Lee et al. 2006). A related finding is the reported association of increased meningioma risk with breast carcinoma (Custer et al. 2002, Wahab and Al-Azzawi 2003, Claus et al. 2005). There is a possibility of female reproductive hormones decreasing the risk of glioma, yet with no consistent evidence (Felini et al. 2009). A case-control study on reproductive hormones and brain cancers (glioma and meningioma) from the Nordic countries and United Kingdom reported some association between endogenous female sex hormones and intracranial tumours, but the results were not coherent (Wigertz et al. 2008). A recent study with over a million postmenopausal women found that the incidence of CNS tumours was slightly (statistically significantly) increased in the current users of hormone replacement therapy (particularly with estrogen-only

therapy) when compared to never users (Benson et al. 2010). There was no significant difference between tumour types (gliomas, meningiomas and VS) (Benson et al. 2010).

Other factors proposed to play a role in intracranial tumour etiology include e.g. hair products and air pollution. Hair sprays and dyes containing N-nitroso compounds, either as personal or maternal exposure, have not been reported consistently to increase the brain tumour rates (Preston-Martin and Mack 1996, Efird et al. 2005), neither has air pollution related to traffic (Raaschou-Nielsen et al. 2001).

Prior cancers (other than CNS tumours) are not believed to influence patients having an excess risk of subsequent primary brain tumours (Maluf et al. 2002, Inskip 2003b). Even if more brain tumour cases were detected, it would result probably from better medical follow-up or cancer treatment (e.g. radiotherapy) (Inskip 2003b).

#### 2.2.1.8. Risk factors for vestibular schwannomas

Risk factors for VS differ somewhat from those for gliomas and meningiomas. As for gliomas and meningiomas, the only established etiological factors at present are ionizing radiation and neurofibromatosis 2 (NF2) (Preston-Martin and Mack 1996, Louis et al. 2007). NF2 accounts for a larger fraction of VS than meningioma or glioma, but still only for 4–7% of all schwannoma cases (Evans et al. 2005, Louis et al. 2007). Suggested possible risk factors include loud noise (Edwards et al. 2006, Schlehofer et al. 2007, Hours et al. 2009), radiation exposure in childhood (Schneider et al. 2008), long-term ipsilateral mobile phone use (exposure at the same side as the tumour location) (Schoemaker et al. 2005, Khurana et al. 2009), allergies (Schlehofer et al. 2007), epilepsy (Schoemaker et al. 2007) and certain occupational exposures (Prochazka et al. 2010, Samkange-Zeeb et al. 2010).

#### 2.2.1.9. Mobile phones

Even if mobile phones emit electromagnetic fields, they are considered separately from the other EMFs (**2.2.1.5.**) in this review of the literature, as they deserve some special emphasis.

The use of mobile phones is one of the potential etiologic factors for intracranial tumours causing most public concern. Ever since the beginning of 1990s, the use of mobile phones has increased rapidly, now with over two billion users worldwide (Ahlbom et al. 2009). The radiofrequency (RF) electromagnetic fields emitted by mobile phones are non-ionizing, and believed to be non-carcinogenic. However, they have some thermal effects raising the temperature in the tissues, and could cause certain molecular effects in brain.

A possible mobile phone effect would be based on tumour promotion or progression, rather than initiation (Kundi et al. 2009).

Specific absorption rate (SAR) represents absorbed radiofrequency (RF) energy transmitted to the body (power per unit mass of body tissue, W/kg). The SAR from a mobile phone decreases strongly with distance, on average to a tenth within the 5 cm length of brain tissue (Cardis et al. 2008). SAR is used as a dosimetric quantity in guidelines of EMF. For example, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) gives recommendations for SAR-value-limits for mobile phone models (below 2 W/kg, per 10 g volume).

Since its introduction, wireless connection technology (and particularly mobile phone technology) has rapidly evolved. The first analogue mobile phones were introduced in the early 1980s. In Europe, two principal mobile phone network types have been used. The analogue NMT-system (Nordic Mobile Telephone) operates with frequencies of 450 MHz and 900 MHz, whereas the digital system GSM (Global System for Mobile Communication), launched in 1991, operates with frequencies of 900 MHz and 1800 MHz. A recently introduced 3G-system (also known as UMTS, Universal Mobile Telecommunication System) uses frequencies of 1900 MHz and 2150 MHz. This 3G-system will not be considered in this thesis for its novelty.

The NMT- and GSM-systems differ in power levels, as NMT phones emit radiation at a constant level (1 W), whereas GSM phones use pulsed signals with a varying maximum average output power (up to 1 W, average output of 0.25 W (GSM 1800 MHz), and 2 W, average output of 0.125 W (GSM 900 MHz)) (Jokela et al. 2006). Thus, NMT phones have higher maximum SAR values than GSM phones, due to the difference in output power.

Several studies on mobile phone use and brain tumours have been conducted over the years. Recently, several meta-analyses and reviews have been published (Lahkola et al. 2006, Hardell et al. 2008, Kan et al. 2008). The most recent review at the time of writing this thesis studied separately gliomas, meningiomas, VS and salivary gland tumours (Ahlbom et al. 2009). A meta-analysis including also other types of cancers than brain, was also published recently, but had some methodological problems (such as pooling heterogeneous cancer sites (with different localized mobile phone exposure) or using blinding as a measure of quality in the case-control studies included) (Myung et al. 2009).

In the review by Ahlbom et al. (2009) pooling all studies showed an OR of 1.0 (95% CI, 0.9–1.1) for risk of glioma in short-term use of mobile phone, and with long-term use (≥10 years) an OR of 1.1 (95% CI, 0.8–1.4). For meningioma, short-term use of mobile phone resulted in a decreased OR of 0.8 (95% CI, 0.7–0.9), and long-term use gave an OR of 1.2 (95% CI, 0.7–2.2). Similarly for

VS, no significant association with mobile phones was found in the review. Short-term use had an OR of 1.0 (95% CI, 0.7 – 1.4) for risk of VS, and long-term use an OR of 1.4 (95% CI, 0.7 – 2.5).

Laterality analyses were also covered in this review by Ahlbom et al. (2009), but these were difficult to interpret due to methodologic problems (e.g. possible recall bias). With gliomas, the risk estimates were close to unity in most studies with ipsi/contralateral use (exceptions in Hardell et al. 2002, Hardell et al. 2006) and all relative risks remained non-significant for long-term use. Ipsilateral use did not increase the risk of VS in most studies, although with long-term ipsilateral use there was some borderline significant increase in risk. Laterality was not considered with meningiomas.

Two separate research groups can be identified as directing the studies of risk of intracranial tumour with mobile phone use, in addition to several smaller research groups. These two groups, the group by Hardell et al. and the Interphone group, have differences in their methods, which is thought to lead to dissimilar conclusions. These distinctions between the two groups (e.g. prevalence vs. incidence sampling, interviews vs. mailed questionnaires, blinded data processing, inclusion of cordless phones) are not dealt with detail here, but there are several reviews discussing the differences between the two groups (Ahlbom et al. 2009, Kundi 2009, Myung et al. 2009, Lahkola 2010).

To summarize, there is absence of evidence of increased risk of any type of brain tumour associated with mobile phone use based on the current evidence. As information on long-term users still remains deficient, the association of mobile phone and slow-growing tumours (VS and meningioma) and glioma among long-term users cannot be ruled out due to the insufficient observation period. Yet, there are limitations in the methodology used in the present studies, which could not be overcome even with a longer study period. All mobile phone studies accomplished so far have been case-control studies, which indicates that several biases are bound to be present (e.g. recall biases, selection biases). However, a large prospective cohort study of mobile phone users (Cosmos) is launched in 2010, but obtaining results from this study will take quite some time (the initial plan is to follow the users up to over 25 years) (Schüz et al. 2010).

## 2.3. Occurrence of intracranial tumours

### 2.3.1. Measures of occurrence

Cancer epidemiology deals with occurrence of cancer in populations. In order to do this, the definition of a cancer case, the population where the cancers derive from and the period under study must be clearly identified (dos Santos

Silva 1999). The data from the cancer registries should include by default verified cancer cases with a confirmed date of diagnosis. Information on the population is often readily available to the researchers. When these three issues are carefully defined and when proceeding to descriptive cancer epidemiology research, certain definitions should be clear.

Prevalence represents the persons with the disease (cancer) in a population at a particular point in time or during a period of time. Prevalence is not a rate (as rate is associated with the rapidity of change per unit of time) (Elandt-Johnson 1975). In analytical cancer epidemiology, prevalence is not used widely. However, e.g. in oncological health care planning, cancer prevalence can be used as a measure. In cancer epidemiology particularly, problems are encountered with defining the prevalence, as cancer cases are not always cured, even if the disease status is considered to have ended (e.g. no relapse in a five year follow-up). This difficulty in defining recovery (of the disease) is typical to cancer cases, in comparison to e.g. viral infections.

Prevalent cases are all those cases with the particular disease in the population (existing cases), whereas incident cases are new cases (persons, who develop the disease during the time period under focus, thus transforming from healthy to diseased).

Incidence rate is the occurrence of incident (cancer) cases diagnosed during a given time-period among people from a defined population at risk (during that time-period). The incidence rate is expressed by cases per person-years. Incidence rates and the changes (trends) in incidence are of prime interest in cancer epidemiology studies. The term cumulative incidence is often used for a proportion of a stable population at risk that becomes diseased within a given period of time.

Mortality rates represent people dying from the disease (cancer). Mortality is the incidence of death (probability of death in a year). Survival quantifies the probability (percent) of surviving for a specified time period. Survival is an important measure in e.g. clinical cancer research and is often presented as 3-year, 5-year and/or 10-year survival percentages. The (survival) percentage indicates the proportion of all diseased still alive at a given point in time (e.g. ten years after diagnosis).

Age-standardization accounts for different population structures and allows international comparison between country-specific rates. The direct age-standardization applies the age-specific rates in the population in question to a standard population. Age-specific rates are obtained by dividing the occurring cases into age-groups (cases in a certain age-group in relation to the person-years of that age-group).

Several standard populations are available (e.g. world standard population, European, Nordic). Throughout this thesis the world standard population by

Segi (1960) has been used. Even if the distribution of age-groups has changed in fifty years, this distribution by Segi may well be used for comparisons of rates (Bray et al. 2002). It should be clear for researchers that the age-standardized incidence rates are good for comparing rates from two distinct populations, however for estimating the cancer cases (actual numbers of cases) in a certain population, crude rates should be used.

Even if the measures of occurrence include e.g. incidence rate (density), incidence proportion and prevalence, in this thesis we are concentrating on the incidence rates rather than other measures. This choice of excluding prevalence completely from the thesis is justified by several factors. Prevalence is not as relevant for etiological studies as incidence, and this thesis was focusing on the occurrence of intracranial tumours as an aspect of etiology, in addition to assessing various sources of data available for studies on cancer epidemiology particularly in reporting incident cancer cases (i.e. incidence rate).

### 2.3.2. Cancer registration in studies on cancer epidemiology

By collecting, storing, analysing and reporting data, cancer registries have become the prime source in epidemiological research concentrating on measures of cancer occurrence. Information derived from cancer registries identifies priorities for public health and helps plan public health measures such as cancer control strategies, including primary and secondary prevention, and provides means for identifying risk factors. Without cancer registries, evaluating the effects of screening and other interactions on population would be very difficult, if not impossible. Cancer registries are a valuable resource for research on cancer allowing large-scale studies to be performed with reasonable cost, and achieving generalisable and valid results.

Cancer registries are either population-based or hospital-based in their design. A population-based cancer registry contains systematically collected information from cancer cases in a defined population (dos Santos Silva 1999). Population-based cancer registries are vital for research in cancer epidemiology. These registries are national or regional, and are formed from a well defined geographical area with accurate demographic information. Hospital-based registering is used mainly for administrative purposes. However, to an extent, hospital-based registers may also be used for epidemiological research.

Many population-based cancer registries are tempted to remain only as data collectors, by simply storing information. However, it is difficult to maintain a good cancer registry without an active research programme, with a research-minded personnel taking care of the daily routines of the registry keeping in mind constantly the data quality aspect (Teppo et al. 1994). Continuous activity

to obtain the data as well as to process, analyse, and interpret the registry information is required to maintain a registry of high quality. Fortunately, many registries produce also their own direct epidemiologic research and take an active approach in implementing control programs, particularly screening (Parkin 2006).

There is great international variation in cancer registries. In some countries the registers are based on voluntariness, while in others there is an obligation (controlled by legislations) to report all cancer cases. In some registries only malignant cancers are recorded.

The latest *Cancer Incidence in Five Continents* (vol IX) reported the population coverage of cancer registries being one tenth of the world population (Curado et al. 2007). At the change of the millennium, nationwide cancer registration was present only in twelve countries, from where it gradually increased, to eighteen nationwide registries in 2006 (dos Santos Silva 1999, Parkin 2006). To lessen international variation in registering, an international association, IACR (International Association of Cancer Registries) was founded in 1966. One of its functions is to develop and standardize cancer case collection methods internationally. Briefly, the information of each cancer case include e.g. details recorded with a personal identification number (PIN), the nature of the cancer, accurate date of diagnosis and a precise diagnosis with international standards used. (The personal identification numbers are simply numbers used for registration purposes within the registry, while in some registries numbers through a population-wide numeric system are used, such as in Finland (each citizen has a unique social security number).) Variations in classifications will be summarized later (**4.1.3.**).

Cancer registries should aim for accuracy (specificity) and comprehensiveness (sensitivity). Validity in cancer registries means both completeness of coverage and accuracy of the information. Once established, the quality of cancer registries ought to be of a high standard. Information should preferably be rather of high specificity and low sensitivity, than *vice versa*, in order to produce more reliable data relevant for studies (including only true cases).

### 2.3.3. Variations in reported occurrence of intracranial tumours

Even though brain tumours are some of the most lethal cancer types and their etiology is poorly known, several studies show increasing incidence rates for brain tumours over the past few decades in several populations (Fleury et al. 1997, Davis et al. 2000, Liigant et al. 2000, Batchelor et al. 2001, Jukich et al. 2001, Christensen et al. 2003, Hess et al. 2004, Johannesen et al. 2004,

Chakrabarti et al. 2005, Klaeboe et al. 2005, Hoffman et al. 2006, Fisher et al. 2007, Campbell et al. 2009, Deltour et al. 2009). However, some studies suggest the rates have stabilized in the past decades or even show a decreasing trend (Legler et al. 1999, Gurney and Kadan-Lottick 2001, Cordera et al. 2002, Kaneko et al. 2002, Lönn et al. 2004a, Deorah et al. 2006, Houben et al. 2006, Boyle and Levin 2008, Arora et al. 2010). It would be important for neuro-oncologic research to know whether the increase is real. This might suggest risk factors, which we are not yet familiar with, increasing in the population.

#### 2.3.3.1. Changes in diagnostics and reporting

One of the reasons for this possible increasing trend is the introduction of CT in the 1970s and MRI in the early 1980s which enabled better tumour detection (Kallio 1993, Helseth 1995, Preston et al. 2002, Lönn et al. 2004a). The ability to visualize the intracranial tissue non-invasively, to scan the head quickly, safely and relatively inexpensively, contributed to increased diagnosis of intracranial tumours, particularly as incidental findings. This increase in diagnosing increased the incidence rates of brain tumours (which are not necessarily treated) especially among the elderly (Inskip et al. 1995, Legler et al. 1999, Deorah et al. 2006). Prior to the era of imaging, elderly patients could not undergo heavy diagnostic procedures. With time, also other changes enable more efficient diagnosing of brain neoplasms, like more neurosurgeons and neurologists per inhabitant, better access to health care, new diagnosing methods in addition to CT and MRI (e.g. stereotactic biopsy) (Inskip et al. 1995, Wrensch et al. 2002). Also, potential variations in reporting and coding (classifying) practices affect the incidence rates (Boyle and Levin 2008).

Other factors possibly having an impact on the 'real rates' of the intracranial tumours are the changes in coding and reporting practices. These issues will be dealt in more detail in the discussion-section (**6.1.**).

The incidence rates vary greatly according to the source of information and the intracranial tumour type under focus. However, a few studies consider all intracranial tumours combined (including benign tumours) reporting annual trends with some observed constant increase. The annual increase of all intracerebral tumours combined was 0.6% (95% CI, 0.4–0.7) in Nordic men and 0.9% (95% CI, 0.7–1.0) in women in 1969–98 (Lönn et al. 2004a), and 1.1% (95% CI, 0.8–1.4) for both sexes together in the USA in 1985–99 (Hoffman et al. 2006).

As mentioned earlier, the prevalence of intracranial tumours will not be discussed in detail. Altogether not many prevalence estimates on intracranial tumours are published (Wrensch et al. 2002); an approximation from the USA in 2000 suggests a prevalence of 0.1% (both sexes combined), with an estimate of 0.03% for a malignant and 0.1% for a benign intracranial tumour (Davis et al. 2001).

#### 2.3.3.2. Differences between countries and populations

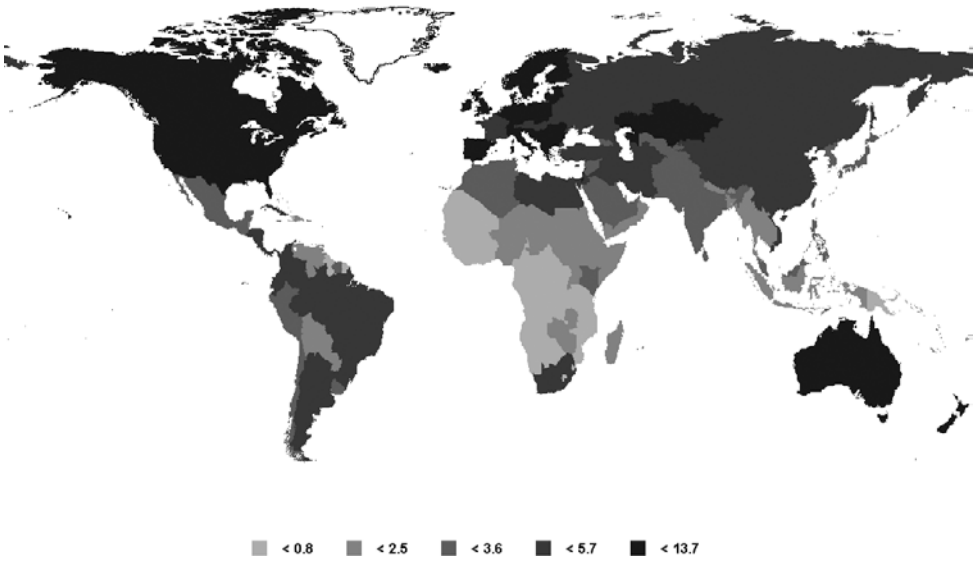
There is variation in incidence rates of brain tumours between countries. As an example, the incidence rates for malignant brain tumours in Japan are half of those in Northern Europe (Wrensch et al. 2002). In previous studies, the incidence rates of gliomas in Finland have been among the highest in the world, whereas the rates of meningiomas have been similar to other industrialized countries (Kallio 1993). However, compared to other types of cancers, intracranial tumours do not show as much international variation (Preston-Martin and Mack 1996). In general, rates in incidence among Caucasians in Europe, North America and Australia can be considered fairly similar (Preston-Martin and Mack 1996).

Yet, the international incidence rates of brain tumours are interpreted with difficulty due to differences in e.g. diagnosing, coding, registering and reporting. Registering of intracranial tumours varies greatly between countries, even between industrialized countries, unlike with many other tumour types. To illustrate, graphs based on generally available data are shown (**Figures 3a–3b**) (GLOBOCAN 2010). Even if the graphs are derived from sources of information that are very incoherent in their consistency (e.g. others including benign tumours, others not), a clear difference can be seen between the industrialized countries and countries under development. Thus, the pronounced differences are likely to be at least partly due to variations in registration of cases. All information for GLOBOCAN is derived from population-based cancer registries, and these populations may cover entire national populations, but more often they cover only subnational areas. In many (developing) countries the incidence numbers are only estimates (e.g. derived from numbers in the neighbouring countries), as there may not even be a subnational cancer registry. The most important source of information on cancer incidence for GLOBOCAN is the successive volumes of *Cancer Incidence in Five Continents* (Curado et al. 2007).

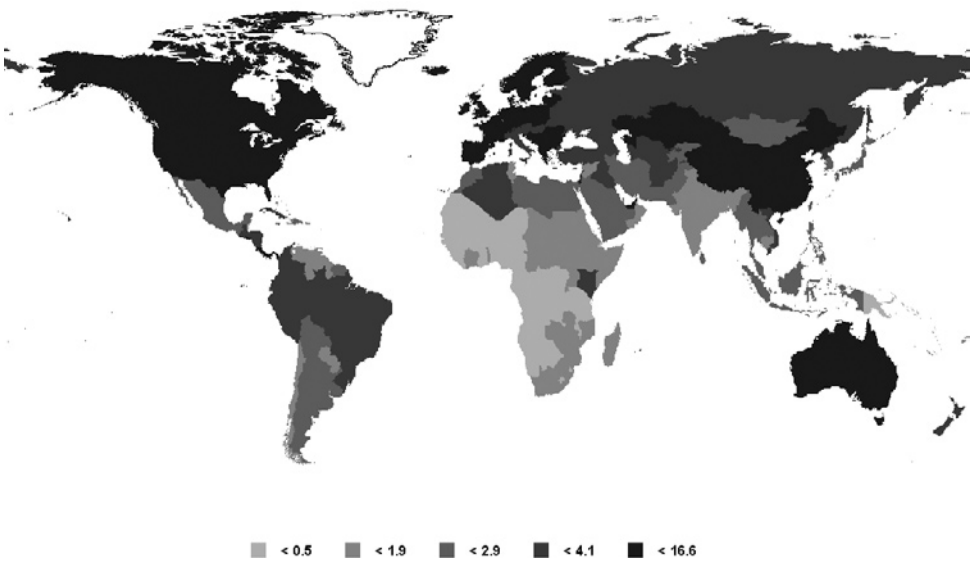
Ethnic variations in the incidence of brain neoplasms are interpreted with difficulty, as differences between countries cannot be disregarded. In the USA, more Caucasians have gliomas than African Americans, whereas the incidence of meningioma is almost similar among Caucasians and African Americans (Preston-Martin and Mack 1996, Wrensch et al. 2002, Deorah et al. 2006). Interestingly, it seems that immigrants adopt the incidence rates of the destination country suggesting stronger environmental than genetic factors (Batchelor et al. 2001). However, registering and coding may differ greatly between the two countries.

Most studies have shown a higher risk of malignant brain tumours in urban than rural populations (Preston-Martin and Mack 1996, Deorah et al. 2006). However, this may also be caused by differences in both diagnosing and registering cases as well as in access to health care. Higher incidence of brain

**3a.** Men




**3b.** Women

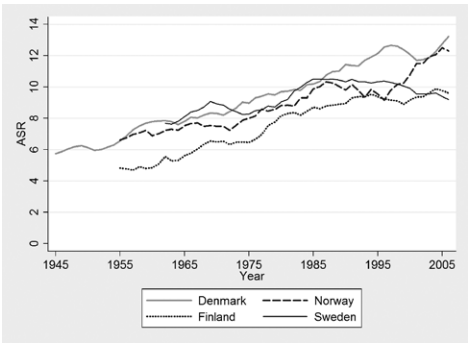



**Figures 3a, 3b.** Age-standardized incidence rates of CNS tumours globally (per 100,000; standardized to world standard population). (GLOBOCAN 2010)

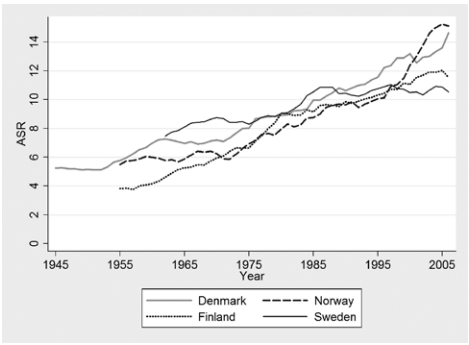
tumours is clearly associated with higher social class, even if mainly seen in gliomas (especially low-grade gliomas) and VS, whereas more meningiomas are found in lower social classes (Preston-Martin and Mack 1996, Inskip et al. 2003a).

This thesis focused mainly on Nordic countries. Nordic countries are believed to be relatively similar in both population structure and in the accuracy and completeness of the cancer registries. The incidence rates of all CNS tumours in the Nordic countries are presented below (**Figures 4a–4d**) (NORDCAN 2010). Though, similar to GLOBOCAN, these graphs (information on the graphs) are unfortunately not entirely comparable due to differences in registering e.g. inclusion of benign or unspecified tumours. Still, they are much more

**4a.** Men

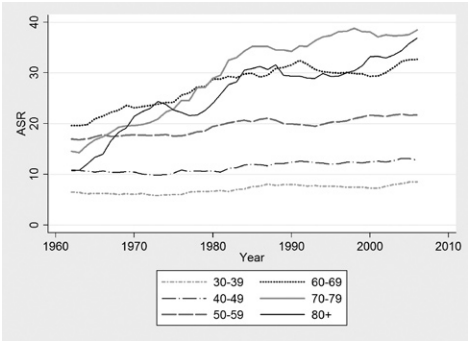



**4b.** Women

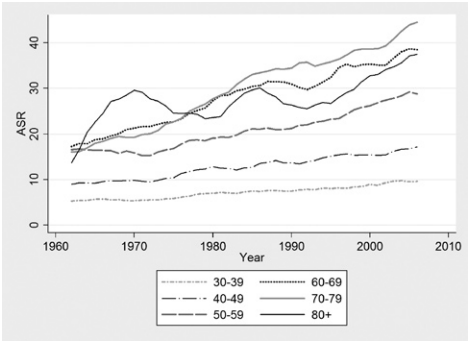



**Figures 4a, 4b.** Time trends of CNS tumour incidence rates in the four Nordic countries (per 100,000; standardized to world standard population). (Figures are based on data from NORDCAN 2010.)

**4c.** Men




**4d.** Women




**Figures 4c, 4d.** Time trends of CNS tumour incidence rates by age in the four Nordic countries (per 100,000; standardized to world standard population). (Figures are based on data from NORDCAN 2010.)

comparable in the Nordic countries than in the worldwide data, as the legislations are relatively similar in the Nordic countries (discussed later, see **6.1.3.**).

The graphs show an increasing incidence of CNS tumours in all Nordic countries, both for men and women. Nevertheless, the increase is mostly seen among the older age groups suggesting a stronger component of incidental findings or otherwise improved diagnostic methods and/or registration.

### 2.3.4. Incidence rates of gliomas

Gliomas are 40% more common among men than among women (Wen and Kesari 2008, CBTRUS 2010). The incidence of astrocytic tumours rises progressively from the age of twenty until the age of 70 years, when the incidence starts to decrease (Inskip et al. 1995). Childhood gliomas, such as pilocytic astrocytomas and ependymomas, peak in children under 10 years of age. The average age of a glioblastoma patient is 60–65 years (Wrensch et al. 2002). Oligodendrogliomas and oligoastrocytomas peak in the age group of 40–65 (Inskip et al. 1995).

According to previously published studies, the incidence rates of gliomas are approximately 1.9–8.5 per 100,000 person-years among men and 1.3–5.8 per 100,000 among women (**Table 2**). Studies published in the past ten years are included. Unfortunately the rates are not directly comparable, as the populations are standardized to several standard-populations and confidence intervals are not always indicated.

In two studies reporting increasing trends of gliomas in the Nordic countries, one of the studies found a minor, although significant, increase of less than 1% for both sexes (0.7% for men, 0.6% for women) in 1969–1998 (Lönn et al. 2004a), whereas for a slightly later period from 1974–2003 the increase was even less pronounced (0.5% for men, 0.2% for women (increase non-significant in women)) (Deltour et al. 2009). The third study reporting the annual changes in trends from the Netherlands found no statistically significant increase or decrease in 1989–2003 (Houben et al. 2006). A recent study from England found an increase in the average annual percentage change for neuroepithelial tumours for all age groups (statistically significant for all age groups) in 1979–2003, even if it varied depending on the age group (2.2% in 0–14 years, 1.6% in 15–24 years, 0.4% in 25–64 years and 2.9% in 65–84 years) (Arora et al. 2010).

Few studies have addressed incidence rates of gliomas by subtype. The age-adjusted incidence rates of GBM ranged between 3.3–5.1 per 100,000 for men and 2.0–3.5 for women standardized to different populations (McKinley et al. 2000, Lönn et al. 2004a, Chakrabarti et al. 2005, Brown et al. 2009). One study investigated incidence trend of GBM finding a statistically significant increase of 2.4% in 1977–2000 (Hess et al. 2004). The incidence trends of types

**Table 2.** Summary of the incidence rates of gliomas from selected * studies in 1999–2010 (rates shown per 100,000 person-years).

| Publication | Study period and area | No. of cases | Rate for both sexes | Rate for males | Rate for females |
|---|---|---|---|---|---|
| Surawicz et al., 1999 [a] | 1990–1994, USA | 10,635 | 6.04 (95% CI, 5.93–6.16) [b] | 7.20 (95% CI, 7.01–7.38) [b] | 5.05 (95% CI, 4.90–5.20) [b] |
| Liigant et al., 2000 | 1986–1996, Estonia | 713 | 3.41 (95% CI, 3.13–3.69) [c] | 4.32 (95% CI, 3.86–4.78) [d] | 3.60 (95% CI, 3.21–3.99) [d] |
| Kaneko et al., 2002 | 1973–1993, Japan | NS | NS | **1.9–4.1** [e] | **1.3–3.3** [e] |
| Christensen et al., 2003 | 1943–1997, Denmark | 11,935 | **2.22–4.04** [c] | **2.66–5.57** [c] | **1.80–3.35** [c] |
| Elia-Pasquet et al., 2004 | 1999–2001, Gironde, France | 149 | 7.0 [f] | 8.5 [f] | 5.6 [f] |
| Lönn et al., 2004a | 1969–1998, Nordic countries | NS | NS | **6.5–8.3** [g] | **4.2–5.8** [g] |
| Houben et al., 2006 | 1989–2003, the Netherlands | 9,290 | NS | **5.9–6.1** [h] | **3.8–4.2** [h] |
| Sadetzki et al., 2008 | 2001–2003, Israel | 548 | 5.82 [c] | 7.11 [c] | 4.75 [c] |
| Arora et al., 2009 [a] | 1995–2003, England | 28,814 | 5.24 [c] | 6.26 [c] | 4.29 [c] |
| Arora et al., 2010 [a] | 1979–1983, England | 70,048 (1979–2003) | 4.16 [c] | NS | NS |
| | 1984–1988, England | NS | 4.55 [c] | NS | NS |
| | 1989–1993, England | NS | 4.68 [c] | NS | NS |
| | 1994–1998, England | NS | 5.26 [c] | NS | NS |
| | 1999–2003, England | NS | 5.22 [c] | NS | NS |
| CBTRUS report, 2010 [a] | 2004–2006, USA | 54,301 | 6.46 (95% CI, 6.41–6.52) [i] | 7.64 (95% CI, 7.55–7.72) [i] | 5.46 (95% CI, 5.39–5.53) [i] |

NS = not specified, [a] Including all tumours of the neuroepithelial tissue, not only gliomas, [b] Adjusted to US standard population (1970), [c] Adjusted to world standard population (1960), [d] Crude rates, [e] Adjusted to Japanese standard population (1985), [f] Adjusted to French population (year not specified), [g] Adjusted to Nordic standard population; rates obtained from a figure with 2-year moving averages, [h] Adjusted to European standard population; rates obtained from a figure with 3-year moving averages, [i] Adjusted to US standard population (2000).Range of rates shown in bold letters (if no precise value was present, or reported as a range).

*selected by going through publications (at the minimum titles / abstracts) in Ovid/Medline corresponding to the search of: **Brain Neoplasms/ and Incidence/** OR ***Brain Neoplasms/ep [Epidemiology]** OR ***Central Nervous System Neoplasms/ep [Epidemiology]** OR **Glioma/ and Incidence/** OR ***Glioma/ep [Epidemiology]**, with the limits of English language and publication year 1999 to current [search done on the 30.11.2010]; only publications with cases >100 were included and with sufficient detail in the histological classification. CBTRUS report is included.

of gliomas other than GBM (e.g. oligodendroglioma) may be difficult to assess, as an increase in a particular type of glioma may indicate that the classification has improved and the number of unspecified glioma cases has decreased, while the total number of gliomas may remain stable (McCarthy et al. 2008). However, for GBM, the classification has remained relatively constant over the years (Kleihues et al. 2002). One study from Denmark approximated an average annual crude incidence of oligodendroglioma of 0.40 per 100,000 for men and 0.35 per 100,000 for women, which was somewhat higher than in previous descriptive epidemiological studies on oligodendroglioma, but the numbers of cases had been very modest (starting from 13 cases) (Nielsen et al. 2009).

### 2.3.5. Incidence rates of meningiomas

Meningiomas are 2–3-fold more common among women than among men (Bondy and Ligon 1996, Barnholtz-Sloan et al. 2007, Campbell et al. 2009). Meningiomas are rare among children, pediatric meningiomas account for less than 2% of all meningiomas and less than 3% of childhood brain tumours (Bulsara et al. 2004, Ragel and Jensen 2005). The incidence of meningiomas increases with age, with the peak in the seventh decade of life (Bulsara et al. 2004).

The incidence rates of meningiomas based on earlier studies are approximately 0.4–3.8 per 100,000 person-years among men and 0.8–8.4 per 100,000 among women (**Table 3**).

In a paper by Longstreth et al. (1993) nine different studies reporting incidence rates of meningiomas in different study periods between 1950

**Table 3.** Summary of the incidence rates of meningiomas from selected * studies in 1999–2010 (rates shown per 100,000 person-years).

| Publication | Study period and area | No. of cases | Rate for both sexes | Rate for males | Rate for females |
|---|---|---|---|---|---|
| Surawicz et al., 1999 | 1990–1994, USA | 5,257 | 2.78 (95% CI, 2.70–2.86) [a] | 1.95 (95% CI, 1.86–2.05) [a] | 3.51 (95% CI, 3.39–3.62) [a] |
| Kuratsu et al., 2000 | 1989–1996, Kumamoto, Japan | 504 | 3.1 (95% CI, 2.4–3.8) [b] | 1.5 (95% CI, 0.7–2.3) [b] | 4.4 (95% CI, 3.1–5.7) [b] |
| Liigant et al., 2000 | 1986–1996, Estonia | 326 | 1.63 (95% CI, 1.44–1.82) [c] | 0.96 (95% CI, 0.74–1.18) [d] | 2.77 (95% CI, 2.43–3.11) [d] |
| Kaneko et al., 2002 | 1973–1993, Japan | NS | NS | **0.9–1.7** [e] | **1.0–4.4** [e] |
| Christensen et al., 2003 | 1943–1997, Denmark | 4,845 | **0.61–2.42** [c] | **0.43–1.53** [c] | **0.78–3.29** [c] |
| Klaeboe et al., 2005 | 1968–1997, Nordic countries | 18,630 | NS | **1.4–1.9** [c] | **2.6–4.5** [c] |
| Arora et al., 2009 | 1995–2003, England | 8,619 | 1.28 [c] | 0.84 [c] | 1.69 [c] |
| Brown et al., 2009 | 2001–2005, California, USA | 7,819 | 4.5 (95% CI, 4.4–4.6) [f] | 2.7 (95% CI, 2.5–2.8) [f] | 6.1 (95% CI, 5.9–6.3) [f] |
| Arora et al., 2010 | 1979–1983, England | 19,721 (1979–2003) | 0.94 [c] | NS | NS |
| | 1984–1988, England | NS | 1.04 [c] | NS | NS |
| | 1989–1993, England | NS | 1.07 [c] | NS | NS |
| | 1994–1998, England | NS | 1.24 [c] | NS | NS |
| | 1999–2003, England | NS | 1.29 [c] | NS | NS |
| CBTRUS report, 2010 | 2004–2006, USA | 53,455 | 6.29 (95% CI, 6.23–6.34) [f] | 3.76 (95% CI, 3.70–3.83) [f] | 8.44 (95% CI, 8.35–8.52) [f] |

NS = not specified, [a] Adjusted to US standard population (1970), [b] Adjusted to Japanese standard population (1992), [c] Adjusted to world standard population (1960), [d] Crude rates, [e] Adjusted to Japanese standard population (1985), [f] Adjusted to US standard population (2000). Range of rates shown in bold letters (if no precise value was present, or reported as a range).

* selected by going through publications (at the minimum titles / abstracts) in Ovid/Medline corresponding to the search of: **Brain Neoplasms/ and Incidence/** OR ***Brain Neoplasms/ep [Epidemiology]** OR ***Central Nervous System Neoplasms/ep [Epidemiology]** OR **Meningioma/ and Incidence/** OR ***Meningioma/ep [E pidemiology]**, with the limits of English language and publication year 1999 to current [search done on the 30.11.2010]; only publications with cases >100 were included and with sufficient detail in the histological classification. CBTRUS report is included.

and 1986 were compared. Four of the studies reported crude incidence rates varying from 1.0–1.5 per 100,000 for men and 1.5–3.1 per 100,000 for women, while five studies reported age-adjusted rates ranging from 0.4 to 4.9 per 100,000 for men and from 0.8 to 7.6 per 100,000 for women (standardized to different populations). However, there was much heterogeneity in terms of number of cases, study populations and study periods between the articles, in addition to the fact that the studies included were dated in a time over twenty years ago.

As meningiomas are mostly benign, and thus most probably underreported, the incidence rates may be strongly underestimated. In a study conducted in the Netherlands, the authors found a substantial prevalence of incidental meningiomas on brain MRIs, 1.1% in women and 0.7% in men (Vernooij et al. 2007). In a recent meta-analysis, a prevalence of 0.3% of incidental meningiomas on brain MRI was reported (Morris et al. 2009; Vernooij et al. 2007 included in the meta-analysis). Thus, it is believed that asymptomatic meningiomas are relatively commonly not diagnosed and thus not reported.

A statistically non-significant annual increase of approximately 1% was reported for young people (0–24 years, both sexes combined) in meningioma incidence, a significant increase of 1.3% for those aged 25–64, and a significant increase of 3.0% for the elderly (over 65 years) was observed in England (in 1979–2003) (Arora et al. 2010).

### 2.3.6. Incidence rates of vestibular schwannomas

VS are relatively equally common among men and women, though some studies have suggested female predominance (Preston-Martin and Mack 1996, Propp et al. 2006, Louis et al. 2007). Rare among children and adolescents, VS incidence begins to increase at the age of 30 years, and is highest in the fifth decade of life and later decreases after 65 years of age (Inskip et al. 1995, Matthies and Samii 2004, Propp et al. 2006).

The incidence rates of VS have been approximately 3–16 per 1,000,000 person-years among men and 4–16 per 1,000,000 among women (**Table 4**).

Tos et al. (2004) combined various studies reporting incidence rates of VS. The rates varied from 1 per 1,000,000 inhabitants in Connecticut, USA, in 1935–1964, to 20 per 1,000,000 inhabitants in Cambridge, England in 1981–1991 (Schoenberg et al. 1976, Moffat et al. 1995). It is, however, unlikely that the rates of VS were 20-fold in England in comparison to USA, or that there was a 20-fold increase in incidence over those years, but this discrepancy is probably caused by several differences in reporting and registering (coding).

**Table 4.** Summary of the incidence rates of vestibular schwannomas from selected * studies in 1999–2010 (rates shown per 1,000,000 person-years).

| Publication | Study period and area | No. of cases | Rate for both sexes | Rate for males | Rate for females |
|---|---|---|---|---|---|
| Howitz et al., 2000 | 1977–1995, Denmark | 795 | **5–10** [a] | **5–9** [a] | **5–11** [a] |
| Kaneko et al., 2002 [b] | 1973–1993, Japan | NS | NS | **2.8–13.2** [c] | **3.6–16.0** [c] |
| Stangerup et al., 2004 | 1976–2001, Denmark | 1,446 | 11.5 (range **5.1–19.3**) [d] | NS | NS |
| Tos et al., 2004 | 1996–2001, Denmark | 542 | 17.4 [d] | NS | NS |
| Evans et al., 2005 | 1990–1999, NW England | 419 | 11.8 [d] | NS | NS |
| Nelson et al., 2006 | 1979–1997, England, Wales | NS | **2.4–7.6** [e] | NS | NS |
| Propp et al., 2006 | 1995–1999, CBTRUS, USA | 1,424 | 5.5 (95% CI, 5.2–5.8) [d] | 5.6 (95% CI, 5.2–6.0) [d] | 5.5 (95% CI, 5.1–5.8) [d] |
| | 1995–1999, LACCSP, USA | 256 | 8.2 (95% CI, 7.1–9.2) [d] | 8.3 (95% CI, 6.8–9.9) [d] | 8.0 (95% CI, 6.6–9.4) [d] |
| Arora et al., 2009 [b] | 1995–2003, England | 3,716 | 6.6 [a] | 6.7 [a] | 6.6 [a] |
| Arora et al., 2010 [b] | 1979–1983, England | 8,709 (1979–2003) | 4.9 [a] | NS | NS |
| | 1984–1988, England | NS | 5.5 [a] | NS | NS |
| | 1989–1993, England | NS | 6.1 [a] | NS | NS |
| | 1994–1998, England | NS | 7.0 [a] | NS | NS |
| | 1999–2003, England | NS | 6.3 [a] | NS | NS |
| CBTRUS report, 2010 [b] | 2004–2006, USA | 13,733 | 16.1 (95% CI, 15.9–16.4) [f] | 16.3 (95% CI, 15.9–16.7) [f] | 16.0 (95% CI, 15.7–16.4) [f] |
| Gal et al., 2010 | 2004–2005, SEER, USA | 1,621 | 11 [f] | 11 [f] | 10 [f] |

NS = not specified, [a] Adjusted to world standard population (1960), [b] Nerve sheath tumours, [c] Adjusted to Japanese standard population (1985), [d] Crude rates (at least no standardization shown in the original publication), [e] Adjusted to European standard population, [f] Adjusted to US standard population 2000. Range of rates shown in bold letters (if no precise value was present, or reported as a range).

LACCSP = Los Angeles County Cancer Surveillance Program, SEER = the Surveillance Epidemiology and End Results Program of the National Cancer Institute.

* selected by going through publications (at the minimum titles / abstracts) in Ovid/Medline corresponding to the search of: **Brain Neoplasms/ and Incidence/** OR ***Brain Neoplasms/ep [Epidemiology]** OR ***Central Nervous System Neoplasms/ep [Epidemiology]** OR **Acoustic Neuroma/ and Incidence/** OR ***Acoustic neuroma/ep [Epidemiology]**, with the limits of English language and publication year 1999 to current [search done on the 1.12.2010]; only publications with cases >100 were included and with sufficient detail in the histological classification.

Similarly to meningiomas, these tumours may often be only mildly symptomatic and therefore there certainly are latent VS in the population. In a study from USA, approximately 0.02% of the population had an incidental VS (Lin et al. 2005). This number was tenfold in the study by Vernooij et al. (2007) with 0.2% prevalence of incidental VS. A recent meta-analysis found a prevalence of 0.03% of VS (Morris et al. 2009; Vernooij et al. 2007 included in the meta-analysis).

A statistically significant annual increase of 5.9% in nerve sheath tumours in men, but not in women, was reported in the USA (in 1985–1994) (Jukich et al.

2001). The annual increase of nerve sheath tumours varied depending on the age group according to a recent study from England for the period of 1979 to 2003 (Arora et al. 2010). The increase was not significant in 15–24 years (0.4%), and was significantly decreasing in 0–14 years (–4.6%), while there was statistically significant annual increase in the older age groups (2.2% in 25–64 years, 1.5% in 65–84 years) (Arora et al. 2010).

# 3. Objectives

The general objective of this dissertation was to describe the occurrence of gliomas, meningiomas and VS, and to assess various aspects (of their occurrence) in all separate analyses. Also, the objective was to evaluate the completeness and validity of the cancer registry data.

The aims of the individual studies were the following:

**I** To evaluate the completeness of meningioma incidence in the Finnish Cancer Registry (FCR) and to provide corrected estimates.

**II** To describe trends in incidence rates of VS in the four Nordic countries.

**III** To determine the anatomic distribution of gliomas in the brain.

**IV** To evaluate the location of gliomas in relation to mobile phone use.

# 4. Materials and methods

This chapter summarizes the materials and methods used in the present studies. Detailed information is further presented in the original publications (I–IV).

## 4.1. Materials

The study populations, study periods and the inclusion criteria of each study are presented in a summary table (**Table 5**). All studies in this thesis were based on cases with a reported intracranial tumour (glioma, meningioma or VS). The analyses were made in relation to data source, year, country or anatomic site.

**Table 5.** Descripition of the materials for each study.

| Article | Study population | | | Study period | Included cases |
|---|---|---|---|---|---|
| | Number of people | Age range | Catchment area | | |
| **I** | 447,051 | All ages | Tampere University Hospital (Pirkanmaa) | 11/2000–06/2001 | All incident meningiomas |
| **II** | 24.15 millions | All ages | Whole of Denmark, Finland, Norway, Sweden | 01/1987–12/2007 [a] | All incident vestibular schwannomas |
| **III** | 3.37 millions | 20–69 | Finland (Åland and Northern Lapland excluded) | 11/2000–09/2002 | All incident gliomas, and more specifically those with a given location |
| **IV** | NS | 20–69 [b] | Areas of Denmark, Finland, Germany, Italy, Norway, Sweden, UK (South) | 09/2000–01/2004 [b] | All incident gliomas with an assigned location |

NS = not specified
[a] Sub-analysis done for Norway and Sweden for 01/1965–12/2007.
[b] Varied depending on the country.

### 4.1.1. Different data sources

Four separate datasets were used in this thesis. Two datasets were part of the international Interphone study (III, IV), while two were register-based (I, II).

#### 4.1.1.1. Interphone study

The lnterphone study is an international case-control study on intracranial tumours and mobile phone use. It was launched in 2000 and is coordinated by IARC (International Agency for Research on Cancer), with thirteen countries taking part in. Its main objective was to assess whether mobile phones increase the risk of brain cancer (Cardis et al. 2007b, Cardis et al. 2010). A common study protocol was followed in all countries with some differences between countries. The protocol is described in detail elsewhere (Cardis et al. 2007b).

In this thesis, glioma cases from the Interphone study from Finland were used in one of the papers (III), whereas material on detailed location of gliomas was included from seven countries (Denmark, Finland, Germany, Italy, Norway, Sweden, United Kingdom (South)) in the other manuscript based on the Interphone data (IV). In this dissertation, only gliomas were used from the Interphone data. The cases were limited to those with a known location (crude (III) or more detailed location (III, IV)), apart from non-participants (N = 61) with no information on location available (III).

#### 4.1.1.2. Register-based materials

The two register-based datasets were formed by combining data from several sources. The material for meningiomas included meningioma cases from the Finnish Cancer Registry (FCR) and four clinical data sources in Tampere University Hospital (the neurosurgical clinic, the pathology database, the hospital discharge register and the clinical autopsy register) (I). The other register-based dataset included VS cases obtained from the national cancer registries of Denmark, Finland, Norway and Sweden (II).

For the meningioma study (I), several registers were linked. The database from the neurosurgical clinic is an unofficial database kept by clinics' neurosurgeons and secretaries on all patients seen at the neurosurgical clinic in Tampere University Hospital, either as out-patients or ward patients. For this study, all meningioma cases (ICD-10 code D32), in addition to all unclear cases (such as no diagnosis indicated or only a vague note (e.g. 'suspected hydrocephalus')), from the neurosurgical clinic's database were further reviewed by the author of this thesis (S.L.) going through the patients' medical records. The pathology database is based on each CNS histological sample registered by a neuropathologist, with each patient's PIN and type of tumour (using SNOMED classification). Both registers are intended to be comprehensive, but their completeness has not been evaluated.

Neither has the completeness of Tampere hospital discharge register data been assessed, but the Finnish hospital discharge register data is believed to cover all discharges. Its validity has been studied mainly on reproductive health and psychiatric disorders (Gissler and Haukka 2004), but the validity has been good also in cancer cases in the past (Teppo et al. 1994). All cases with an ICD-10 code (D32) obtained from the hospital discharge register were reviewed. Furthermore, diagnoses of all autopsied (clinical autopsies) patients during the study period were reviewed from an autopsy list (including all diagnoses from the autopsies), and those with a meningioma code (either as immediate or underlying cause of death) were further studied. Thus, to summarize, the medical records of all potential meningioma cases (ICD-10 code D32 or

an unclear case) obtained from the FCR or any of the four clinical data sources were examined by the author of this thesis.

The VS cases used in this thesis were obtained from the national cancer registries from four Nordic countries, Denmark, Finland, Norway and Sweden. The validity of cancer registry data will be dealt in more detail in the discussion-section (**6.1.**).

### 4.1.2. Contents of the materials

The population numbers grouped by calendar year, sex and five-year age group were acquired from the national population registries in all studies counting the incidence rates (I–III).

The Interphone data included, in addition to general information (e.g. PIN, age, sex, date of diagnosis and a specific morphologic code for each glioma) a crude anatomic location (III, IV), except in those not participating in the study (only used for incidence counts) (III). A subset of the cases had a more detailed location described with coordinates of the mid-point(s) of the glioma (n=89 (III), n=888 (i.e. all cases included in the study) (IV)). In the original data, only certain gliomas were chosen for assignment of a mid-point(s). Based on the Interphone protocol, the selection was indicated by 'a specific topographic location was given when possible' (Cardis et al. 2010). This selection of gliomas (for mid-point(s) assignment) varied between countries, e.g. in Germany locations were given to all gliomas, but not if the neuroradiologists found defining the mid-point(s) very problematic/ambiguous; in Sweden there was no sufficient funding to do localization for all glioma cases (thus a decision was made to cover all gliomas of two of the four geographical regions included in the study); and in United Kingdom it was not possible (due to practical matters) to receive neuroradiological information from a certain hospital, etc.

The inclusion criteria for these studies with Interphone data were the age of 20–69 years (the inclusion ages differed between countries), no prior diagnosis of brain tumour and a histological confirmation of a glioma or an unambiguous diagnostic imaging (Cardis et al. 2010). Information on potential mobile phone use (duration, amount, frequency of use) was also available in the Interphone data. For information on mobile phone use (IV), regular use was defined as at least one call per week for a period of six months or more, according to the Interphone protocol. Use in the eighteen months prior to glioma diagnosis was not included in the analyses, neither was use of hands-free-devices or cordless phones (DECT). Information on past mobile phone use was collected in a face-to-face interview with the study subject, or a proxy. This information on mobile phone use was collected if the study subject had ever been a regular

mobile phone user. The interviews were conducted by a trained interviewer (study nurses recruited from the neurosurgical clinics) with a computer-assisted questionnaire (or a paper version in Finland).

Information on the meningioma cases contained PIN, age, sex, dates of hospital contacts and possible operations and treatments (I). The incident VS cases had information on age, sex and date of diagnosis (II).

According to the study period chosen for each original publication, the date of diagnosis defined the inclusion of cases (among other inclusion criteria) (I–IV). The date of diagnosis in the data from the cancer registries was the date when the histological sample was taken. If no biopsy was taken, the date was defined by other methods, based on the hierarchy by guidelines from European Network of Cancer Registries, such as date of admission to the hospital due to this malignancy (personal communication from R. Sankila). However, in datasets not based on cancer registries, the date of diagnosis was chosen to be the date when the first most certain diagnosis (e.g. strong suggestion based on radiological imaging) was set. This condition held true, as long as the possibly later confirmed diagnosis was similar to the first diagnosis (if not, date of diagnosis was changed to the date of confirmation, e.g. date of taking a pathological sample).

Some delay in informing cases to the cancer registry was taken into consideration with meningiomas (I). The original data from the FCR contained all incident meningioma cases notified to the FCR from November 2000 to June 2004 (three-year delay). All meningioma cases were checked through their medical records to make sure that the first suspicion of meningioma was indeed during the study period. For gliomas, study nurses in the university hospitals reported all incidental glioma cases to the Interphone coordinator (III, IV). This information was later confirmed from the cancer registries (in order to catch possible cases outside university hospitals, if any), but no specific time for delay in notifying the glioma cases to the FCR was reserved, as all glioma cases were obtained directly from the clinics rather than the FCR database.

### 4.1.3. Classification of intracranial tumours

Different diagnostic coding systems were used in the materials of this thesis. Even if the data from the cancer registries ought to follow a uniform coding (classification) system, international variation exists in addition to changes in coding over time. Different coding systems are illustrated below (modified from Jensen et al. 1991 and Sankila et al. 2008) (**Figure 5**). In this thesis, original data were classified according to ICD-O-3, ICD-7, ICD-9, ICD-10, SNOMED and MOTNAC systems.

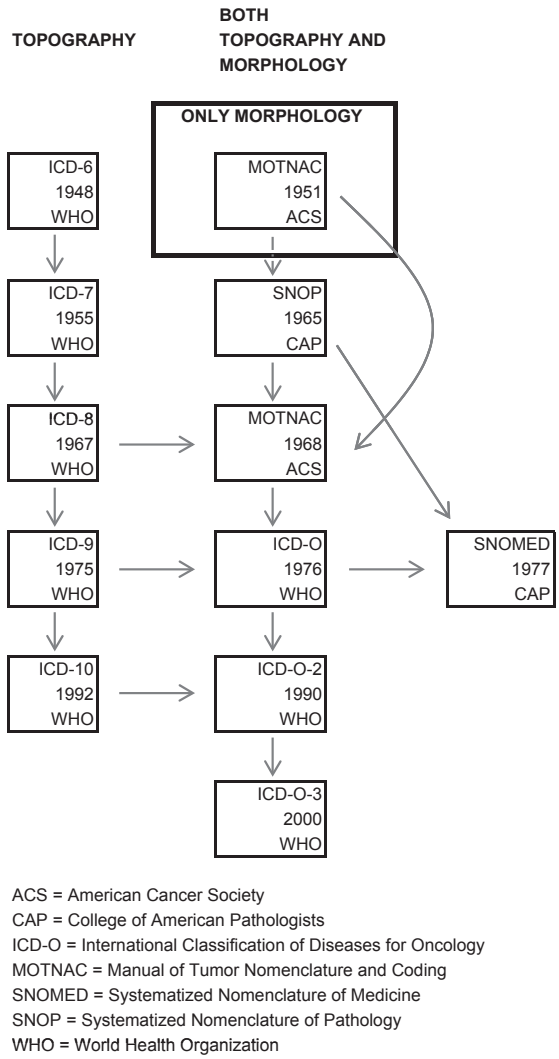



**Figure 5.** History of tumour coding. (Adapted from Sankila et al. 2008).

Gliomas in this thesis were classified according to the ICD-O-3 system (codes 9380–9480) (III, IV). Gliomas were further grouped into broad morphologic categories in the two studies concentrating on gliomas in the thesis, with three classes (*1.* glioblastomas, *2.* diffuse and anaplastic astrocytomas, *3.* mixed gliomas and oligodendrogliomas) (III) and two groups (*1.* glioblastomas, *2.* other gliomas) (IV).

Meningiomas were defined by ICD-10 code (D32). VS were coded in various ways depending on the country and the period of time (**Table 6**).

**Table 6.** Classification of vestibular schwannomas by period and country in 1965–2007.

| | |
|---|---|
| **Denmark** | |
| 1965–1986 | Incomplete coverage prior to 1987 |
| 1987–2007 | National variation of ICD-7 (293.2) |
| **Finland** | |
| 1965–1978 | Incomplete coverage prior to 1979 |
| 1979–2007 | National coding system (937) |
| **Norway** | |
| 1965–1992 | ICD-7 (193.1), MOTNAC (9560) |
| 1993–2007 | ICD-10 (C72.4), MOTNAC (9560/09, 9570/09) |
| **Sweden*** | |
| 1965–1986 | ICD-7 (193.0), PAD (451, 456) |
| 1987–1992 | ICD-9 (192.0), SNOMED (9560/0, 9560/3) |
| 1993–2007 | ICD-10 (C72.4, C72.5, C72.9)**, SNOMED (9560/0, 9560/3; also 8000/0, 8000/3 with C72.5 or C72.9) |

* The guidelines of the Swedish cancer registry for classifying VS. However, in this study we used ICD-9 (192.0) combined with PAD (451, 456) for the main study period (1987–2007), and ICD-7 (193.0) with PAD (451, 456) for the total period (1965–2007), to provide consistency over time.

** A considerable proportion of VS have been classified under the codes C72.5 (for other and unspecified cranial nerve) and C72.9 (for central nervous system, unspecified) in previous Swedish VS studies (unpublished data).

#### 4.1.3.1. Classification of gliomas by topography

All gliomas were given a topographic location using ICD-10-coding (III, IV). The topographic location (ICD-10 code) for the Finnish gliomas (III) was assigned by the author of this thesis (S.L.) based on the medical records. However, some simplification had to be used at times, especially with gliomas in the deep or unspecified parts of the cerebrum. These gliomas were coded preferably in the cerebral lobes than in an unspecified location if there was any borderline ambiguity, in order to maximize specificity (e.g. gliomas of the sphenoidal wing were coded to the frontal lobe). Problems with skull base tumours are generally known, and shortly after having completed (S.L.) the task of classifying the locations of tumours, a consensus conference on CNS tumour registration recommended an additional code specific for skull base tumours (code C70.2) (McCarthy et al. 2005). This new coding was not used in any of the classifications of this thesis.

In the evaluation of the distribution of gliomas in cerebral lobes, the number of gliomas was related to the tissue volume of each lobe (III). Previously published estimates of the tissue volume in each lobe relative to the occipital lobe were used (Burger et al. 1991). Frontal lobe is three times the volume of the occipital lobe, and temporal and parietal lobes twice the volume of the occipital lobe (Burger et al. 1991). The ratio was used to adjust for different sizes of anatomic structures and to estimate incidence corrected for tissue volume.

The mid-point(s) of each glioma were assigned by neuroradiologists based on CT/MR images using a software programme (GridMaster, Vompras,

Düsseldorf, Germany) specially designed for the Interphone study (Cardis et al. 2007b). These more specific coordinates were given in a three-dimensional (3D) 1 cm × 1 cm × 1 cm -grid with three projections (axial, coronal and sagittal). In the two glioma studies, a more detailed location (with three assigned coordinates) was given to 89 cases (27%) in the study based on the Finnish data (III), while the location was available for all gliomas in the multinational study (as only cases with an assigned location were included in the study) (IV). In the seven countries included in our study participating in the Interphone study, a specific glioma location was assigned to 912 cases, i.e. 63% of all glioma cases diagnosed during the study period that fulfilled the Interphone study inclusion criteria (N = 1447). The final number of glioma cases used in the study IV was 888 cases. Cases with mid-points in non-adjacent cells (of the grid) were excluded from the study (N = 24).

In the study IV, a case-specular analysis was used, where each case was assigned a hypothetical referent, called *specular* (explained in further detail in **4.2.1.**, presentation in **Figure 6**). Speculars were identical to cases in other terms than the anatomic location. In the case-specular analysis, coordinates (in GridMaster) were appointed for speculars by using 'mirror imaging' through a determined focal point (centre-point) in the brain. This focal point was based on the mean coordinates of all glioma cases among never-regular users (the unexposed group). Speculars were formed in order to demonstrate a scenario where each case was imaginarily moved to another location that would be equally likely, if there was no exposure effect. Further reflection on the choice of the focal point is found in the discussion-section (**6.2.2.1.**).

Laterality was not addressed in the case-specular analysis (except in a small sub-analysis), thus only two coordinates (axial and coronal) of the speculars were different in relation to the (true) glioma case. If a case had several mid-points, the average of these (centre of the mid-points) was used in calculations and graphical presentations.

## 4.2. Statistical methods

Two of the studies examined the locations of gliomas (III, IV). However, these studies used different statistical methods. The study III mainly described the anatomic locations of gliomas in the brain (and evaluated the heterogeneity in distribution), while the study IV assessed the locations of gliomas in relation to a source of exposure (mobile phone). In the study III chi-square tests were used to assess statistical significance (of the differences in the distribution of gliomas in the brain), whereas in the study IV logistic regression models were mainly used.

The meningioma study described data with no outcome measures (I). Confidence intervals were calculated for incidence rates (using the formula for single rates) and age-standardization was done by five-year age groups (I). World standard population was used in all the studies of this thesis as a reference for age-standardization (Segi 1960).

In the VS article the outcome measures were incidence rates and average changes over time, assuming the numbers of cases to follow a Poisson distribution (II). The annual changes in incidence rates, crude and age-standardized incidence rates were calculated both separately and combined for all countries, age-groups (by five-year age group) and sexes.

The occurrence measures were restricted to incidence rates in all analyses.

### 4.2.1. Methods in analysing glioma location

In the article III, the distribution of locations of gliomas was evaluated broadly by cerebral lobes and in more detail by 3D-coordinates. When assessing the glioma distribution by lobe (assuming a uniform distribution of gliomas across the lobes), the chi-square test was used. With the more detailed data, a method of simulation was applied for describing the distributions. Altogether 890 different combinations of the three given coordinates were found. Each of the 89 gliomas (with a detailed location) was allocated separately to one of the cells formed by three coordinates (890 different choices). This simulation (i.e. random allocation to a location, that is, allocation of a combination of three random coordinates) of the 89 gliomas was repeated 999 times to obtain sufficient precision. The value obtained from a random hypothetical location assigned was compared to the chi-square test for each detailed glioma location (assuming no difference between squares). A cut-point equivalent to a significance level of $p = 0.05$ was obtained if 49 simulations of 999 (ca. 5%) had similar or larger chi-square values.

In the paper IV, when assessing the distance of glioma from a hypothetical mobile phone (with the detailed coordinates), an exposure line from the external orifice of the ear canal to the corner of the mouth was indicated to represent the likely position of the phone. The line was divided in a hundred equally long segments. Using vectors, distance from each glioma mid-point (expressed by three coordinates) was calculated separately to each of the hundred points. The final distance of each glioma to the exposure line was the minimum of the obtained values (distances). Distance of glioma was calculated to the closest hypothetical exposure line irrespective of the patient's side of mobile phone use. Laterality of mobile phone use was only considered in separate sub-analyses.

The hypothetical alternative location of the case (i.e. specular) was assigned symmetrically through a centre-point in the coronal and axial axes of the 3D-brain model. For the sagittal projection, an identical coordinate on the sagittal axis was used (i.e. the specular location had identical distance to the longitudinal fissure as the actual case). The procedure for the axial coordinate is illustrated in **Figure 6**.

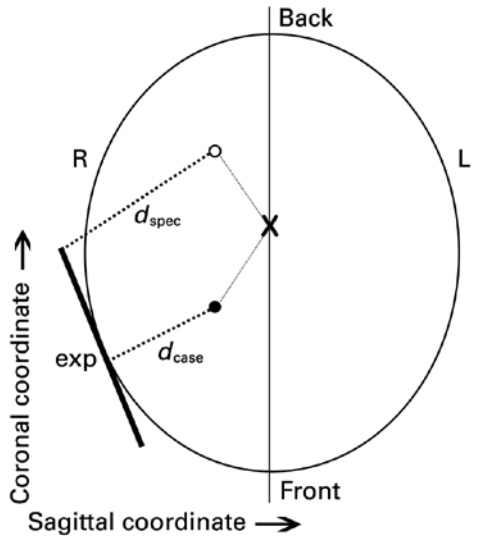



**Figure 6.** A representation of assigning the coronal coordinates for the specular case in the axial projection. The mid-point for a case is indicated with a solid circle and the corresponding specular location with an open circle. The distance from the source of exposure (**exp**) is denoted by **d**, separately for the case ($\boldsymbol{d}_{case}$) and for the specular ($\boldsymbol{d}_{spec}$). Axial coordinates were obtained in a similar fashion using a coronal projection (R = right, L = left). (IV)

In the study IV, two models were used for the statistical analyses. The case-case analysis compared differences in distance from the glioma case to the mobile phone among cases by contrasting exposure levels of mobile phone use. The case-specular analysis defined the distance from the exposure line for each case and its hypothetical pair (**Figure 6**).

Unconditional logistic regression was used in the case-case analysis and conditional logistic regression in the case-specular analysis. The main outcome in the case-case analyses was the distance of glioma from the closest hypothetical mobile phone (irrespective to the side of mobile phone use). Whereas, in the case-specular analyses, the case status (case or specular) was the outcome with

distance as the explanatory variable. Distance was used both as a categorical and a continuous variable.

In the unconditional logistic regression glioma's distance from mobile phone was regarded as a binary outcome (≤ 5 cm, > 5 cm). Analyses were made for regular use of mobile phone, cumulative call-time (0.001 – 46 hours, 47 – 339 h, > 339 h), laterality and duration of use in years (18 months to 4 years, 5 – 9 yrs, ≥ 10 yrs). All were compared to never-regular mobile phone users. Adjusting was made for age, socioeconomic status, country and sex.

Analyses were performed using the software *Stata 8.2* (StataCorp, College Station, Texas, USA) (II – IV).

## 4.3. Ethical issues

Ethics in medical research are esteemed high in the Declaration of Helsinki and in the Nuremberg Codes (Storm et al. 2004). A common principle for recording personal data on living subjects is that the subject's consent should be obtained, unless national legislation declares otherwise. Population-based cancer registration would not be possible if an informed consent was required on all cancer patients, thus a legislation, such as the European Directive, provides an exemption from this requirement for cancer registration (95/46/EC Article 8) (Storm et al. 2004). In the past decade(s), there has been debate on how to find an acceptable balance between increasing demands for personal autonomy and society's need to obtain information from individual patients in order to learn about their disease (cancer).

All the four studies were carried out retrospectively. The author of the thesis (S.L.) did not contact any patients personally. One of the studies (one of the two studies based on the Interphone data) included information obtained from interviewing patients. When using the Interphone data from several countries, the study protocols were approved by local Ethics Review Boards (Cardis et al. 2007b) (III, IV). The study protocol for the Interphone study in Finland was approved by the National Ethical Review Board of the Ministry of Health and Social Welfare (ETENE/TUKIJA) (III, IV). The study subjects (or their relatives) gave a written informed consent (III, IV). For the patients who did not give consent, some basic additional information on the histologic type of the gliomas was obtained from the FCR, in order to describe the incidence by histologic type (III).

Two of the studies were register-based. For the meningioma study several datasets were used in addition to the cancer registry data. The study protocol was approved by the National Research and Development Centre for Welfare and Health (STAKES) (I), thus granting permission to collect and combine data

from the clinical registers and the hospital discharge register with the cancer registry data. As patients were not contacted, no informed consent was needed based on the Finnish regulations (I). A permission to go through the medical records of all (suspected) meningioma patients was obtained from the clinical director (chief medical officer) of the Tampere University Hospital (I).

The Nordic and EU legislations permit the use of cancer registry-based (anonymous) materials for retrospective medical studies. Data extraction and requests for data for research projects, even external to the country, are legal. Therefore no special allowance was needed for the VS study, especially as no personal information with identification was needed for the study (II). Identifiable data should not normally be transmitted to other countries. Only if a research project is allowed by national law and the level of protection is satisfactory should any information be transmitted (Storm et al. 2004).

# 5. Results

## 5.1. Incidence rates

### 5.1.1. Incidence rates of gliomas, meningiomas and vestibular schwannomas

The age-standardized incidence rates of gliomas were 4.9 (95% CI, 4.2–5.6) per 100,000 person-years for men and 4.5 (95% CI, 3.8–5.2) for women in the whole of Finland from November 2000 to September 2002 (III).

The age-standardized rates of meningiomas for the best estimate were 2.9 (95% CI, 0.7–5.0) per 100,000 person-years for men and 13.0 (95% CI, 8.7–17.3) for women in Pirkanmaa region from November 2000 to June 2001 (I). However, the rates from the FCR, obtained for the same period and study area, were 2.2 (95% CI, 0.3–4.1) per 100,000 person-years in men and 9.6 (95% CI, 5.6–13.6) in women.

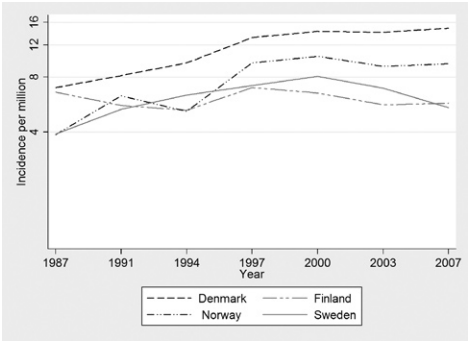
For VS, the age-standardized incidence rates ranged from 6.1 (95% CI, 5.4–6.7) to 11.6 (95% CI, 10.4–12.7) per 1,000,000 person-years for men and from 6.4 (95% CI, 5.7–7.0) to 11.6 (95% CI, 10.5–12.8) per 1,000,000 for women in 1987–2007 in the four Nordic countries. The lowest rates for men were found in Finland and for women in Sweden, whereas the highest rates for both sexes were in Denmark (II).

### 5.1.2. Trends in incidence of vestibular schwannomas

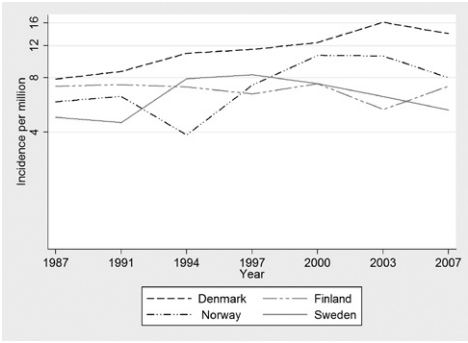
An annual increasing trend in incidence of VS was observed with an increase of 2.8% (95% CI, 2.3–3.2) with all countries and both sexes combined during the study period of twenty-one years (1987–2007) (**Figures 7a–7b**). Denmark had the highest incidence rate in the beginning and the steepest annual increase during the period (5.0% (95% CI, 3.8–6.2) among men, and 4.5% (95% CI, 3.4–5.7) among women). Norway had also a steady increase of 5.0% (95% CI, 3.4–6.6) for men and 4.1% (95% CI, 2.5–5.7) for women, whereas Finland and Sweden showed relatively constant rates and even some decrease in the Finnish women.

The annual average increase was highest in the age group 65 years or older in both sexes; 3.4% (95% CI, 1.9–4.9) for men and 3.0% (95% CI, 1.7–4.3) for women. Incidence increased during the study period in all age groups, except not statistically significantly in women aged 55 to 64 years (increase of 1.0% (95% CI, −0.21 to +2.2)). In the age groups of highest increasing incidence (ages 65+) and lowest (ages 55–64), the increase was more pronounced before 1997 than after (1987–1997 vs. 1998–2007), as no significant further increase occurred in either of these two age groups in the latter period (**Figures 8a–8b**).

**7a.** Men

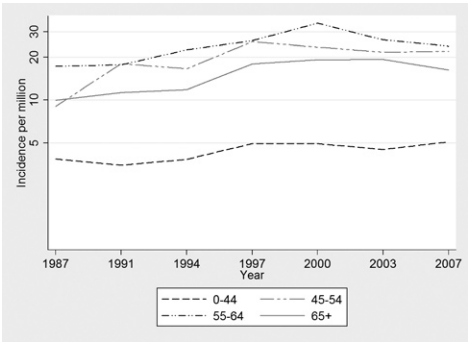



**7b.** Women

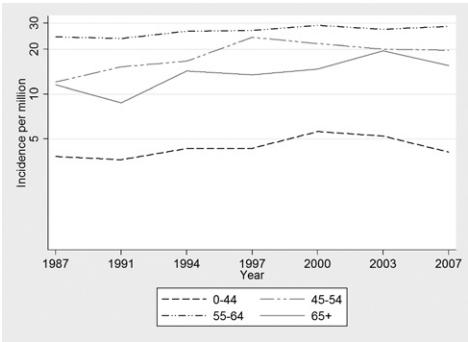



**Figures 7a, 7b.** Age-standardized incidence rates (logarithmic scale) of VS in the four Nordic countries. (III)

**8a.** Men




**8b.** Women




**Figures 8a, 8b.** Age-specific incidence rates (logarithmic scale) of VS in the four Nordic countries. (III)

The results from an analysis by age and birth cohort from all the four countries indicated a cohort effect with a higher incidence for later birth cohorts in all age groups. The incidence also increased by age, with the exception of the oldest birth cohort in women showing a decline after age 60.

In Norway and Sweden the data were available from 1965 to 2007, thus further analyses were conducted with a longer study period. The study period was sub-divided into two periods; 1965–1985 and 1986–2006. The average annual increase in the first period in Norway was 1.0% (95% CI, –0.67 to +2.7) and in the second period 5.3% (95% CI, 4.1–6.5). In Sweden, the annual increase in the first period was 3.6% (95% CI, 2.5–4.7) and in the second period –0.52% (95% CI, –1.7 to +0.26) (using similar coding (ICD-7 code 193.0) through the entire period

in Sweden). Thus, the increase was more rapid in the latter period in Norway, while in Sweden there was a decrease in the incidence in the second period.

The impact of the changes in the coding systems was estimated in Norway and Sweden. The coding systems did not change in Denmark or Finland, therefore the sensitivity analyses on the changes in coding could not be performed in these two countries. By comparing the proportion of VS out of all the other cranial schwannomas in the later years (1993–2007), when more accurate codes were used, it was possible to estimate the proportion of VS of all the schwannomas in the earlier data, assuming a similar proportion of tumours at various sites over time.

In Norway, all schwannomas of the cranial nerves were included in the rates before 1993. Since the introduction of ICD-10-coding in 1993, VS could be distinguished from the other cranial schwannomas. The proportion of schwannomas arising from other cranial nerves than VS was 0.5% (olfactory and optic nerves), while those of unknown or unspecified site made up to 7% of the total number of schwannomas diagnosed in 1993–2007. When assessing the Norwegian rates (1993–2007) an assumption had to be made that none of the unspecified schwannomas was a VS, even if most likely a great many of these unspecified schwannomas were VS. However, to contemplate the validity of this assumption, we conducted a sensitivity analysis assuming that all the cases without a specific site were vestibular and none of the other cranial nerves, or *vice versa*. Even such an exaggerated assumption had no effect on the annual increasing incidence trend in Norway for 1993–2007, which was 4.4% with both methods. The crude incidence rates for Norway for that period assuming that none of the unspecified schwannomas was a VS were 11.5 (95% CI, 10.4–12.7) per 1,000,000 for men and 10.8 (95% CI, 9.7–11.9) for women, and assuming all the unspecified cases (ICD-10 code C72.5) were VS, the rates were 12.4 (95% CI, 11.2–13.6) and 11.6 (95% CI, 10.4–12.7), respectively.

In Sweden, the older more unspecific system (ICD-9 coding together with PAD (pathologic anatomic diagnosis)) was being used in the VS study (II) for the main analyses for the period 1993–2007 to provide consistency over time (even if the newer ICD-10 coding was introduced in 1993). The trends and incidence rates in 1993–2007 obtained with different coding systems were compared using three different protocols: **1.** the older (introduced in 1987) system (ICD-9 (192.0 for malignant neoplasm of cranial nerve) + PAD (451, 456; 451 for neuroma and 456 for malignant neuroma)), **2.** the coding used systematically for VS during that period in the Swedish Cancer Registry (ICD-10 (C72.4, C72.5, C72.9; C72.4 for acoustic nerve, C72.5 for other and unspecified cranial nerve and C72.9 for central nervous system, unspecified) + SNOMED (9560/0, 9560/3; 9560/0 for neuroma and 9560/3 for malignant neuroma; and 8000/0, 8000/3 if either C72.5

or C72.9; 8000/0 for benign neoplasm and 8000/3 for cancer)) (see **Table 6**), and **3.** the most accurate coding for VS (ICD-10 (C72.4) + SNOMED (9560/0, 9560/3)).

With the older coding system (**1.**) the crude incidence for men was 8.9 (95% CI, 8.1–9.6) per 1,000,000 and 9.2 (95% CI, 8.5–9.9) for women in 1993–2007, and with the currently used coding in the Swedish Cancer Registry (**2.**) the rates were 10.8 (95% CI, 10.0–11.6) and 10.9 (95% CI, 10.1–11.7), respectively, and with only including the most certain VS cases (**3.**), the rates were 7.5 (95% CI, 6.9–8.2) and 7.8 (95% CI, 7.2–8.5), respectively. Following the same principle, the annual trends for that period (1993–2007) were –2.1% (95% CI, –3.4 to +0.82) (**1.**), –2.6% (95% CI, –3.7 to –1.4) (**2.**) and –2.3% (95% CI, –3.6 to –0.87) (**3.**).

### 5.1.3. Completeness of meningioma registration

The completeness of reporting meningiomas to the FCR was 69% (95% CI, 55–83). FCR had registered 29 meningioma cases during the study period, while a total of 42 cases were identified from the FCR and Tampere University Hospital databases together. However, as two of the meningioma cases registered by the FCR were recurrent cases instead of being incident, the FCR material included 27 meningiomas of the total (64%) (95% CI, 50–78).

The coverage of the FCR depended much on the age of the patient and confirmation method of the tumour (**Table 7**).

**Table 7.** Numbers of meningiomas in Pirkanmaa Hospital District by data source, November 2000 – June 2001.

| | | FCR | Neurosurgery | Discharge | Pathology | TOTAL [a] | FCR coverage (% of total) |
|---|---|---|---|---|---|---|---|
| **Sex** | Male | 5 | 5 | 4 | 4 | **7** | **71** |
| | Female | 22 | 24 | 22 | 22 | **35** | **63** |
| **Age** | 15–29 | 2 | 1 | 2 | 2 | **2** | **100** |
| | 30–39 | 2 | 1 | 2 | 2 | **2** | **100** |
| | 40–49 | 2 | 3 | 2 | 2 | **3** | **66** |
| | 50–59 | 6 | 5 | 4 | 5 | **7** | **71** |
| | 60–69 | 8 | 8 | 8 | 11 | **12** | **67** |
| | 70–79 | 4 | 4 | 2 | 2 | **5** | **80** |
| | 80+ | 3 | 7 | 6 | 2 | **11** | **27** |
| **Confirmation** | Radiology | 4 | 11 | 8 | 0 | **14** | **29** |
| | Histology [b] | 23 | 18 | 18 | 26 | **28** | **82** |
| **TOTAL** | | 27 | 29 | 26 | 26 | **42** | **64** |

[a] As a case may be registered in several data sources, the row total may not equal the sum of the cell frequencies, but indicates the total number of meningiomas (N = 42).

[b] With or without radiological support for the diagnosis.

Younger cases were notified comprehensively (100% of patients below 39 years old) to the cancer registry, whereas less than one third (27%) of the patients over 80 years old were reported. Confirmation method of the meningioma affected the rate of reporting substantially. Less than one third (29%) of patients diagnosed only radiologically were reported to the FCR.

Altogether, there were sixteen patients older than 70 years. Only three of them underwent surgery, while the rest of them were still at the time of collecting the data (spring 2005) under watchful follow-up (five cases) or had died (either during follow-up or before a planned surgery) (seven cases). One case was diagnosed at autopsy.

Less than third of the meningioma cases (31%) were covered by all the three most comprehensive databases (FCR, neurosurgical database and hospital discharge database) (**Figure 9**). The pathology database was not thoroughly inclusive, as it contained only histologically diagnosed cases.

Seven cases (27%) from the hospital discharge register and twelve cases (41%) from the neurosurgical clinic were not reported to the FCR. Four cases (15%) from the pathology database were not reported to the FCR, even though this procedure should be fully automatic (computerized). The total number of cases from the most comprehensive three databases (FCR, neurosurgery and hospital discharge databases) adds to 41 cases in **Figure 9**, as one case was only recorded in the pathology database.

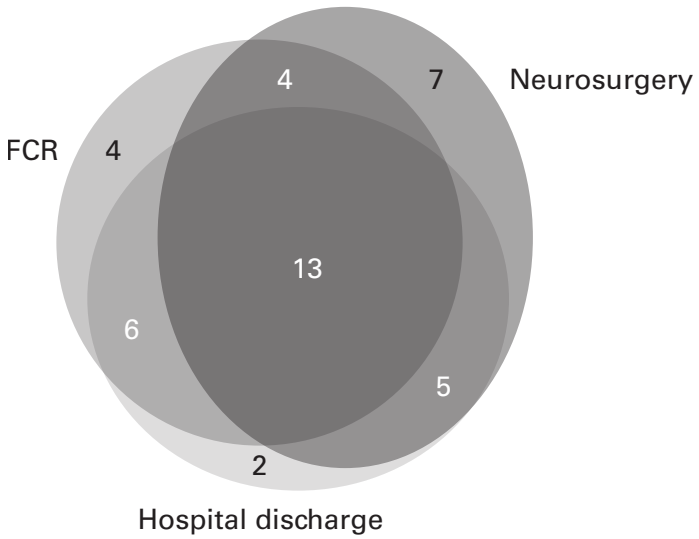



**Figure 9.** The numbers of meningioma cases from Pirkanmaa Hospital District. The area reflects the number of cases in each source and their overlap. (I)

Four meningioma cases from the FCR data were not included in the neurosurgical or hospital discharge database (**Figure 9**), but one of the cases was found in the pathology database. Of the remaining three cases not found in any datasets of Tampere University Hospital (except when going through medical records), all had been in-patients at the hospital. One case was histologically verified, whereas two were diagnosed based on radiological images.

## 5.2. Location of gliomas

Most gliomas (86%) were located in the four cerebral lobes, with 40% in the frontal lobe, 29% in the temporal, 14% in the parietal and 3% in the occipital lobe (III). Gliomas were situated more frequently in the right than in the left hemisphere (51% vs. 40%) (III). However, when assessing locations with the larger material from seven countries (IV), the sites of the tumours were distributed somewhat differently. Gliomas were equally distributed between the hemispheres, with 46% on the right and 46% on the left. Again, most gliomas were in the cerebral lobes (83%), with 35% in the frontal lobe, 25% in the temporal, 19% in the parietal and 6% in the occipital lobe (IV).

When the number of gliomas was assessed in relation to the tissue volume of each brain lobe, the frequency of gliomas was more than four-fold in the frontal and temporal lobes and more than two-fold in the parietal lobe in comparison to the occipital lobe in the Finnish data ($p < 0.001$) (III). With the larger material the differences were more moderate, with the frequency of gliomas of slightly over two-fold in the temporal lobe and nearly two-fold in the frontal and parietal lobes in comparison to the occipital lobe ($p < 0.001$) (IV) (**Table 8**).

**Table 8.** Number and frequency of gliomas relative to tissue volume by cerebral lobe, separately for both glioma studies (III, IV).

| LOCATION OF GLIOMA BY LOBE | RELATIVE VOLUME [a] | FREQUENCY (No. of gliomas) (III) | FREQUENCY/ VOLUME [b] | FREQUENCY: VOLUME RATIO RELATIVE TO OCCIPITAL LOBE [c] [d] | FREQUENCY (No. of gliomas) (IV) | FREQUENCY/ VOLUME [b] | FREQUENCY: VOLUME RATIO RELATIVE TO OCCIPITAL LOBE [c] [d] |
|---|---|---|---|---|---|---|---|
| Frontal | 3 | 107 | 36 | 4.5 | 293 | 98 | 1.9 |
| Temporal | 2 | 77 | 39 | 4.8 | 220 | 110 | 2.2 |
| Parietal | 2 | 37 | 19 | 2.3 | 169 | 85 | 1.7 |
| Occipital | 1 | 8 | 8 | 1 | 51 | 51 | 1 |

[a] Burger et al. 1991
[b] Number of cases relative to tissue volume.
[c] Frequency adjusted for tissue volume, with occipital lobe as the reference (assigned a value of 1).
[d] p-value for difference between lobes < 0.001.

Gliomas were located more anteriorly and subcortically than in other parts of the brain (III). In the coronal projection, a clear distribution in the shape of an inverted U was seen ($p < 0.001$ for homogenous distribution of gliomas in the brain) and in the sagittal projection gliomas were located in the anterior areas and around sella ($p = 0.02$ for right hemisphere, $p = 0.007$ for left). The distribution was more homogeneous in the axial projection, with a tendency towards anterior subcortical parts ($p = 0.06$) (**Figure 10a**). No significant differences were noticed in location between three histologic subtypes (GBM, diffuse and anaplastic astrocytomas, oligoastrocytomas and oligodendrogliomas) (III). With the larger, multinational data, the detailed distribution of locations in the brain was not further evaluated, however figures are shown for descriptive purposes (IV) (**Figure 10b**).

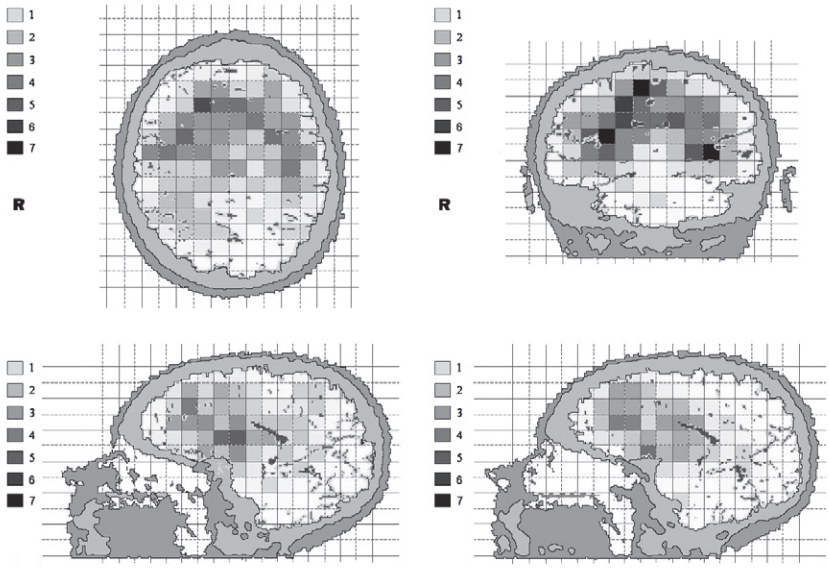
The locations of gliomas were not significantly related to mobile phone use by several exposure characteristics, even if some variation was observed (IV). The mean distance of glioma from the presumed (hypothetical) source of exposure was 6.25 cm (laterality neglected). Glioma cases were non-significantly closer to the mobile phone, when the person had not used mobile phone regularly (6.19 vs. 6.29 cm), phone was held contralateral to the glioma (6.29 vs. 6.37 cm), the person had been talking less than the median (< 133 hours) (6.27 vs. 6.33 cm) or had used mobile phone over five years, but less than ten years (6.28 cm for 5–9 years vs. 6.38 cm for ten years or more).

In the case-case analysis, comparing the distances to the source of exposure in mobile phone users (by various exposure characteristics) and in never-regular users, decreased ORs for gliomas located within 5 cm of the presumed mobile phone location were found for ever-users (vs. never-regular users) (**Table 9**). However, all confidence intervals covered unity. The decreased ORs indicated that there are no more gliomas in the parts of brain closest to the mobile phone (i.e. highly exposed parts) among regular mobile phone users.

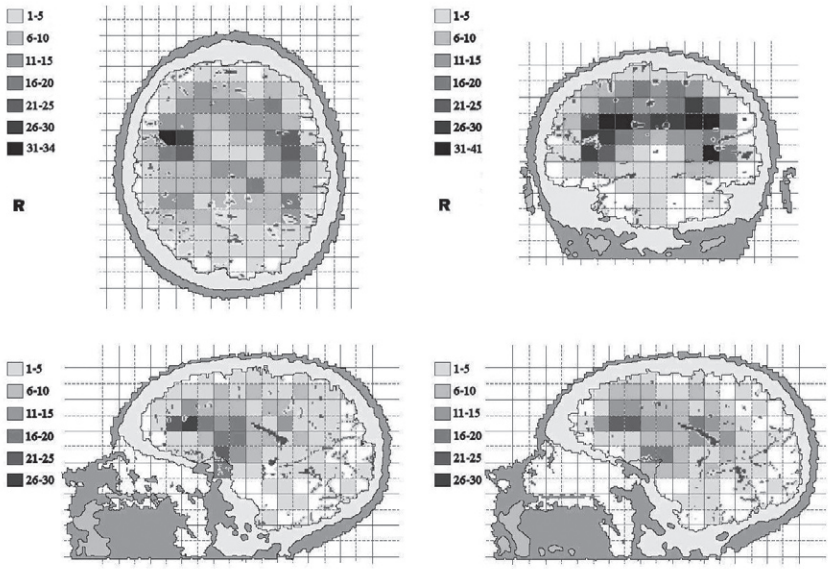
In the case-specular analysis, a somewhat larger proportion of glioma cases than speculars were within 5 cm of the presumed mobile phone location when distance was used as a categorical outcome (**Table 10**). Nevertheless, the confidence intervals included the value one, with no significantly increased ORs for regular users or those with the highest exposure. However, an OR of 2.0 was found for over ten year mobile phone use, but with a wide confidence interval also including unity (95% CI, 0.68–5.85). In the analyses with distance as a linear variable the OR remained very close to unity for all exposure variables (results not shown).

The main results (**Table 9, Table 10**) were relatively similar even when excluding cases with multiple (adjacent) mid-points or cases with only proxy respondents (potential confounders). The results from the main analyses did not differ substantially when analysing digital and analogue phones separately,

**10a.** The Finnish Interphone data. (III)




**10b.** The international Interphone data (seven countries). (IV)




**Figures 10a, 10b.** The anatomic distribution of gliomas in different projections of the brain, from left to right, top to bottom: the axial projection (frontal part at top), the coronal projection (facing the front) and the sagittal projections, sagittal right and sagittal left. The colours represent the number of gliomas in each 1 × 1-cm square, smoothing based on adjacent squares.

nor when gliomas were assessed by histological sub-groups (GBM and other gliomas separately). The average distance between glioma and source of exposure did not differ significantly between countries (mean distance 6.08 cm in Denmark vs. 6.51 cm in Italy, p = 0.29), which may also have been a potential confounder (several neuroradiologists).

**Table 9.** Case-case analysis: OR (with 95% confidence interval) for distance ≤ 5 cm between glioma mid-point and typical position of mobile phone by exposure characteristics, all compared to never-regular users. (IV)

| | CRUDE OR (95% CI) | ADJUSTED OR (95% CI) [a] |
|---|---|---|
| **Frequency of use** | | |
| Regular | 0.87 (0.63 – 1.20) | 0.80 (0.56 – 1.15) |
| **Cumulative call time (hours)** | | |
| 0.001 – 46 | 0.82 (0.52 – 1.29) | 0.82 (0.51 – 1.31) |
| 47 – 339 | 1.04 (0.67 – 1.60) | 0.97 (0.60 – 1.56) |
| > 339 | 0.72 (0.46 – 1.15) | 0.58 (0.35 – 0.96) |
| **Laterality of use** | | |
| Ipsilateral | 0.82 (0.56 – 1.21) | 0.80 (0.52 – 1.22) |
| Contralateral | 0.87 (0.56 – 1.34) | 0.77 (0.47 – 1.24) |
| **Duration of use (years)** | | |
| 1.5 – 4 | 0.86 (0.60 – 1.23) | 0.85 (0.57 – 1.25) |
| 5 – 9 | 0.84 (0.53 – 1.35) | 0.71 (0.43 – 1.18) |
| ≥ 10 | 0.99 (0.47 – 2.08) | 0.85 (0.39 – 1.86) |

[a] Adjusted to age, education, sex and country.

**Table 10.** Case-specular analysis: OR (95% confidence interval) for distance between glioma mid-point and typical position of mobile phone as a categorical (≤ 5cm) variable by exposure characteristics, all compared to speculars (case vs. specular).

| | OR for case ≤ 5cm (95% CI) |
|---|---|
| Case vs. specular | 1.22 (0.99 – 1.51) |
| **Never or non-regular users** | |
| Regular | 1.19 (0.89 – 1.59) |
| Never-regular | 1.30 (0.95 – 1.80) |
| **Cumulative call time (hours)** | |
| 0.001 – 46 | 1.39 (0.81 – 2.38) |
| 47 – 339 | 1.21 (0.74 – 1.97) |
| > 339 | 1.00 (0.59 – 1.69) |
| **Duration of use (years)** | |
| 1.5 – 4 | 1.15 (0.80 – 1.66) |
| 5 – 9 | 1.04 (0.61 – 1.76) |
| ≥ 10 | 2.00 (0.68 – 5.85) |

# 6. Discussion

This thesis focused on occurrence studies of intracranial tumours as a tool for cancer epidemiology. This dissertation concentrated on defining the challenges in interpreting trends of intracranial tumours, on evaluating the validity of the cancer registry data and on contemplating on further potentials of the materials on intracranial tumours beyond cancer registry data.

Cancer epidemiology studies factors affecting cancer, in order to distinguish possible trends and patterns in the occurrence of cancer and to detect potential causes of cancer. It focuses on groups of people rather than individuals, which distinguishes it from clinical cancer studies. Even if (cancer) epidemiology is considered as an independent research field, often it cannot be separated from other fields of science, as the epidemiological methods are widely used in many types of research. Therefore, epidemiology can be regarded as a multidisciplinary field.

The main focus of this thesis was on the quality and contents of the study materials. The most important factor in good research is the quality of the data (validity and completeness) and the relevance of the contents of the material. Valuable data are the basis for all research, and with problems of any kind in the material, severe complications are encountered. Mistakes (or in extreme: frauds) in the methods can often be checked and corrected by other researchers, but it is difficult (or impossible) to go back to the sources of the data. Therefore, the study material should be of very high quality (recognising the limitations of the available resources).

The reliability of the data should be critically assessed by the researcher. Things to consider would be the evaluation of sources of information (are all available sources used?) and completeness of cases (are all cases included?) (i.e. sensitivity of the data). Also, the correctness of the data should be evaluated (are the definitions of the variables unambiguous and systematic? Are the classifications of the cases correct?) (i.e. specificity of the data). Potential biases should be eliminated and possible confounding acknowledged and controlled.

In cancer epidemiology, cancer registry data are used widely. Cancer registry data are often accepted with satisfaction without questioning the reliability of the data, even if the validity of other data may be evaluated thoroughly. The researchers should also contemplate whether the data in cancer registry are accessible at a sufficient precision (in comparison to the information available for the clinicians reporting the cancer cases) and thus consider further potentials of the data.

This thesis evaluated the reliability of the cancer registry data, and reflected whether the data are available at the level of detail required.

## 6.1. Assessment of the cancer registry data

While cancer registries should pay attention to their accuracy and completeness (Teppo et al. 1994), problems were encountered in both fields in this dissertation. Deficiency in registering all cancer cases (completeness) and variations in cancer coding (accuracy) affected the rates strongly. Most challenges were experienced with low rates of reporting only clinically diagnosed intracranial tumours, especially among the elderly, and with changes in classification of tumours over years.

Even if cancer registry material is the base for most descriptive cancer epidemiology research and is readily available in many parts of the world, a researcher should be acquainted with certain potential defects in cancer registry data in order to interpret the findings critically.

### 6.1.1. Evaluating the completeness of the cancer registry data

We found that underreporting of meningiomas to the FCR was as high as 31% (I). Most of the cases that were not reported to the FCR were from the neurosurgical database; the reporting by the neurosurgeons was the lowest (57%). Less than one third of the cases diagnosed only radiologically or in patients over 80 years old were reported to the FCR. Underdiagnosed cases (particularly in patients over 80 years old) will be discussed later.

The underreporting of meningiomas observed in this thesis is higher than in an earlier Finnish study; in that study one-fifth of all benign CNS tumours were not reported to the FCR (in 1985–88), despite high proportion of registration among other types of tumours, particularly malignant tumours (Teppo et al. 1994). However, our results are not comparable to those results, as in the earlier study all benign tumours of the CNS were included as one group (not only meningiomas), the whole of Finland was covered (not only Tampere University Hospital), the study period was over a decade earlier and only the hospital discharge register data were compared to the FCR data (instead of data from several registers). In our study 62% of the cases from the hospital discharge register were covered by the FCR.

In a study from two English counties, one fifth of patients with a diagnosis of a brain tumour were not admitted to hospital (Pobereskin and Chadduck 2000). In their studies (Pobereskin and Chadduck 2000, Pobereskin 2001), the population in two English counties was screened by reviewing CT and MRI scans of the head over a 5-year period and then the numbers of cases were compared to pathology and operative databases (i.e. secondary sources), and then later all observed cases were compared to the regional cancer registry data. Only somewhat over a half of the cases (52%) appeared in the cancer registry

data. Not surprisingly, malignant tumours were more likely to be registered. For those cases not operated less than one-third were registered. Even among those admitted to hospital for surgery, only 64% were notified to the registry. Secondary sources were shown to add very few additional cases. The incidence rates from their studies were twice as high for meningeal tumours, 1.4-fold for neuroepithelial tumours and three times higher for cranial nerve tumours than those derived from the regional cancer registry. Based on these results the authors claimed that case finding methods (such as CT/MRI scans) capturing those cases not admitted to the hospital should be used for incidence studies. Nevertheless, the rationality of routine case finding methods in incidence studies can (and should) be strongly argued (see for example **6.1.1.1.** and **6.1.1.2.**).

In a Scottish study, 54% of primary intracranial tumours appeared in the regional cancer registry, when the cancer registry data were compared to cases identified retrospectively using multiple sources (Counsell et al. 1997). Most neuroepithelial tumours (84%), while only a few meningiomas (22%), were found in the cancer registry. However, despite the problems with completeness, the diagnostic accuracy of the cancer registry was good (Counsell et al. 1997).

Cancer registries usually obtain their data from two sources; from the clinicians (as a generalisation) (several clinicians, including pathologists; with clinical and pathological sources separated) and from the death certificates. This additional information received from the death certificates provides a way to ascertain the completeness of the coverage. However, a benign and slow-growing tumour often results in a low mortality due to the disease (vs. mortality for malignant tumours). As the FCR receives information on the death certificates automatically (from Statistics Finland) if death was attributed to cancer (a cancer diagnosis (or some specified ICD-10 D-codes) mentioned), dying from another cause than cancer produces fewer case reports to the cancer registry. Each case report (from the death certificate) is later compared with clinical medical records, and if proven to be a true cancer case, the information is added to the cancer registry database. Thus, with benign and non-lethal tumours, there is one source of information less. In our study (I), no meningioma cases were received from the death certificates only.

Similarly to meningiomas, underreporting of VS to the cancer registries was suspected, being also a benign and slowly-growing tumour, but this was not further evaluated within the scope of this dissertation.

#### 6.1.1.1. Misclassification in the cancer registry data

The main type of misclassification in the cancer registry data of benign brain tumours is false negatives, as false positives are much rarer in benign tumours (see **6.1.2.**). Underreporting and failure to ascertain cases (underdiagnosing)

result in lower incidence rates than in 'reality', even if these two concepts (underreporting, underdiagnosing) should be separated. The former one suggests deficiency in the information flow from the diagnosing physician to the cancer registry database, while the latter merely indicates there are undetected cases. All attempts to eliminate underreporting are recommended to produce reliable cancer statistics. The role of underdiagnosing is not as simple. One example on this would be benign intracranial tumours, especially in the elderly. Diagnosing asymptomatic, slow-growing intracranial tumours by aggressive diagnosing (e.g. CT/MRI-scans) is seldom beneficial either for the individual or the community.

The level of underdiagnosing of intracranial tumours can be evaluated by estimating the prevalence of these tumours incidentally found in e.g. autopsies. Similarly to autopsy studies, research on incidental findings of brain parenchyma by imaging technology is related to underdiagnosing, as these brain tumours detected would not have been diagnosed without the studies in question.

In our study only two meningioma cases were detected in autopsy out of 210 clinical autopsies (1%) performed during the study period (I). In a previous study dating to the 1980s, two thirds of all meningiomas were diagnosed initially at autopsy (Kurland et al. 1982). However, nowadays the diagnostics preceding death are improved in comparison to studies thirty years old and the autopsy numbers are lower (indicating a more carefully selected reason for an autopsy). Nearly 70% of all deaths underwent autopsy in the study by Kurland et al. (1982), whereas in the 1990s the proportions of post-mortem examined deaths were much lower (ranging from 4% in France up to 69% in Hungary; average autopsy ratio of 25% in the eight countries listed) (Burton and Underwood 2007). In addition, it is noteworthy that the autopsy ratios had strongly decreased over time (decrease of 30–70% from the initial autopsy ratios in the eight countries with a varying time span) (Burton and Underwood 2007). In a study from Finland, an overall of 31% of all deaths (in those deceased at age one year or more) had undergone autopsy in 1995 (Lahti and Penttilä 2001).

In studies estimating the prevalence of incidental findings of the brain by variable imaging technology (typically MRI), gliomas were found incidentally in 0–0.8% of the cases, meningiomas in 0–5.5% and VS in 0–0.4% of the cases (Kamiguchi et al. 1996, Katzman et al. 1999, Lin et al. 2005, Vernooij et al. 2007, Morris et al. 2009).

In the meningioma study we observed a high rate of underreporting meningiomas especially among the elderly. However, it is likely that the number of meningioma cases in the elderly that are underdiagnosed is similar or even higher than the underreported cases, but this is speculation based on

the knowledge that the prevalence of all incidental neoplastic brain findings increases with age (Morris et al. 2009). Based on the numbers presented above, with meningiomas found in only 1% of all autopsies performed during the eight months of our study period, the rate of underdiagnosing appears to be lower than the rate of underreporting, but both the study period and the number of people autopsied were limited. Autopsies are generally performed mainly for the elderly (more deaths), while the studies on incidental findings of the brain contain usually patients with a wider range of age groups (e.g. ages 46–97 in the meta-analysis by Morris et al. 2009) and therefore the numbers of incidental findings of e.g. meningiomas in brain imaging studies are expected to be lower than in autopsy studies.

#### 6.1.1.2. Deficiency of diagnosing and reporting in the elderly

A detection bias among the elderly was suspected with VS; the highest incidence of VS rates were found in the age groups 45–54 and 55–64 years. This lower incidence among the elderly is atypical for neoplastic disease and probably indicates a lower rate of diagnosis in old age. On the other hand, the highest annual increase was seen in the oldest age group (65+ years), suggesting that the increasing incidence of VS may be due to an increasing diagnostic activity in the elderly. Also, as some elements of the age-period-cohort analysis were utilized in the VS study, the incidence rates were observed as being higher in the younger cohorts denoting that the diagnostic activity is improving over the years even in the elderly. (We restricted the use of the age-period-cohort analysis into a simple version of the analysis by presenting the cohort effect of VS incidence in two figures (presented by age and sex) in the original VS article (II)).

Both types of problems (underreporting and underdiagnosing) leading to an undercount of cases occurred most frequently among the elderly. In our study only 25% of meningiomas in patients over 70 years of age were confirmed histologically (I). In an earlier Japanese study, the proportion was 55% (Kuratsu and Ushio 1997). Nevertheless, even if the diagnosis of a benign tumour is often confirmed only radiologically among the elderly, these tumours should be reported to the cancer registry. Thus, underreporting is present partly due to lack of histological verification.

In our meningioma study, less than one third of the patients older than 80 years were reported to the FCR. This underreporting in the elderly can be due to several reasons, e.g. more imaging for other reasons than suspicion of meningioma (e.g. non-specific symptoms such as dizziness or syncope followed by routine CT) leading to incidental findings, which are reported less frequently, as meningioma is not the primary interest of the CT. Or the underreporting may be caused by more conservative treatment, as operated tumours with

pathological confirmation are often more promptly reported. The elderly are less often operated on, due to poor performance status and comorbidity, or due to a limited remaining lifespan estimate in which slow-growing tumours will have no time to cause clinically relevant problems considering that all intracranial surgical operations have associated significant risks.

Even if we did not evaluate the level of glioma registration in this thesis, not only benign cancers are underreported. Similarly to benign tumours, the majority of underreporting of malignant tumours is observed among the elderly. In a recent study from Sweden, only 70% of men and 77% of women over 70 years of age with a malignant tumour of the CNS were reported to the Swedish Cancer Registry (Barlow et al. 2009). In a Japanese study, only approximately two-thirds of anaplastic astrocytomas, GBM and schwannomas among the elderly and even less (40%) of low-grade astrocytomas had a pathological confirmation (Kuratsu and Ushio 1997). Usually histological confirmation increases cancer registry reporting.

It is rather difficult to reflect on how the concepts of underreporting and underdiagnosing of intracranial tumours in the elderly should be dealt with. Obviously the statistics should be as correct as possible, and underreporting of any kind should be minimized. Yet, considering the underdiagnosing of intracranial tumours in particular in the elderly is much more difficult. Benign intracranial tumours among the elderly are seldom treated due to various reasons (as described above) and thus, if not treated (or followed) in any way, the tumours do not influence the nation's health care resources and expenses by any means. On the other hand, these underdiagnosed cases would hypothetically play an important role in etiological exposure studies, if for example a cohort exposed to a certain factor had an excess of intracranial tumours. Nevertheless, any type of "random screening" (resulting in diagnosis of cases that would be otherwise underdiagnosed) should certainly be avoided, and this principle can be generalised to cover also benign brain tumours, even if this concept of avoiding "random screening" has been much more discussed with other types of tumours (e.g. prostate cancer in the elderly men).

### 6.1.2. Challenges in the classification systems

Variations in coding systems are major concerns in interpreting cancer trends. If the classification of a certain tumour changes in the cancer registry data, evaluating trends over time may become impossible, even if theoretically the data derived from the cancer registries were complete and valid at any given time. Also problems may be encountered when comparing rates between countries as the coding systems may differ substantially. The coding protocols

of VS differed considerably between and within the countries, but the greatest challenge was with classification systems changing over time (II).

The VS data for analysing cancer incidence trends had several shortcomings and the requirements to produce reliable cancer trends were not fulfilled (incomparability of information across time and place), based on several elements to be considered in obtaining valid time trends (Muir et al. 1994). Valid evaluation of trends would require that the definition of the cancer site being studied had not changed (this is not an issue for VS as site had not changed), neither had the criteria of malignancy (again not an issue for VS, it had remained benign) or the likelihood that a cancer will ever be diagnosed (requirement not fulfilled for VS). The progress of cancer from inception to diagnosis should not have been modified by early detection or screening programmes (not fulfilled for VS), and ascertainment of incident cases and deaths should be equally accurate throughout the period of study (not fulfilled for VS). Also valid trends would require that the indexing in the ICD coding had not changed (not fulfilled for VS), the accuracy and specificity of coding had remained consistent over time (not fulfilled for VS) and the statistics had been available in sufficient detail (not fulfilled for VS) (Muir et al. 1994).

Coding of VS had changed in Norway and Sweden (even if indexing in the ICD system was not changed, some variations appeared with new coding systems), resulting in lower precision (lower sensitivity) and lower validity (lower specificity) of classification over time. The most accurate coding (used at present) for VS in Norway and Sweden was introduced in 1993 (ICD-10). The changes in coding could not be overcome in Norway. However, a rapid increase in incidence rates seen in Norway (from the late 1990s to the early 2000s) could not be explained by the changes in coding, as these changes in classification should have decreased instead of increasing the number of cases diagnosed as VS. This phenomenon (of changes in coding influencing the rates) was not observed in Sweden, despite the fact that Sweden also changed their coding system into ICD-10 in 1993, as for the analyses of incidence trends a uniform (older) coding was used over time.

To observe the changes in trends (and to reflect on the role of the changes in the classifications) an analysis with a subdivision of the time period was used with the Norwegian and Swedish data (as these two countries had available data from 1965 to 2007). The analysis was conducted by assigning the mid-point of the study period as the cut-point, as the purpose was to observe the difference in the annual increase in incidence between the former and the latter part of the study period (two periods of similar length). The analysis was restricted to this distinct question in focus (i.e. was the increase higher in the beginning of the study period or at the end?), and thus, no true joinpoint analysis was being used.

The sensitivity analyses of the changes in classification of VS were only performed for Norway and Sweden. The analyses evaluated the potential impact of the unspecified data on the incidence trends. No substantial differences in the annual increasing (or decreasing) trends for 1993–2007 were observed either in Norway or Sweden, when comparing the different coding systems. In Norway, the annual trend was similar (annual increase 4.4%) assuming either that none of the unspecified schwannomas was a VS, or assuming that all unspecified schwannomas were VS. Similarly, the Swedish rates did not show substantial differences in the trends for those years with different classification systems (annual increasing trend ranging from –2.1% to –2.6%).

Nevertheless, larger differences were seen in the incidence rates, than for the annual trends, in Norway and Sweden with the different classification systems. The crude incidence rates were approximately 7% higher supposing all unspecified schwannomas were VS in Norway. However, an assumption this extreme is very unlikely to be true, even if the incidence rates are most certainly higher than those reported in our study (II), as probably most (but not all) of the unspecified schwannomas are VS. Thus, the incidence rates in Norway are somewhat, but less than 7%, higher than the rates presented in the VS study (II). It is unknown if the proportion of VS of all unspecified cranial schwannomas is similar to the ratio of VS of cranial schwannomas with known site. If the proportion was comparable, most of the unspecified cases ought to be included in the VS rates. However, VS may, for instance, be more easily identified and classified more frequently correctly (coded as a VS instead of an unspecified cranial schwannoma), while the opposite may be true for other cranial schwannomas.

In Sweden, the crude incidence rates in 1993–2007 were approximately 20% higher for both sexes with the coding system currently in use (in Sweden) in comparison to the coding used for the main analyses in the study II. However, neither the older system (ICD-9) nor the newer system (ICD-10) distinguished the true VS cases from other cranial schwannomas. The ICD-9 system does not separate schwannomas in different cranial nerves from one another, whereas, the ICD-10 system has a specific code for VS (C72.4), but in our study schwannomas coded under C72.5 (other and unspecified cranial nerve) and C72.9 (central nervous system, unspecified) had to be included in the calculations. This inclusion (of C72.5 and C72.9) was justified by previous Swedish studies, showing that a substantial proportion of VS had been classified under these codes (unpublished data). With only the most accurate VS code (ICD-10 code C72.4), the crude incidence rates were, on the other hand, approximately 15% lower in comparison to the rates obtained with the coding system used for the main analyses in the study II (ICD-9 classification). However, these lower values

with the inclusion of only the most specific coding underestimate the occurrence of VS according to the previous Swedish studies (which encourage the inclusion of the unspecific ICD-10 codes (C72.5, C72.9) for catching all VS). According to the results obtained using the three different coding systems in Sweden, the Swedish rates presented in the study II (with the older coding system, ICD-9 coding) are likely to be rather realistic, with a potential margin of error (due to different coding systems) of a maximum of one-fifth.

Inaccurate classification may distort the reported incidence rates. However, based on earlier literature, the specificity (accuracy in defining the correct histological type) of the reported cases of benign tumours to the cancer registry has been high. The consistency of the histological diagnosis (from the pathological confirmations to the cancer registries) has shown good concordance (double-checking, by another pathologist) for benign tumours (95% consistency for meningioma, 89% for nerve sheath tumour (including VS)), whereas inconsistency is larger for malignant brain tumours (discrepancy up to 23% in gliomas, or up to 43% with all brain tumour cases combined) (Bruner et al. 1997, Aldape et al. 2000, Castillo et al. 2004). This inconsistency in classification of malignant brain tumours is due to the diversity in the classification of malignant brain tumours, and the presence of an unspecified histologic group.

The coding protocols of VS differed substantially between countries, but it was not possible to assess the impact of these differences on the rates.

To summarize, the variations in tumour classification over time and between countries may influence the reported occurrences of cancer substantially. In many situations the differences cannot be overcome, but still the researcher should justify well the classification criteria used for each study, and pursue attempts of correction (e.g. by sensitivity analyses).

### 6.1.3. Cancer registries internationally

Inaccuracy and incompleteness was observed in the cancer registry material, even if Nordic cancer registries are regarded as being of a high standard (Lönn et al. 2004a, Klaeboe et al. 2005, Deltour et al. 2009). There is a legislation in Nordic countries to notify all cancer cases to the cancer registry apart from in Denmark and Iceland (Curado et al. 2007). In Denmark the legislation was replaced by an administrative order (i.e. no specific law), in Iceland there is no obligation to report (Curado et al. 2007). The Nordic registries were founded in an early period of the history of cancer registering; Denmark as early as in 1942, followed by Finland and Norway (1952), Iceland (1954) and a few years later Sweden (1958).

Even if cancer registry data are available in many countries of the world, and often used as the base for studies on cancer epidemiology, the data should not be used uncritically, especially as the international registries vary widely (see **2.3.2.**). Certain issues should be clear, when using and interpreting data obtained from the cancer registries.

Primarily, the cancer registry may have problems with both diagnostics and reporting, as discussed. Population size may be difficult to estimate, especially if cancer registries are based on subnational units. Also the definition of residents may be difficult in subnational units, as there may be duplicate registration in non-nationwide registries (due to moving population or residents seeking health care services from outside own community). However, all the Nordic registries are nationwide (apart from the Swedish system, where the registry consists of several sub-units, all pooled together covering the entire nation) and with unique identification numbers (preventing potential duplications), which facilitates the population estimates.

Problems are encountered when registering multiple primary tumours, as cancer registries ought to consist of only incident cancer cases (Bray and Parkin 2009). Similarly, difficulties are observed when defining an incident from a recurrent case. Screen-detected cancers may suggest an increase in prevalence, due to lead-time (earlier diagnosis). Screening also increases incidence, if some cases would not have been detected or diagnosed without screening. In a similar fashion incidental diagnoses (e.g. through autopsy, CT/MR-imaging) increase the incidence (overdiagnosis), which is observed with intracranial tumours. However, these two latter issues, problems with screening and overdiagnosing, are not – strictly speaking – problems of cancer registries or registration, yet they lead to difficulties in interpreting the rates.

Despite the fact that in this thesis it was conceived that the completeness and validity of the Finnish and the Nordic cancer registries are far from perfect in registering benign intracranial tumours, it can be still claimed that the material for these studies for the dissertation – in particular the VS study concentrating on trends (II) – could not have been better anywhere else in the world. Even if the data were far from perfect, it most certainly is similarly so, and most likely even more incomplete, anywhere else. All the Nordic countries have a nationwide cancer registration with clinicians' obligation to report all cases (apart from Iceland), the registries have a long history, and thus experience in maintaining a cancer registry, and each Nordic citizen has a personal identification number (social security number) providing accurate personal information. Therefore the cancer registry data from the Nordic countries, despite its deficits, can be considered belonging to the best cancer data worldwide.

### 6.1.4. General considerations in interpreting occurrence of intracranial tumours

Most challenges in describing and analysing trends in brain tumours are, however, not directly related to the sensitivity and specificity of the cancer registry data. Yet, these issues must be briefly discussed here as they influence incidence trends. As discussed in the review of literature (**2.3.3.1.**), there are a few possible artefacts partly explaining the spurious increase in incidence of brain cancers.

The most important artefact, in addition to changes in reporting and coding, would be the introduction of CT and MRI in the 1970s-80s (Helseth 1995, Preston et al. 2002, Lönn et al. 2004a). This resulted in an increase particularly in the incidence of asymptomatic, benign tumours (such as meningiomas and VS), while the numbers of gliomas had been better estimated already previously due to their more aggressive clinical course. The diagnosing (and thus the reported incidence rates) of malignant brain tumours were less affected by the introduction of CT scans and MRI than benign tumours, as malignant tumours generally present with easily recognizable symptoms (Desmeules et al. 1992). Variations in other diagnostic procedures may also affect the incidence rates (Inskip et al. 1995, Wrensch et al. 2002, Boyle and Levin 2008).

Also, it has been discussed whether the introduction of CT and MRI had a more substantial impact on the diagnosing rate among the elderly. However, a study by Desmeules et al. (1992) demonstrated that the level of detection of brain tumours did not differ between the younger and the older patients, despite the presence of CT or MRI. In the study, patients were selected for a diagnostic re-evaluation performed by a neurologist not having access to the results of any CT scans or MRI (or biopsy results or information on further treatment). The overall misclassification of brain tumours was similar for younger and older patients (23% vs. 24%, respectively). This finding is significant, as the increase in rates is more pronounced among elderly people in many types of brain tumours, and the level of misclassification would have been expected to be higher among the elderly if the increased rates were only due to improved diagnostics. However, in the study by Desmeules et al. (1992), the study period was nearly thirty years ago, and therefore these findings cannot entirely present the situation today, as brain imaging is much more frequent nowadays and also technically better than it was in the 1980s.

That the brain is a frequent site for metastases (metastases counted wrongly as primary tumours earlier) may have an impact on the incidence trends (Boyle and Levin 2008). However, it can be argued that improved coding of metastases would likely cause a decrease, rather than an increase, in trends (if metastases were previously coded as primary brain tumours).

All in all, brain tumour diagnostics have greatly improved over the years (e.g. better quality and availability of radiological equipments, diagnostic alertness among clinicians and potentially public awareness (internet)). This improvement in various fields has certainly had an impact on the rates of intracranial tumours, but the extent of these factors cannot be determined in detail in the current context.

### 6.1.5. Validity of the occurrence findings

The incidence rates of gliomas have varied from 1.9–8.5 per 100,000 person-years in men and 1.3–5.8 per 100,000 among women according to earlier research (Surawicz et al. 1999, Liigant et al. 2000, Kaneko et al. 2002, Christensen et al. 2003, Elia-Pasquet et al. 2004, Lönn et al. 2004a, Houben et al. 2006, Sadetzki et al. 2008, Arora et al. 2009, Arora et al. 2010, CBTRUS 2010). In our study (III), the rates for gliomas (with 4.9 and 4.5 per 100,000 in men and women, respectively) were somewhat lower, particularly in men, than in most European and North American reports. However, the rates were standardized to different reference populations (making direct comparisons impossible).

In our study on glioma incidence, only ages 20 to 69 were included due to the Interphone protocol (III). This age selection may have had a diminishing effect on the rates (truncated rate), if a substantial proportion of glioma cases occurred in the age group of 70 or more. Yet, usually the peak in glioma incidence is prior to the age of 70 (see **2.3.4.**). A previously published study with a truncuated rate standardized to the same population (world standard population) showed a rate of 7.7 per 100,000 (truncuated to ages 20 to 85, with all neuroepithelial tumours included) (Arora et al. 2009).

Underreporting of malignant tumours is much rarer than underreporting of benign tumours, therefore we may expect that the completeness of gliomas was reasonable. In addition, in a recent Swedish study most of the underreporting was seen in the elderly – who were excluded from our study. The completeness of reporting malignant CNS tumours to the Swedish Cancer Registry was 95% for men aged 0–69 and 93% for women, while it was only 70% for men over age 70 and 77% for women (Barlow et al. 2009). Also, the completeness of gliomas was believed to be comprehensive in our study (III), as special study nurses in the university hospitals reported all incident glioma cases to the Interphone coordinator. However, for this supposition (of comprehensiveness) we had to assume that all glioma patients visited the neurosurgical clinic at least as out-patients.

We may also assume that the level of underdiagnosing is not significant for gliomas, as underdiagnosing malignant CNS tumours is not as common as

underdiagnosing benign tumours. In a meta-analysis quantifying the prevalence of incidental findings on MRI of the brain, no high-grade gliomas were found in nearly 20,000 people (the prevalence of low-grade gliomas was 0.05%) (Morris et al. 2009).

The incidence rates of meningiomas have been 0.4–3.8 per 100,000 person-years in men and 0.8–8.4 per 100,000 in women in previously published studies (Surawicz et al. 1999, Kuratsu et al. 2000, Liigant et al. 2000, Kaneko et al. 2002, Christensen et al. 2003, Klaeboe et al. 2005, Arora et al. 2009, Brown et al. 2009, Arora et al. 2010, CBTRUS 2010). We found incidence rates of 2.9 per 100,000 among men and 13.0 per 100,000 among women (I), being considerably higher for women than in earlier studies. These much higher incidence rates of meningiomas in women are probably due to the use of several registries with more meningiomas being detected. Nevertheless, using the meningioma cases based solely on the Finnish Cancer Registry data, the incidence rates were 2.2 per 100,000 for men and 9.6 for women, still higher in women than in previous studies. Yet, in our meningioma study, the number of cases was small (42 meningiomas) and the study period was short (8 months). Based on our results no generalised conclusions, whether the Finnish meningioma rates are different from the previously published estimates, can be derived.

In these studies on gliomas and meningiomas, estimation of overall incidence was not the primary aim of the research, thus these incidence rates are based on small numbers of cases (331 gliomas, 42 meningiomas) (I, III). Whereas, for the VS study, our main objective was specifically to assess the incidence rates of VS (II).

In previous studies, the incidence rate of VS among both men and women has been approximately 3–16 per 1,000,000 person-years (with all nerve sheath tumours included in some studies) (Howitz et al. 2000, Kaneko et al. 2002, Stangerup et al. 2004, Tos et al. 2004, Evans et al. 2005, Nelson et al. 2006, Propp et al. 2006, Arora et al. 2009, Arora et al. 2010, CBTRUS 2010, Gal et al. 2010). In our study, we found an average crude incidence rate ranging from 8 to 16 per 1,000,000 person-years both in men and women. These rates are similar to earlier studies. However, these were crude rates, the age-standardized rates being somewhat lower (6–12 per 1,000,000 for both men and women) due to the higher proportion of younger age groups in the world standard population than in the Nordic countries. These age-standardized rates are also similar to earlier studies, yet the comparisons between rates standardized to different reference populations are difficult. However, based on the studies with standardization to the same population, the standardized rates with 5–10 per million were relatively comparable (Howitz et al. 2000, Arora et al. 2009, Arora et al. 2010),

and also the crude rates with a wide range of 5.5–19.3 per million person-years (Stangerup et al. 2004, Propp et al. 2006).

The VS rates showed an increase in all age groups and in all countries, with the exception of Finnish women (also, the increase was not statistically significant in women aged 55–64, and in Finnish men and Swedish women). There were considerable differences in VS incidence between countries, Denmark exhibiting the highest incidence rate throughout the study period, and the difference even widened in the later years. In Finland, the other country with a constant classification system (coding being similar over the study period), the incidence rates remained rather stable during the study period. For Norwegians, there was a rapid increase in the incidence rates in the late 1990s for both sexes, but the increase levelled off in the 2000s. However, this steep increase in the 1990s was not caused by the changes in the classification (as these changes should have, on the contrary, decreased the rates). In Sweden (where old coding systems were maintained in parallel with the newer coding systems over the years; and a similar coding was used for our trends) the rates increased modestly until the end of the 1990s, when the incidence started to decrease slowly. The incidence of VS increased in all the four countries combined by 3.2% (95% CI, 2.5–3.9) per year in men and by 2.4% (95% CI, 1.7–3.0) in women. Most of the increase was seen before the end of the 1990s. Whether this increase is genuine, or if it is due to true change in detection of incident tumours or due to differences in classification and registering practices remains unclear. (Also, different factors may have happened at the same time in different countries resulting in an overall increase (just as an example: a true increase in Denmark *and* a higher incidence due to changing classification in Norway).)

Even if VS have remained classified as benign during the years (criteria of malignancy have not changed) and the definition of the cancer site has been the same, diagnostic methods have developed notably and thus ascertaining incident VS cases has increased. By the end of 1990s, when most of the increase had happened, most of the currently used radiologic imaging technologies important for detecting a VS were widely available in the institutions responsible for diagnosing a VS in the Nordic countries.

The recommendations for treatment of VS show variation between countries, as there is no gold standard for optimal treatment of VS (see **2.1.2.**). Also, VS can be followed and operated in the neurosurgical or ENT (ear, nose and throat) departments. This variation in treatments has naturally an impact on the reporting rates, as histologically confirmed cases are reported more frequently than only radiologically diagnosed cases. It is also probable that reporting activity differs between e.g. neurosurgeons and ENT physicians, but this cannot be evaluated any further.

Denmark, with clearly the highest incidence rates of VS in the Nordic countries examined in our study, has a nationwide clinical database, which contains all histologically verified VS cases from all six neurosurgical departments that treat patients diagnosed with a VS in Denmark (Howitz et al. 2000). This nationwide clinical database does not exist in any other Nordic country, possibly explaining the higher rates in Denmark (with systematic reporting and registration for this type of tumour, as physicians are aware of an active nationwide clinical database).

Few studies on the incidence rates of VS have been conducted and to the author's knowledge never internationally. The earlier research has been based on much smaller numbers, whereas in this study we had over 5,000 VS cases, more than three times the number of the second largest study based solely on VS (not nerve sheath tumours as a whole) (**Table 4** in **2.3.6.**).

Our VS study may not have provided the most reliable incidence rates (likewise to all VS studies), as the incompleteness of registration and variations in VS coding cannot be overcome. Yet, it has provided important information to the researchers and physicians by raising awareness of the poor compliance (reporting and registration) with cancer registration for this type of tumour, and the consequences of changes in coding systems over time. In addition, this example of VS trends highlights the limitations in cancer registration studies in providing consistent and comprehensive information over time.

In this thesis, two publications (I, II) presented important aspects to consider when working with cancer registry data. To conclude, valid incidence rates of benign intracranial tumours obtained from cancer registries are challenged by underreporting and changes in classification (especially with VS). Even with a large number of cases (large sample size) these problems cannot be overcome due to the misclassification in registering and classifying benign intracranial tumours.

## 6.2. Beyond cancer registry data

Even if cancer registry is often the source of material for studies in cancer epidemiology, the information based solely on cancer registries may not be sufficient. More information is inevitably needed in analytical studies where an association of the cancer with an etiological factor (exposure) is studied, as cancer registry can provide only the cancer cases (and the population data). More information is frequently needed on the exposure and the researcher must collect data from various sources (e.g. pharmaceutical information from the Social Insurance Institution) and by various means (e.g. interviews, questionnaires).

There are situations when more information on the actual cancer case is also warranted. The cancer registry data are (and have to be, in order to remain manageable) simplified, and consequently sometimes lack information on the cancer case that was already available at the time of completing the cancer registry report. Also, the time of completing the report is important (impact on e.g. TNM classification, treatment(s)). All the information accessible (on the cancer) to the clinician filling the cancer report is not submitted; examples on this would be the size, proliferation index or the specific location of the tumour. Even if a TNM classification of malignant tumours is used in the cancer registry data, it does not specify the accurate size of the tumour or the biological aggressiveness of the cancer (e.g. grade Ki-67 protein), which both have an impact on the behaviour of the tumour and on survival and mortality (thus, prevalence) of the patient. In a similar fashion, the specific location of the tumour is in certain situations very important, as it affects e.g. treatment options (possibilities of surgical procedures). When this further information is needed, the researcher must return to the primary source of information, i.e. medical records.

In this thesis, the information on the location of gliomas was used. Knowledge on the location is readily available already for the clinician completing the cancer registry report, however for this dissertation medical records of the patients had to be reviewed to obtain this information. Not only is the specific location of a brain tumour important when considering different possibilities of treatment, but it may be relevant for etiological studies, too.

The location of gliomas was used as an outcome both independently and in association with mobile phones. If considering for example mobile phone as a potential etiological factor of intracranial tumours, it is far more relevant to study the influence of RF field of a mobile phone in relation to the specific location of the tumour rather than a crude approximation of the location (e.g. side of head). If the RF fields emitted by mobile phones increased the numbers of intracranial tumours, the excess would occur most typically in the anatomic sites in proximity to mobile phones, i.e. in frontal and temporal lobes and by the ear (e.g. VS). This assumption for a preferential location is justified by some highly localized nature of the exposure due to the energy absorbed from the RF fields of mobile phones being strongly dependent on the distance from the source of exposure.

### 6.2.1. Specific topographical locations of gliomas

Gliomas can evolve anywhere within the glial tissue, yet we found a larger number of gliomas frontally and temporally, even after accounting for differences

in the masses of the cerebral lobes. The smaller study based solely on Finnish gliomas, showed prominence in the anterior and superior parts of the brain (III). The study based on the multinational material focused on the location of gliomas in relation to the typical position of a mobile phone, yet in the same fashion as with the Finnish data, most of the gliomas were situated in the frontal and temporal lobes (IV).

In several studies, focusing on different subtypes of gliomas, the locations of gliomas were comparable to our study. The percentages of gliomas in the frontal lobe ranged 42–53%, 23–31% in the temporal, 11–25% in the parietal and 2–3% in the occipital cerebral lobe with GBM, low-grade glioma (not otherwise specified) and oligodendroglioma (Simpson et al. 1993, Zlatescu et al. 2001, Johannesen et al. 2003). The results from the study III concurred with these estimates, though they were somewhat less frequently located in the frontal lobe (40%). Similarly, the study IV showed less cases frontally (35% of all brain), but more cases occipitally (6%).

In a study from Sweden, astrocytoma cases were less frequently located in the frontal lobe (32%) and more frequently in the occipital lobe (4%) than in previous studies, temporal and parietal lobes being presented in the same frequencies (Hardell and Carlberg 2009). Yet, the proportion of multiple locations or unknown data were up to one fourth of all the indicated locations.

The location of gliomas reported by CBTRUS differed from our results, as in the CBTRUS report gliomas were located less frequently in the frontal (25%) and temporal lobes (20%) than in our data, whereas parietal (13%) and occipital (3%) lobes were more similarly represented (CBTRUS 2010). However, only 61% of gliomas reported to CBTRUS are registered as being located in the cerebral lobes, whereas in our data 86% (III) and 83% (IV) of the gliomas were assigned to a cerebral lobe. The unspecific location of 'other brain' was used in our data in <1% (III) and 6% (IV) of gliomas ('other brain' or information on the crude location missing), whereas in the CBTRUS data in 20% of gliomas (CBTRUS 2010). If the information on the location of 'other brain' was evaluated in the CBTRUS data, estimating a similar proportion of cases in the cerebral lobes (approximately 85%) as in our studies, the frequencies of glioma cases also in the frontal and temporal lobes would be more similar to previous publications; 35% in the frontal and 28% in the temporal lobe. Anatomic sites in the frontal and temporal lobes are more ambiguously defined (thus, more easily indicated as 'other brain') than other parts of the brain, including parietal and occipital lobes, as their anatomy is relatively complex. For instance, gliomas of the sphenoidal wing were coded to the frontal lobe in our data (III), whereas those gliomas could be well justified as being located in the 'other brain' (discussed in **4.1.3.1.**).

In addition, the information on the two datasets, our data (based on the Interphone material) and CBTRUS data, are not fully comparable with each other. The CBTRUS database has been developed by compiling data from state cancer registries, which have some differences in their registry structures and methods (Curado et al. 2007). The cases from the Interphone data included only patients who had given a consent to participate in a case-control study, with possible selection bias present. The participants were more often highly educated and regular mobile phone users. The populations in the participating countries of the Interphone study and the US population may differ. Still, these differences in population or registries are not expected to influence the locations of tumours substantially, but the differences are instead due to diversity in coding the topographical location.

#### 6.2.1.1. Preferential locations of gliomas

Our studies did not address the reason why gliomas are located in some typical locations rather than in others, apart from the relation with mobile phones (IV). However, the distribution of gliomas within the brain was certainly heterogeneous.

The reason, why there are more gliomas in certain anatomic locations of brain, has not yet been widely studied, but several hypotheses have been proposed. These include mainly internal factors (characteristics of certain areas in the brain tissue) instead of external causes (such as radiation).

Heterogeneity of energy metabolism and differences in extracellular matrix in different parts of the brain may offer an explanation for the diversity in brain tumour locations (Goldbrunner et al. 1999, Aubert et al. 2002, Gibson et al. 2007). It is not yet known if differences in energy metabolism influence the location of brain tumours, but areas with high and low neural activation differ substantially (brain being activation-dependent), e.g. in the consistency of mitochondria with more enzymes in other parts than others (Aubert et al. 2002, Gibson et al. 2007). Glioma cell invasion into the adjacent brain tissue is dependent on the interaction of glioma cells with the extracellular matrix and the subsequent destruction of matrix barriers (Goldbrunner et al. 1999). Differences in neural activation in different parts of the brain may influence the transformation of certain glial cells into gliomas, as neural activity influences regulation of glial cells (e.g. proliferation, differentiation and myelination) (Fields and Stevens-Graham 2002). An allelic loss (in chromosomes 1p and 19q) has been associated with location of oligodendroglioma, with a lower frequency of oligodendrogliomas in the temporal lobe versus frontal lobe (Zlatescu et al. 2001). It has also been speculated that the uneven topographical pattern within the brain tissue may be due to the differences in cytological distribution (different

cell-types in different areas of brain) in the brain, with a majority of low-grade gliomas located in supplementary motor area and insular region with specific cell types (an excess of agranular cells) (Duffau and Capelle 2004). The reason for the more frequent location close to agranular cells is unknown (Duffau and Capelle 2004).

### 6.2.2. The association of mobile phone use and location of gliomas

An interesting possibility affecting the anatomic site of a brain tumour, in addition to the natural variation of locations for various reasons (as stated above), is the proximity to mobile phones. Cardis et al. (2008) showed that whatever the frequency band of the mobile phone, 97–99% of the energy is absorbed to the hemisphere next to the mobile phone, and 50–60% of the energy remains in the temporal lobe.

Our study showed no excess numbers of gliomas in the proximity of the source of exposure (mobile phone). We did not find gliomas located more frequently in the temporal lobe among mobile phone users than never-regular users. Gliomas were more frequently closest to the source of exposure among contralateral than ipsilateral users, even if nearly all of RF energy is absorbed to the hemisphere close to the phone (Cardis et al. 2008). In conclusion, we did not find evidence suggesting gliomas being located closer to the mobile phone among regular mobile phone users than never-regular users.

In this thesis a novel approach to studying gliomas in relation to the specific location was utilized (III, IV). The approach was used for studying the etiology of gliomas and the focal effects of RF fields emitted by mobile phones. Most previous studies have concentrated on crude indicators of phone use, however our method with specific tumour location enabled focusing on risk in relation to the expected distribution of the RF field within the brain. This method offers a physically and biologically more meaningful and more specific measure of RF exposure compared with phone usage pattern. The method of using data based on specific anatomic locations of gliomas has rarely been applied, and especially not in relation to mobile phones (Takebayashi et al. 2008, Hartikka et al. 2009).

The strength of these studies was in the accuracy of the information on tumour location (III, IV). In this thesis, the specific locations (mid-points of the tumour) were unambiguously defined by neuroradiologists from radiological images. Even if the mid-points were assigned separately in each country (by one or several neuroradiologist(s)), the consistency of the data should be high, as defining the mid-point of each glioma was done from unequivocal radiologic images (CT/MRI). Also, the mean distances from the gliomas to

the source of exposure were relatively similar between countries indicating that there is no substantial information bias due to variation of procedures between countries (IV). Previous studies with brain tumour site have only used information on brain lobe, apart from few studies based on locations obtained from 3D-radiological images (from CT/MRI) (but these have not been analysed applying any 3D-designs) (Duffau and Capelle 2004, Takebayashi et al. 2008, Hartikka et al. 2009).

Yet, even if the use of accurate location is seen as a major advantage in this thesis, defining the point of origin of the tumour instead of the mid-point of the tumour would be more relevant for studying the effects of the RF field distribution in the brain. Unfortunately, this cannot be done at the time of tumour diagnosis, as the point of origin is no longer identifiable at that time. Thus, the mid-point is considered as the best estimate of the original location of the glioma.

The mid-point is a crude measure with limitations especially for irregularly shaped, large gliomas close to the margin of the brain tissue. The size of gliomas in relation to mobile phone use has been reported being smaller in regular phone users, but with a relatively small number of glioma cases (Christensen et al. 2005). However, larger tumour size for VS among regular phone users than never-regular users has been observed, though no association with amount of use was found (Christensen et al. 2004). It is possible that larger gliomas do not grow symmetrically around their point of origin, but e.g. towards the centre of the brain, thus the mid-point being further from the cortex and also further from the source of exposure. Larger glioma size among mobile phone users could therefore potentially cause a bias towards the null. In our study, gliomas with several mid-points (i.e. a more irregular tumour) were slightly further away from the exposure line than those with only one mid-point (6.44 cm vs. 6.22, $p = 0.15$).

Only one of the four studies included in this thesis concentrated on mobile phones. Based on that study, gliomas were not located nearer to the source of EMF exposure (typical position of a mobile phone during use), which would indicate that the RF fields emitted by mobile phones do not seem to increase the risk of gliomas. Cumulative call-time, duration of use and laterality were not consistently associated with the location of the gliomas. Yet, the effects of mobile phones may be related to other exposure characteristics than field strength, that is, to another exposure characteristic (such as frequency or modulation), but this is highly implausible.

#### 6.2.2.1. Location of gliomas using case-specular design

Some of the study methods used were novel and unique in this study setting (IV). The case-specular method has not been used in brain tumour studies earlier.

The analysis is similar to a case-case study, but potential confounding is avoided by having identical cases apart from the location. The case-specular method can be applied in a situation where cases are the only subjects available to test a certain hypothesis (such as assessing location of a case from a defined source of exposure with no controls available) (Rothman et al. 2008). This study method can be used if the exposure under study is defined by proximity to a source of environmental exposure and the distance between the source of exposure and the subject (case) can be determined unambiguously.

The case-specular method has opened new possibilities for research. Previously, the study approach has only been used to investigate the association of residential EMF from powerlines and childhood cancer (Zaffanella et al. 1998, Ebi et al. 1999). In these studies, the geographical location of the residence in relation to power line was the exposure indicator, for which specular pairs were formed. In our study, hypothetical glioma locations were obtained following the same principle. To the author's knowledge, this was the first time the case-specular method was applied using the anatomic tumour location (or any other anatomic, rather than a geographical, setting). The advantage of using specular locations as controls was to obtain an objective exposure indicator. As only cases were included, the locations of the hypothetical controls (i.e. speculars) had to be constructed.

When defining the locations of speculars, the locations of glioma cases were explicitly determined, but the sites of specular locations were constructed as a 'mirror image' through a hypothetical focal point (centre-point) of the brain. The choice of the focal point was considered carefully, as this naturally affected the entire case-specular analysis by defining the specular locations, and thus their distances from the exposure source. The anatomic centre-point of the brain was first considered as being unambiguous. However, as there is heterogeneity and asymmetry in the location of gliomas, the use of the centre-point may result in biased results. Thus the mean of the mid-points of gliomas among unexposed cases was chosen as the centre-point (for the 'mirror imaging'), according to the null hypothesis (i.e. location of gliomas is similar among regular and never-regular mobile phone users).

The use of case-specular method in an anatomic setting provided new comprehension on the method's potential. This method would be useful in other study questions with anatomic settings and a well located exposure, especially as the method is devoid of confounding (in comparison to case-case-studies). However, the anatomical setting (organ or tissue) should be homogenous and preferably symmetric in form, which limits the use of the method, and the exposure should be more or less linearily dependent on the distance from a specific (point) source (e.g. ultrasound, brachytherapy).

#### 6.2.2.2. Methodological considerations in mobile phone studies

Completely new potential risk factors for intracranial tumours emerge seldom. As the established risk factors for intracranial tumours at present are scarce, further variations of the known risk factors are developed with difficulty. Cohort studies are laborious to conduct, as brain cancer is a rare disease. Since the beginning of mobile phone technology, mobile phone use has interested greatly researchers studying the etiology of brain tumours. Therefore, despite the relatively short time that mobile phone technology has existed, several meta-analysis reviews, and consensuses, have been conducted based on the published studies (Lahkola et al. 2006, Hardell et al. 2008, Kan et al. 2008, Ahlbom et al. 2009, Myung et al. 2009, SCENIHR 2009). However, there are certain methodological problems that must be taken into account when studying mobile phones and their possible health effects. Even if only one of the four studies in this thesis regarded the potential association of mobile phone use and intracranial tumours, these methodological questions have been so important (and debated) in all mobile phone and brain tumour studies that they cannot be overlooked in this thesis.

First, in epidemiological studies the agent conferring the risk should be measured accurately. Yet, the optimal (most relevant) exposure metric is unknown for mobile phones, as the mechanism of action remains unknown. The exposure assessment has been considerably crude in all epidemiological studies on mobile phones conducted so far. Information on call-time has been used in addition to laterality (of use), and whether the phone is analogue or digital, but no assessment of exposure intensity has been done in most of the studies (proxy indicators have been e.g. number of calls per day or hours of use per month).

The absorption of electromagnetic energy to the body from a mobile phone is determined by several factors (e.g. mobile phone model, network characteristics (such as distance from the base station, presence of physical obstacles), anatomical characteristics of the user, habits of use (such as indoor vs. outdoor use, speaking vs. listening)). Phone models, and thus their SAR-values, vary substantially (Chan et al. 2004, Kuster et al. 2004). Different systems have been used (e.g. NMT, GSM), which complicate the comparison of long-term use (Hansson Mild et al. 2005). The mobile phone types vary in their emitted power levels; analogue NMT phones emit radiation at a constant power level of 1 W during speech, while digital GSM phones adapt the power level using pulsed signals with an average output power level of 0.25 W or 0.125 W (Jokela et al. 2006). Power levels of mobile phones differ also in urban and rural areas. A Swedish study showed that mobile phone calls in the rural area in Sweden operate at output power levels higher than in any other areas, which probably is explained by the lower density of base stations (Lönn et al. 2004b). In Italy more

substantial differences were observed between indoor and outdoor use (Ardoino et al. 2004), while in the USA regional differences dominated (Erdreich et al. 2007, Morrissey 2007).

Second, in epidemiological studies, the duration of exposure should be a considerable fraction of the etiologically relevant time period in disease development (carcinogenesis). In our study, only 42 cases had used mobile phone for over ten years, thus even if there were some associations with long-term use, the power to detect an effect of long-term exposure was low (IV). At present the longest times of mobile phone use are approximately twenty years. It is believed that the induction of a radiation-induced solid cancer takes at least ten years (UNSCEAR 2000, Lönn et al. 2005). The induction periods for meningiomas and VS are believed to be 20 to 40 years and also decades for gliomas (Kundi 2009). However, even if an influence during the initiation phase cannot be excluded, the current opinion is that if there is an effect at all, it is an effect on tumour promotion or progression rather than on initiation (Muscat et al. 2000). Thus, EMF is hardly an initiator of the process of malignancy.

Third, specific types of a disease (histological types of tumour) should be homogeneous enough to assume a similar etiology. However, brain tumours are histologically a highly variable group not supporting the assumption of uniform etiology. In addition to being histologically vague as a group, even histopathologically similar brain tumours are at certain extent believed to have varying patterns of development, and thus also different etiology (at molecular and genetic level). Such an example would be GBM, which is now believed to develop by one of at least two pathways: either by progression from a lower grade astrocytoma, associated with TP53 mutation, or as a *de novo* GBM, associated with EGFR amplification (epidermal growth factor receptor oncogene) (Schwartzbaum et al. 2006). On the other hand, with some cancer types that are histologically unlike, a common risk factor can be demonstrated (e.g. tobacco associated with both small cell and squamous cell carcinoma of the lung).

Despite these deficiencies described above, some of the common problems encountered in most mobile phone and intracranial tumour studies (most being case-control studies) have been avoided in our study (IV). As controls were not used in our study, selection bias due to lower participation than among cases (related to e.g. education) was avoided. In a Finnish study, non-participants (subjects who declined the full interview on mobile phone use in the Finnish part of the Interphone study, but took part in a brief telephone interview focusing on mobile phone use) used less mobile phones than participants among both cases and controls, thus reducing slightly the magnitude of the result (i.e. the potentially observed association of mobile phones and intracranial tumours)

(Lahkola et al. 2005). Mobile phone users tend to estimate wrongly the duration of their calls; light users underestimated and heavy users overestimated their mobile phone use (Vrijheid et al. 2006). In addition, especially gliomas may severely affect the cognitive functions of a patient leading to problems in remembering correctly the usage. Throughout the Interphone data, glioma cases had a higher proportion of subjects judged by their interviewer to having poor memory or to be non-responsive, than the controls (Cardis et al. 2010).

One common concern is that interviewed brain tumour patients may memorize having used mobile phone more on the side of the tumour than on the opposite ('healthy') side. In our study this recall bias (of laterality of use) was avoided, as the laterality of use was not considered (except in a sub-analysis) and the distances were calculated to the exposure line on the same side as the glioma irrespective to the reported side of phone use.

Based on the Interphone protocol, regular mobile phone users were defined as those having used mobile phone over six months at least once a week. Mobile phone use in the eighteen months prior to glioma diagnosis was excluded from the analyses, as well as use of hands-free-devices. Use of cordless phones (DECT) was not analysed. This definition of a regular vs. never-regular mobile phone user is unambiguous, yet not the best form of classification, as it is much more relevant to focus on the cumulative time of usage. Therefore, the cumulative time was used in our analyses as one of the main exposure indicators.

The typical location of the mobile phone was defined as a line from the external orifice of the ear canal to the corner of the mouth (IV). The entire phone was considered as the source of exposure, as most GSM phones use an integrated antenna, thus the whole body of the phone emits a RF field. Analyses where NMT phones were separated from GSM phones (NMT with a typically external antenna) were originally conducted in a sub-analysis (IV), but in those analyses simply the differences in distance of the glioma from the source of exposure were compared (expecting a similar exposure line for NMT and GSM phones). The results obtained using cumulative call-time divided by phone type were overall similar to the crude cumulative call-time. Further meaningful analyses assuming the exposure from the NMT phone emitted from an estimated point (location of the antenna) could not be done for various reasons (e.g. estimating location of the antenna was difficult; there were only less than twenty cases who had used an NMT phone only).

The Interphone data were used in this thesis for two studies (III, IV). As discussed earlier (above, and see also section **2.2.1.9.**), there are various methodological considerations for mobile phone studies in general and also for the Interphone study. However, these concerns are mainly related to the characteristics of mobile phone use and selection of cases (to the case-control

studies), and thus the part of the data on precise locations of gliomas should not be influenced (IV).

The results from the Interphone study were finally published in 2010, with no consistent evidence for an association with intracranial tumours and mobile phone use (Cardis et al. (The Interphone Study Group) 2010). But even so, even with no association in the largest study at present on intracranial tumours and mobile phones, controversy whether mobile phones and brain cancer are related will most definitely continue – as will the discussion on the methodological *pro*s and *con*s in all the currently available literature on the topic (Peres 2010). Hopefully the new Cosmos study will find answers to these questions – and with less methodological controversies (Schüz et al. 2010).

# 7. Summary and conclusions

**I** None of the five data sources including the Finnish Cancer Registry had a comprehensive coverage of meningioma cases. Completeness of the FCR was approximately two-thirds of all cases. The highest coverage (69%) was in the dataset from the neurosurgical department. The best estimate of the incidence rates of meningiomas were a third higher than those reported by the FCR.

**II** The overall incidence of VS increased in all the four Nordic countries combined between 1987 and 2007, with notable differences between countries. However, the increase in rates more or less stabilized in the late 1990s, showing relatively constant incidence rates and even some decline after year 2000. The practices of registering (classifying and reporting) VS cases varied in great extent, both over time and between the countries, which renders the interpretation of the results difficult.

**III** Locations of gliomas showed an uneven distribution within the brain. The frequencies of occurrence varied substantially between the cerebral lobes. Even after accounting for different tissue volume of the lobes, gliomas were located considerably more frequently in the frontal and temporal lobes relative to the occipital lobe (4–5 fold), followed by parietal lobe (two-fold). Statistically significant clustering of gliomas was found in the 3D-analysis. Gliomas arose most frequently in the anterior subcortical part of the brain.

**IV** The hypothesis of gliomas being located in the parts of the brain with the highest exposure from mobile phones was not supported by our study. In the case-case analysis, gliomas among never-regular and contralateral users had a shorter distance between glioma mid-point and the source of exposure (mobile phone) than regular and ipsilateral users. Even if the glioma cases were located closer to the mobile phone more frequently than the speculars in the case-specular analysis (OR > 1 by all exposure characteristics that distance between glioma and mobile phone ≤ 5 cm in comparison to speculars), this was not observed in relation to the amount of mobile phone use. Glioma cases were closer to the exposure line among long-term users compared to speculars (OR 2.0; 95% CI, 0.68–5.85), but the differences remained non-significant.

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# Erratum

Original article I: In table 1 the number of meningiomas reported to the FCR for the age group 50 to 59 should read six instead of five.

I

LARJAVAARA S, HAAPASALO H, SANKILA R, HELÉN P and AUVINEN A (2008): Is the incidence of meningiomas underestimated? A regional survey. Br J Cancer 99:182–184.

Short Communication

# Is the incidence of meningiomas underestimated? A regional survey

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**Keywords:** bias; incidence; meningioma; registries

**Abstract:** We assessed the undercount of meningiomas in a population-based cancer registry. A comprehensive material was formed by compiling hospital sources with the Finnish Cancer Registry database. The completeness of each source ranged 62 – 69%. The corrected age-standardised meningioma incidence was 2.9/100 000 for men and 13.0/100 000 for women, a third higher than the cancer registry figures.

Meningiomas are typically benign tumours, arising from the meninges of the brain (in at least 90% of the cases) and the spinal cord (Berger and Prados, 2004). They are benign in more than 90% of the cases, borderline/atypical in approximately 5% of the cases and malignant in less than 5% of the cases (Claus *et al*, 2005). Meningiomas are the most frequently reported intracranial tumours, accounting for approximately one-fourth of all reported primary brain neoplasms (Surawicz *et al*, 1999; Claus *et al*, 2005).

The age-standardised (world population) national incidence rates of meningiomas reported by the Finnish Cancer Registry (FCR) are 1.6 per 100 000 for men and 5.5 for women in 2001. The corresponding rates in the Nordic countries are 1.9 and 4.5 per 100 000 person-years, respectively (Klaeboe *et al*, 2005). In the United States, the incidence rates with similar age-standardisation estimated from figures provided by the Central Brain

Tumor Registry of the United States were 1.8 for men and 4.2 per 100 000 for women in 2006. Incidence of meningiomas varies depending on whether autopsies are included or not (Haddad *et al*, 2003).

Increasing incidence rates of meningiomas have been reported from several industrialised countries since the early 1980's (Christensen *et al*, 2003; Klaeboe *et al*, 2005), and the increase is most pronounced in older age groups (Maurice-Williams and Kitchen, 1993). The increase among the elderly can be explained by several factors. Indolent cases unrelated to the symptom for which the examination was conducted (eg, post-traumatic computerised tomography (CT)) are likely to be most common in older age groups. Also, introduction of new radiological techniques has allowed more non-invasive examinations for inoperable patients.

As meningiomas are benign in at least 9 out of 10 cases, they are not covered by most cancer registries. Nevertheless, in Finland, as in other Nordic countries, all physicians, pathologic laboratories and hospitals are obliged to report all tumours of the central nervous system, both malignant and benign, to the cancer registry.

The nationwide, population-based FCR has a practically complete coverage of solid cancer cases in Finland (Teppo *et al*, 1994). However, the registration of benign tumours of the central nervous system is not as complete as that of malignant neoplasms. Particularly, cases that are not treated surgically and lack histological confirmation are likely to be under-reported.

The aim of our study was to quantify undercount in the cancer registry and provide corrected estimates of meningioma incidence.

## MATERIALS AND METHODS

The meningioma cases were identified from Pirkanmaa Hospital District in Finland, which is the catchment area for Tampere University Hospital with a population of 447 051 in 2000. The study period was from November 2000 through June 2001 (eight months).

The cases were identified from four clinical data sources within Tampere University Hospital: (1) neurosurgical clinic; (2) pathology database; (3) hospital discharge database and (4) autopsy database. The department of neurosurgery provided a list of cases seen by their neurosurgeons, including operated and non-operated cases, outpatients and consultations on patients at other units. The pathology database included all cases diagnosed at the pathology unit (including biopsy). An autopsy database with diagnoses made in post-mortem examinations was also used. The hospital discharge database covers the major diagnoses of all in-patients admitted to the hospital.

The cases based on these clinical data sources and verified from the hospital records were compared with the case list of meningioma patients retrieved from the FCR. Information extracted from each source included the national unique personal identification number,

place of residence, diagnosis, date of diagnosis and method of confirmation. Only residents in municipalities within the Pirkanmaa Hospital District were included. Only incident intracranial meningioma cases from November 2000 till June 2001 were included in this study.

The permission to obtain data from the FCR was granted by the National Research and Development Centre for Welfare and Health (STAKES). The study involved no contact with patients and was, therefore, exempt from a written informed consent in accordance with the Finnish regulations.

The world standard population was used in the age-standardisation (Segi, 1960). The incidence rates were calculated in 5-year age groups (even though presented in 10-year age groups in the tables). Confidence intervals (CIs) for the incidence rates were calculated assuming that the observed numbers of meningioma cases followed a Poisson distribution (Breslow and Day, 1987). CI for cancer registry coverage was estimated applying the general formula for the CI of a proportion.

## RESULTS

Altogether, 42 incident intracranial meningioma patients were identified. The data sources from different hospitals identified a total of 39 patients and the FCR had information on 3 additional patients.

Altogether, the FCR covered 29 intracranial meningiomas during the study period. Of those, 27 fulfilled the inclusion criteria, whereas 2 were not incident cases, but recurrences.

Twenty-nine patients with newly diagnosed meningiomas were identified from the records of the neurosurgical department of Tampere University Hospital. Eighteen patients were operated on and 11 were treated conservatively. Twenty-six patients were identified from the Tampere University Hospital discharge database. Twenty-six patients fulfilling our definitions were found from the pathology database. Two of them were incidental cases detected in the 210 autopsies performed during the study period (*Table 1*).

Of the clinically recorded 39 patients, the FCR had registered 24. Of the 15 missing cases, 2 were found in the hospital discharge register only, based on radiological confirmation. No clinical or pathological cancer registry notifications were received at the FCR for 13 patients; 9 with a clinical diagnosis and 4 with a pathological verification.

The FCR had information on three patients not found in the clinical records: one was a histologically verified case and two were suspected meningiomas based on radiological findings only. All three were in-patients at the Tampere University Hospital, but without a discharge diagnosis of meningioma.

The cancer registry covered 27 of the 42 meningiomas (64%). The completeness of the FCR was 69% (95% CI, 55 – 83) of the 42 cases fulfilling the criteria, including the 2 recurrent cases.

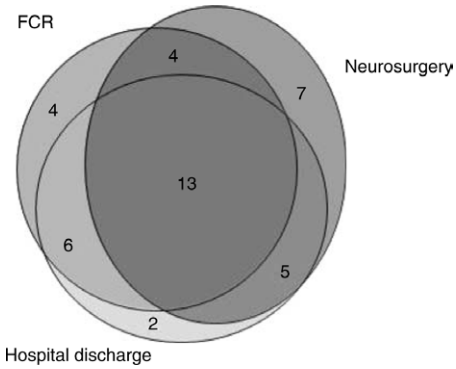


**FIGURE 1. The numbers of meningioma cases from Pirkanmaa Hospital District in the Finnish Cancer Registry, Tampere University Hospital discharge registry and neurosurgical department patient list, November 2000 – June 2001. The area reflects the number of cases in each source and their overlap.**

Of the 42 cases, only 11 (26%) were found in all the four data sources (autopsy database excluded). Only 13 (31%), including the previously mentioned 11 were covered by the three most comprehensive sources of information: neurosurgery department, hospital discharge database and FCR (*Figure 1*).

Diagnoses were histologically confirmed in 28 (67%) cases and based only on radiological finding (CT and/or MRI) in 14 (33%) cases. Under-registration was most common in cases aged 80 years and older (27%), as well as cases confirmed only radiologically (29%) (*Table 1*).

The age-standardised incidence rate of the cases from the FCR was 2.2 per 100 000 (95% CI, 0.3 – 4.1) for men and 9.6 (95% CI, 5.6 – 13.6) for women. The corresponding incidence rates for the best estimates were 2.9 per 100 000 person-years (95% CI, 0.7 – 5.0) for men, and 13.0 (95% CI, 8.7 – 17.3) for women.

**TABLE I. Number of meningioma cases by gender, age, hospital sources and diagnostic confirmation found and missing in the Finnish Cander Registry.**

| | Finnish Cancer Registry | | |
|---|---|---|---|
| | **Yes** | **No** | **Total** |
| **Gender** | | | |
| Male | 5 | 2 | 7 |
| Female | 22 | 13 | 35 |
| **Age (years)** | | | |
| 15 – 49 | 6 | 1 | 7 |
| 50 – 59 | 5 | 2 | 7 |
| 60 – 69 | 8 | 4 | 12 |
| 70 – 79 | 4 | 1 | 5 |
| 80 – | 3 | 8 | 11 |
| **Hospital source** | | | |
| Pathology | 22 | 4 | 26 |
| Neurosurgery | 17 | 12 | 29 |
| Hospital discharge registry | 19 | 7 | 26 |
| **Diagnostic confirmation** | | | |
| Radiological | 4 | 10 | 14 |
| Microscopic[a] | 23 | 5 | 28 |

[a] With or without radiological support for the diagnosis.

## DISCUSSION

None of the five sources including the cancer registry had a comprehensive coverage of meningioma cases. Completeness of the cancer registry was approximately two-thirds of all cases. The corrected incidence rates were a third higher than those reported by the cancer registry.

In our study, the corrected age-standardised incidence rates were 2.9 per 100 000 person-years for men, and 13.0 for women compared with 2.2 per 100 000 for men and 9.6 for women based on cancer registry data alone. The CIs (95%) for the incidence rates did, however, overlap, indicating that the estimates are compatible with each other. The study was limited by the small number of meningiomas. Nevertheless, bias such as under-registration is evaluated based on point estimates, not statistical significance. Despite this limitation, the study succeeded in identifying undercount in registration and providing corrected estimates of meningioma incidence.

There are several reasons for meningiomas not being notified to the FCR, such as asymptomatic meningiomas being followed clinically. In addition, incidental meningiomas, detected at autopsy may not be reported. However, only two meningiomas were found at autopsy in our study. This is less than anticipated, as the proportion of meningiomas in autopsies has been estimated to be as high as a quarter (Klaeboe *et al*, 2005). Also, incidental meningiomas were found in almost 1% of asymptomatic volunteers in a recent study (Vernooij *et al*, 2007).

Our results indicate that the incidence of meningiomas is considerably underestimated. We were able to obtain corrected incidence rates, which provide a more valid indication of the occurrence and disease burden than those based on a single data source. The findings also provide guidance for the conduct of not only occurrence studies, but also etiologic and prognostic studies, as they emphasise the need for case ascertainment and recruitment from several sources.

## ACKNOWLEDGEMENTS

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**II**

**LARJAVAARA S, FEYCHTING M, SANKILA R, JOHANSEN C, KLAEBOE L, SCHÜZ J and AUVINEN A: Incidence trends of vestibular schwannomas in Denmark, Finland, Norway and Sweden in 1987–2007. (Submitted)**

# Incidence trends of vestibular schwannomas

## in Denmark, Finland, Norway and Sweden in 1987–2007

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**Keywords:** neuroma, acoustic; incidence; registries

**Abstract:** BACKGROUND. The reported incidence rates of vestibular schwannomas (VS) vary substantially, but it is unclear to what extent the variation reflects differences in risk or recording practices. Our aim was to describe the incidence rates of VS in Denmark, Finland, Norway and Sweden between 1987 and 2007.

METHODS. Comprehensive data were available from all registries only for the period from 1987 to 2007. An analysis of a longer time period (1965 – 2007) was conducted with the Norwegian and Swedish data.

RESULTS. The average age-standardized incidence rates during 1987 – 2007 varied from 6.1 per 1,000,000 person-years (95% CI, 5.4 – 6.7) among Finnish men to 11.6 (95% CI, 10.4 – 12.7) in Danish men, and from 6.4 per 1,000,000 person-years (95% CI, 5.7 – 7.0) among Swedish women to 11.6 (95% CI, 10.5 – 12.8) among Danish women. An overall annual increase of 2.8% (95% CI 2.3 – 3.2) was observed when all countries and both sexes were combined, with considerable differences between countries. However, the practices of both reporting and coding VS cases varied markedly between countries and over time, which poses a challenge for interpretation of the results.

CONCLUSION. The overall incidence of VS increased in all the four Nordic countries combined between 1987 and 2007, with marked differences between countries. However, the incidence rates more or less stabilized in the late 1990's, showing relatively constant incidence rates and even some decline after 2000.

# INTRODUCTION

Vestibular schwannomas (VS), or acoustic neuromas (or neurinomas), are benign intracranial tumours of the eighth cranial nerve. They develop from glial Schwann cells, which insulate neuronal axons in peripheral nerves in a similar fashion as olidendroglia in the brain. Schwannomas account for approximately 8% of all intracranial neoplasms (Louis *et al*, 2007). VS constitute approximately 60% of all schwannomas (Weller and Cervos-Navarro 1977) and roughly 90% of intracranial schwannomas (Sarma *et al*, 2002; Propp *et al*, 2006).

The aetiology of VS is poorly known. Several risk factors have been proposed, such as radiation exposure in childhood (Schneider *et al*, 2008), loud noise (Edwards *et al*, 2006; Schlehofer *et al*, 2007, Hours *et al*, 2009), allergies (Schlehofer *et al*, 2007), epilepsy (Schoemaker *et al*, 2007), radiofrequency electromagnetic fields induced by long-term mobile phone use (Schoemaker *et al*, 2005; Khurana *et al*, 2009) and certain occupational exposures (Prochazka *et al*, 2010; Samkange-Zeeb *et al*, 2010). However, all these remain still tentative, due to lack of consistent evidence. The only well established aetiological factor at present is neurofibromatosis 2 (NF2) (Welling, 1998). NF2 accounts for less than 5% of all schwannoma cases (Louis *et al*, 2007), with carriers showing a 90-95% lifetime risk of VS, typically with multiple tumours (Asthagiri *et al*, 2009). The large majority of VS cases are, however, sporadic and of unknown aetiology (Louis *et al*, 2007).

The reported incidence rates of VS vary worldwide: from one to twenty cases per million inhabitants per year (Howitz *et al*, 2000; Tos *et al*, 2004; Gal *et al*, 2010). In addition to variation in risk between populations, this may reflect different classification systems with uncertain comparability between registries, as well as varying completeness of registration coverage.

The incidence rates of VS reported for various populations have been consistently increasing in the previous years (Stangerup *et al*, 2004; Tos *et al*, 2004; Propp *et al*, 2006). New diagnostic technologies (e.g. computerised tomography (CT) and magnetic resonance imaging (MRI)) or better awareness of both clinicians and symptomatic patients may have contributed to the increase. In addition, improved registration of brain neoplasms may have affected the reported incidence rates.

However, improvement in the coding systems may paradoxically decrease the numbers of recorded VS. As the classifications may have been inaccurate previously, schwannomas of other cranial nerve could not be distinguished from VS, which could inflate incidence rates (if interpreted as reflecting VS incidence). Thus, incidence could also be underestimated.

The aim of this study was to describe trends in incidence rates of VS in four Nordic countries between 1987 and 2007, and particularly to define temporal trends by country and age group. The major advantages of the material include a long study period and large population of roughly 24 million people.

## MATERIALS AND METHODS

We identified all incident cases of VS notified to the Danish, Finnish, Norwegian and Swedish cancer registries from 1987 to 2007. The annual population sizes by 5-year age group and sex were obtained from the national population registries. Autopsy cases were included (Curado *et al*, 2007).

In the Nordic countries, it is obligatory for all clinicians and pathologic laboratories to notify all malignant and benign neoplasms of brain and the central nervous system (CNS) to the national or regional cancer registries (Curado *et al*, 2007). The Danish Cancer Registry was founded in 1942, but the registration became compulsory by administrative order in 1987. In Finland the reporting of cancer cases has been compulsory since 1961, in Norway since 1953 and in Sweden since 1958.

All the four countries had their own coding systems, and the cancer registries in Norway and Sweden changed their classifications during the study period. In Norway and Sweden, the codes were based on various versions of the *International Classification of Diseases* (ICD) issued by the World Health Organization. However, in Denmark and Finland, national adaptations were used for VS, and these codes remained the same over the study period (*Table 1)*.

In Denmark, a Danish adaptation of ICD-7 was utilized (code 293.2 for VS) (*Table 1*). The coverage was not fully comprehensive before the year 1987, when the notification of malignant tumours as well as all brain and CNS tumours became obligatory in Denmark (compulsory by administrative order) (Curado *et al*, 2007). Incompleteness of the Danish VS data before 1987 has been reported in a previous study (Howitz *et al*, 2000). Due to the limitations of the Danish data in the early years (1965-1986), the main study period was chosen to be from 1987 to 2007.

The Finnish Cancer Registry had its own coding system modified from ICD-7 and *Manual of Tumor Nomenclature and Coding* (MoTNaC) codes, with a topological code for vestibular nerve (937) used with further specification for benign behaviour and histological type (neurinoma) (*Table 1*). These codes were converted into ICD-O-3-codes for the years 1979 – 2007. The Finnish data were comprehensive from 1979 onwards, but used from 1987 to 2007 (according to the common study period), with the exception of the analysis of age and birth cohort, where also data from 1979 to 1986 were included (1979 – 2007).

In Norway, the coding systems applied from 1965 to 1992 were ICD-7 (193.1 for malignant neoplasm of the spinal cord, used systematically for schwannomas for unknown reason, covering schwannomas of all cranial nerves) and MoTNaC (code 9560 for schwannoma). Later, from 1993 to 2007, the coding systems used were ICD-10 (C72.4 for neoplasm of the acoustic nerve) and MoTNaC (9560/09 for unspecified schwannoma and 9570/09 for neuroma of unspecified malignancy) (*Table 1*).

In Sweden, the older coding was used in parallel with the newer coding, i.e. the previous codes were recorded along with the newer codes when new coding practices were introduced.

**TABLE 1. Diagnostic classification of vestibular schwannoma by period and country.**

| Denmark | Finland | Norway | Sweden* |
|---|---|---|---|
| **1965–1986**<br>Incomplete coverage prior to 1987 | **1965–1978**<br>Incomplete coverage prior to 1979 | **1965–1992**<br>ICD-7 (193.1), MoTNaC (9560) | **1965–1986**<br>ICD-7 (193.0), PAD (451, 456) |
| | **1979–2007** | | |
| **1987–2007**<br>National variation of ICD-7 (293.2) | National coding system (937) | | **1987–1992**<br>ICD-9 (192.0), SNOMED (9560/0, 9560/3) |
| | | **1993–2007**<br>ICD-10 (C72.4), MoTNaC (9560/09, 9570/09) | **1993–2007**<br>ICD-10 (C72.4, C72.5, C72.9) **, SNOMED (9560/0, 9560/3; also 8000/0, 8000/3 with C72.5 or C72.9) |

* The coding guidelines to the Swedish cancer registry are presented, however former coding systems were used in parallel with the newer systems.
In this study we used for the main study period (1987–2007) ICD-9 (192.0) combined with PAD (451, 456), and for the total period (1965–2007) ICD-7 (193.0) with PAD (451, 456), to provide consistency.

** A substantial proportion of VS have been classified under the codes C72.5 (other and unspecified cranial nerve) and C72.9 (for central nervous system, unspecified) in previous Swedish VS studies (unpublished data).

The coding system used in Sweden from 1965 to 1986 was ICD-7 (193.0 for malignant neoplasm of brain, reason for the choice is uncertain) supplemented by a PAD (pathologic anatomic diagnosis) code (451 for neuroma and 456 for malignant neuroma). From 1987 to 1992, an ICD-9 code (192.0 for malignant neoplasm of cranial nerve) was utilized with SNOMED classification (*Systematized Nomenclature of Medicine*) (9560/0 for neuroma and 9560/3 for malignant neuroma). From 1993 to 2007, ICD-10 topography codes were used in combination with SNOMED codes (*Table 1*). However, as our primary interest was to evaluate the changes in incidence over time, for the period from 1987 to 2007 the coding ICD-9 (192.0) together with PAD (451, 456) was used (even if more specific coding (ICD-10) was available from 1993 onwards). PAD codes, instead of SNOMED codes, were used together with ICD-9 from 1987 to 2007, as SNOMED codes were missing in many cases, while PAD-codes were available for everyone.

For the longer study period from 1965 to 2007 analyses for incidence trends could be performed for Norway and Sweden. For Norway, the changes in coding could not be overcome, and we had to use two separate coding systems for 1965 – 1992 and for 1993 – 2007 (*Table 1*). Whereas in Sweden, a similar coding had been applied through the entire period (along with the new coding systems), i.e. ICD-7 (193.0) together with PAD (451, 456). Thus, this older system (ICD-7 coding) was used in these analyses for Sweden.

The sensitivity analyses of the changes in classification were performed for Norway and Sweden. The analyses were carried out to evaluate the potential impact of the unspecified data on the incidence trends. Before 1993 the Norwegian data included all schwannomas of the cranial nerves, whereas since the introduction of ICD-10-coding, vestibular schwannomas could be distinguished from other cranial schwannomas. Thus, assuming a stable ratio of non-vestibular schwannomas and VS, we could quantify the extent of bias in incidence rates and trends due to unspecific coding prior to 1993. In Sweden, the older coding system (ICD-9) was used for the main analyses in 1993 – 2007, in order to provide consistency over the years. However, we compared the rates obtained by different coding systems, using the older and newer systems, and evaluated the impact of the different coding systems on the trends.

We calculated the incidence rates by five-year age group and sex with age-standardisation to the world standard population (Segi, 1960). The results were calculated separately for each country and combined for age-specific analyses. The confidence intervals were estimated under the Poisson assumption, the incidence rates of VS were expected to follow the Poisson distribution.

The age groups for the age-specific analyses (0 to 44, 45 – 54, 55 – 64, 65 years and older) were formed aiming at similar numbers of cases in each group.

All data with complete coverage were combined (Denmark (1987 – 2007), Finland (1979 – 2007), Norway and Sweden (1965 – 2007)) in the analysis of age and birth cohort. This choice of accepting varying study periods, instead of only the common period of 1987 – 2007 for all countries, was reasoned to provide most information for the presentation.

For Norway and Sweden with longest period (1965 – 2007), we evaluated whether there is a difference in annual increase in incidence between the former and the latter part of the study period. The mid-point for this purpose was chosen to be the end of year 1985, thus forming two periods of similar length from 1965 to 1985 and from 1986 to 2006.

Poisson regression methods were used to estimate the average change over time. Likelihood ratio tests were applied to evaluate statistical significance of the interaction terms (nested within the main effect models) in the analyses of effect modification, i.e. variation in incidence trends by country, age group and sex. The departure from linearity was assessed comparing year as a continuous variable to three-year categories, also separately for each country.

*Stata 8.2* (StataCorp, College Station, Texas, USA) statistical software was utilized for all analyses.

## RESULTS

A total of 5,133 VS were registered during 1987 – 2007, of which 52% were in women (*Table 2*). When also the cases from 1965 in Sweden and Norway, and from 1979 in Finland, were included until the year 2007, the number increased to 6,911 (3,677 in women, 3,234 in men).

**TABLE 2. Number of VS for both sexes combined by three-year period in Denmark, Finland, Norway and Sweden in 1987 – 2007.**

| | 1987–1989 | 1990–1992 | 1993–1995 | 1996–1998 | 1999–2001 | 2002–2004 | 2005–2007 |
|---|---|---|---|---|---|---|---|
| **Denmark** | | | | | | | |
| Men | 69 | 82 | 98 | 138 | 156 | 159 | 173 |
| Female | 81 | 89 | 114 | 126 | 136 | 190 | 177 |
| **Total** | **150** | **171** | **212** | **264** | **292** | **349** | **350** |
| **Finland** | | | | | | | |
| Men | 56 | 51 | 50 | 71 | 71 | 56 | 59 |
| Female | 70 | 70 | 69 | 70 | 79 | 57 | 74 |
| **Total** | **126** | **121** | **119** | **141** | **150** | **113** | **133** |
| **Norway** | | | | | | | |
| Men | 30 | 46 | 42 | 78 | 90 | 85 | 91 |
| Female | 50 | 46 | 34 | 63 | 93 | 101 | 76 |
| **Total** | **80** | **92** | **76** | **141** | **183** | **186** | **167** |
| **Sweden** | | | | | | | |
| Men | 66 | 86 | 104 | 129 | 139 | 118 | 95 |
| Female | 85 | 75 | 139 | 139 | 133 | 113 | 96 |
| **Total** | **151** | **161** | **243** | **268** | **272** | **231** | **191** |

The crude average incidence rates by country were estimated for a period of 21 years (1987 – 2007). They varied among men from 7.9 per 1,000,000 person-years in Finland to 15.9 in Denmark and among women from 8.3 per 1,000,000 person-years in Sweden to 16.2 in Denmark (*Table 3).* As the world standard population has a higher proportion of younger age groups than the Nordic countries, the age-standardized rates were lower, ranging from 6.1 per 1,000,000 among Finnish men to 11.6 in Danish men. For women, the lowest rates were 6.4 per 1,000,000 in Sweden and highest 11.6 in Denmark (*Table 3).*

An increasing trend was observed in 1987 – 2007, when all countries and both sexes were combined (2.8% per year, 95% CI 2.3 – 3.2) (*Figures 1a, 1b*). The overall annual increase, estimated using Poisson regression, was 3.2% (95% CI, 2.5 – 3.9) for men and 2.4% (95% CI, 1.7 – 3.0) for women. There was borderline interaction between period and country indicating heterogeneity ($p = 0.04$). The trends were comparable for women and men ($p = 0.08$).

In country-specific analyses, the average annual increase ranged from 0.3% in Finland (95% CI, –1.3 to +1.9) to 5.0% in Denmark and Norway (95% CI, 3.8 – 6.2; 3.4 – 6.6;

**TABLE 3. Average incidence rates per 1,000,000 person-years and average annual increase in percentages (with 95% confidence intervals) in 1987–2007.**

| | Crude rate | Age-standardized | Annual increase (%) |
|---|---|---|---|
| **Denmark** | | | |
| Men | 15.9 (14.3–17.5) | 11.6 (10.4–12.7) | 5.0 (3.8–6.2) |
| Women | 16.2 (14.6–17.8) | 11.6 (10.5–12.8) | 4.5 (3.4–5.7) |
| **Finland** | | | |
| Men | 7.9 (7.1–8.7) | 6.1 (5.4–6.7) | 0.26 (–1.3, +1.9) |
| Women | 8.9 (8.0–9.8) | 6.9 (6.2–7.6) | –0.35 (–1.8, +1.1) |
| **Norway** | | | |
| Men | 9.9 (8.9–10.9) | 7.7 (6.9–8.5) | 5.0 (3.4–6.6) |
| Women | 9.8 (8.8–10.8) | 7.5 (6.7–8.2) | 4.1 (2.5–5.7) |
| **Sweden** | | | |
| Men | 8.0 (7.2–8.9) | 6.2 (5.6–6.8) | 1.8 (0.55–3.0) |
| Women | 8.3 (7.5–9.2) | 6.4 (5.7–7.0) | 0.67 (–0.49, +1.9) |

respectively) for men, and for women from a decrease of 0.4% in Finland (95% CI, –1.8 to +1.1) to an increase of 4.5% in Denmark (95% CI, 3.4–5.7). However, the increasing trend was not statistically significant among women in Finland and Sweden or men in Finland, and in women in Finland the average trend was decreasing (*Table 3*). Still, there was a statistically non-significant annual increase also for Finnish women (0.77% (95% CI, –0.16 to +1.7)) when evaluated through 1979–2007. There was no statistically significant departure from linearity in any country (p = 0.72) (*Figures 1a, 1b*).

Incidence increased (with a lower confidence limit above zero) during the study period in all age groups, except in women aged 55 to 64 years (increase of 1.0% (95% CI, –0.21 to +2.2)) (*Figures 2a, 2b*). The incidence trends did not show heterogeneity by age group in the analyses of effect modification (p = 0.23). The annual average increase was highest in the age group 65 years or older in both sexes; 3.4% (95% CI, 1.9–4.9) for men and 3.0% (95% CI, 1.7–4.3) for women. When both sexes were combined, the overall increase was highest (3.2%) in age groups of over 65 years (95% CI, 2.2–4.2), and lowest in ages 55–64 years (1.6%, 95% CI, 0.7–2.5).

In an analysis by age and birth cohort from all the four countries, all data with complete coverage were combined. The results indicated a cohort effect with a higher incidence for later birth cohorts in practically all age groups (*Figures 3a, 3b*). An age effect was also present with increasing incidence by age, with the exception of the oldest birth cohort showing a decline after age 60 in women. The differences by birth cohort were more pronounced among men than women.

In the two countries with available data from 1965 to 2007, further analyses were conducted subdividing the study period in two 21-year segments, 1965–1985 and 1986–2006. In Norway, the average annual increase in the first period was 1.0% (95% CI, –0.67 to +2.7) and in the second period 5.3% (95% CI, 4.1–6.5). In Sweden, the annual

**FIGURE 1A. Men**

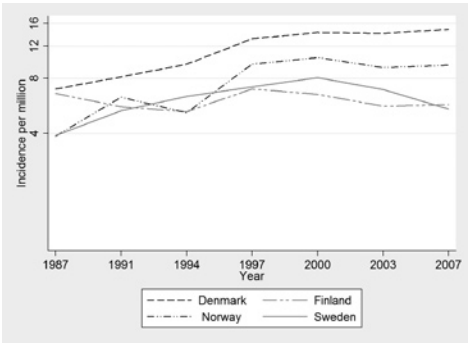
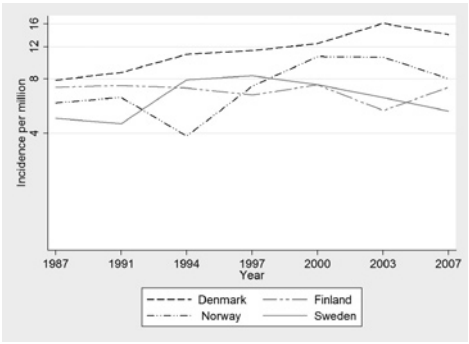



**FIGURE 1B. Women**




**FIGURES 1A AND 1B. Age-standardized incidence rates (logarithmic scale) of VS by three-year period, country and sex.**

**FIGURE 2A. Men**

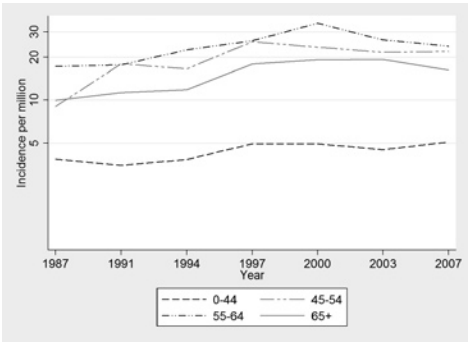
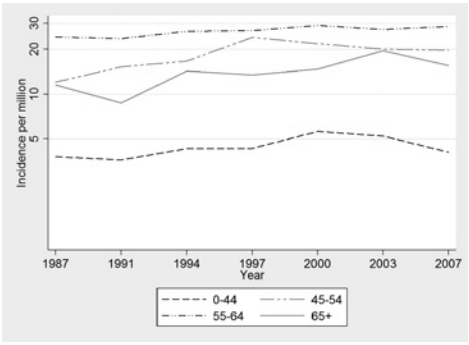



**FIGURE 2B. Women**




**FIGURES 2A AND 2B. Age-specific incidence rates (logarithmic scale) of VS by three-year period and sex.**

**FIGURE 3A. Men**

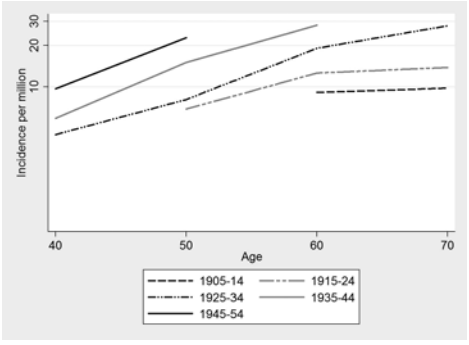
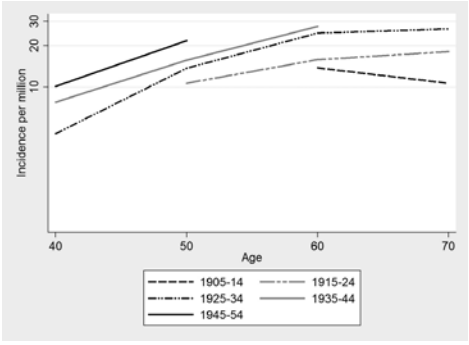



**FIGURE 3B. Women**




**FIGURES 3A AND 3B. Cohort effect (incidence rates by logarithmic scale) of VS by age and sex.**

increase in the first period was 3.6% (95% CI, 2.5 – 4.7) and in the second period –0.52% (95% CI, –1.73 to +0.26) (using ICD-7 193.0 through the entire period).

In Norway, when evaluating the proportion of VS from all intracranial schwannomas, 753 VS (code C72.4) were diagnosed during 1993 – 2007 for men and women combined, while during that time three schwannomas of the olfactory nerve (C72.2), one of the optic nerve (C72.3) and 56 schwannomas of the other and unspecified cranial nerve (C72.5) were diagnosed. Thus, the proportion of schwannomas arising from other cranial nerves was 0.5%, while those of unknown or unspecified site made up to 7% (N = 56) of the total number of schwannomas (N = 813) diagnosed in 1993 – 2007.

The main analyses for Norway for the period 1993 – 2007 were conducted with only confirmed VS cases. Thus, an assumption was made that the unspecified cases did not include any VS (i.e. cranial schwannomas of an unspecified site (C72.5) were not counted as VS). However, these unspecified schwannomas probably had relatively similar proportions of VS (93%) and other cranial nerves (0.5%), as those with a detailed diagnosis (missing at random). For the sensitivity analysis, the maximal and minimal incidence of VS was estimated by assuming that all the cases without a specific site were VS and none of the other cranial nerves, or vice versa. However, even such an extreme assumption had no effect on the increasing incidence trend in Norway for 1993 – 2007 (assuming none of the unspecific schwannomas being VS, the annual increase for the study period was 4.4% (95% CI, 2.6 – 6.1), whereas assuming all unspecific cases (C72.5) being VS, the annual increase was still 4.4% (95% CI, 2.8 – 6.1)). The crude incidence rates for Norway for that period assuming that none of the unspecified schwannomas was a VS were 11.5 (95% CI, 10.4 – 12.7) per 1,000,000 for men and 10.8 (95% CI, 9.7 – 11.9) for women. Whereas, if assuming that all the unspecified cases (C72.5) were VS, the rates were 12.4 (95% CI, 11.2 – 13.6) per 1,000,000 for men and 11.6 (95% CI, 10.4 – 12.7) for women.

In Sweden, in the main analyses for the period 1993 – 2007, the older more unspecific system (ICD-9 in combination with PAD) introduced in 1987 was used to provide consistency over time. Analyses on the impact of changes in coding systems in trends and incidence rates were done by comparing the trends obtained with the more unspecific system (older system, ICD-9 + PAD), the coding used systematically for VS during that period in the Swedish cancer registry (ICD-10 (C72.4, C72.5, C72.9) + SNOMED) (see *Table 1*), and the most accurate and certain coding for VS (including only the ICD-10 code for VS (C72.4) + SNOMED).

The employment of the coding system for previous years (used from 1987 onwards; ICD-9 and SNOMED) rendered the number of VS to 1205 (total for both sexes, in 1993 – 2007), and the crude incidence to 8.9 (95% CI, 8.1 – 9.6) per 1,000,000 for men and 9.2 (95% CI, 8.5 – 9.9) for women. However, with the systematically used coding in Sweden for that period (1993 – 2007) (using ICD-10 and SNOMED, see *Table 1*) the number was considerably (20%) higher (N = 1452), with crude rates of 10.8 (95% CI, 10.0 – 11.6) per 1,000,000 for men, and 10.9 (95% CI, 10.1 – 11.7) for women. Yet, when only the most specific code for VS (C72.4, and not the unspecific codes C72.5 and C72.9) was included, the number of cases

in 1993 – 2007 was substantially reduced (15%) (N = 1026) and the crude rates for men 7.5 (95% CI, 6.9 – 8.2) per 1,000,000 and 7.8 (95% CI, 7.2 – 8.5) for women. Following the same order, the annual trends were –2.1% (95% CI, –3.4 to +0.82), –2.6% (95% CI, –3.7 to –1.4) and –2.3% (95% CI, –3.6 to –0.87), respectively.

## DISCUSSION

This is the largest study carried out on incidence of VS with over 5,000 cases spanning two decades (Propp *et al*, 2006). The average annual increase was 2.8% (95% CI, 2.3 – 3.2) in all countries combined. All countries showed some increase over time except Finnish women (increase ranging between the countries from 0.26% to 5.0% annually in men, and from –0.35% to 4.5% in women). However, the trends differed by age group and the patterns of increase varied across countries. Most of the increase occurred before the late 1990's. These could reflect either genuine increases in occurrence or improved diagnostics or reporting. The fall in registrations in the late 1990's may represent saturation in diagnosing prevalent cases that had not been diagnosed in the earlier years due to inaccurate diagnostic imaging methods (Nelson *et al*, 2006).

Denmark had the highest incidence rate throughout the entire study period, and in later years the difference between Denmark and the other countries even widened. The incidence rates in Finland remained relatively stable during the study period. For Norwegians, there was rapid increase in the incidence rates in the late 1990's for both sexes, but the increase levelled off in the 2000's (in women the numbers of new VS cases even decreased). In Sweden, the rates increased somewhat more modestly until the end of the 1990's, when the numbers of incident VS cases started to gradually decrease.

Highest incidence rates were found in the age groups 45 – 54 and 55 – 64 years. This lower incidence among the elderly is highly unusual for a neoplastic disease and consistent with a detection bias due to lower diagnostic activity at old age. A clear increase over time was found at ages 65 years and older, but the older birth cohorts showed a decrease after age 60 years.

Comparability of information is a major issue in any analysis of time trends over a long time period, as well as in international comparisons. Accurate case counts are dependent on both notification and classification. This is particularly important for benign tumours, which are typically not reported as exhaustively as malignant tumours (Curado *et al*, 2007). Improved diagnostic methods and awareness among the public and physicians may lead to an apparent increase in the VS incidence. Since the introduction of CT in the late 1970's and MRI in the 1980's, incidence rates of brain tumours, especially benign and slow-growing, have increased. A recent study suggests that an indolent VS may be detectable in up to 0.03% of the population (Morris *et al*, 2009). These non-invasive and relatively inexpensive diagnostic methods have affected the detection of latent cases particularly among the

elderly (Inskip *et al*, 1995). In our study, the increase in incidence rates over time was seen mainly among the elderly (≥ 65 years of age). Improved classification of brain neoplasms has certainly an impact on incidence rates, but the rates do not necessarily increase with improving classification as both overestimation and undercount may be reduced.

The coding protocols varied considerably between the countries. Not only did the coding vary internationally, but the classification schemes changed in Norway and Sweden during the study period. This complicated the interpretation of the trends in these two countries, as VS could be distinguished from neurinomas at other locations only towards the end of the study period. However, this change in classification was partly overcome in Sweden, as the former coding systems remained in parallel, when a new coding system was introduced.

The data were incomplete in Denmark and Finland during the early years, and therefore the statistical analyses could only be performed in the study period when all four countries had the most comprehensive data (from 1987 onwards).

Interestingly, the two countries with the longest study period showed different trends in 1965 – 1985 compared with 1986 – 2006. In Norway, the increase was more rapid in the latter period, while in Sweden there was a decrease in the incidence in the second period. The change in the coding protocol could not be overcome in Norway. However in Norway, despite that the sensitivity analysis showed that the improved coding produced lower incidence rates than with the more ambiguous coding prior to 1993 (as we assumed in the calculations for 1993 – 2007 that none of the unspecified schwannomas was a VS (only ICD-10 code C72.4 was included in the counts)), a steep increase was observed particularly during the later part of the latter period. For the years 1986 – 1992 with the 'old coding', the annual increase remained similar to the earlier period (1.0%, 95% CI, –5.6 to +8.2), while for the years 1993 – 2006 the increase was high (6.6%, 95% CI, 4.6 – 8.8). However, the increase in Norway was sharp in the latter period only until the early 2000's, when it stabilized. This increase cannot be due to the changes in coding, as this improvement in coding should have, on the contrary, decreased the numbers of cases diagnosed as VS. Yet, there may be other issues influencing the incidence rates related to the new coding system that are not known to the authors (e.g. raising awareness among clinicians when introducing the new coding system, improvements in case ascertainment). In Sweden, the coding remained the same, but the annual increase has slowly levelled off since the end of the 1990's, which could reflect the impact of the improved detection rate after the introduction of CT and MRI. In the late 1990's these radiologic imaging technologies were widely available in institutions responsible for diagnosing brain tumours in the Nordic countries.

The sensitivity analyses (numbers of cases including also the more unspecific coding compared to the cases with only the most accurate coding of the time) could be performed for Norway and Sweden. The sensitivity analyses were not possible in Denmark and Finland, as they did not change their coding over the years.

The annual trend in Norway in 1993 – 2007 was similar (4.4%) in both analyses, i.e. assuming that none of the unspecified schwannomas was a VS, or vice versa. The crude

incidence rates were approximately 7% higher assuming all unspecified schwannomas were VS. However, this assumption is unlikely to be true, even if it is probable that most (but not all) of the unspecified schwannomas are VS. Thus, the incidence rates in Norway are likely to be approximately 5% (in the range 0 – 7%) higher than the main results of our study suggest.

The interpretation of the results from the sensitivity analyses in Sweden was difficult, as even the most accurate coding (from 1993 to 2007) included non-vestibular schwannomas (and there was no possibility to discriminate true VS from the cases with uncertain location). Nevertheless, we evaluated the rates in Sweden in 1993 – 2007 using three different classifications. The annual trends were relatively similar with all the three different inclusion criteria (ranging from –2.1% with the older coding system (ICD-9) to –2.6% with the system currently in use (ICD-10 including C72.5 and C72.9)). However, the crude incidence rates in 1993 – 2007 were approximately 21% higher in men and 18% higher in women with the system currently in use in Sweden in comparison to the coding used in this study (ICD-9). Yet, there are no means to distinguish the true VS cases from the cases coded under C72.5 (other and unspecified cranial nerve) and C72.9 (for CNS, unspecified), which had to be included in these calculations as a substantial proportion of VS have been classified under these codes in previous Swedish VS studies (unpublished data). Using only the most specific VS code (C72.4), the crude incidence rates were, on the contrary, approximately 16% lower in men and 15% lower in women in comparison to the coding system used for the rates in this study. Therefore, it is reasonable to assume that the rates presented in this study (with the older coding system, ICD-9) are rather realistic, with a potential margin of error of a maximum of one-fifth.

We used different study periods for different countries for the age and cohort analysis, which may have affected the rates in the analysis. If the diagnostic procedures for VS, patterns of development or behaviour of VS differ between countries, the cohort model may not represent reliably the changes over time due to differences in study periods between countries. However, the longest complete study periods from all countries were chosen to provide the best representation of the influence of age and cohort in incidence of VS.

This study had several strengths. The study-period was long (21 years for all countries with up to four decades for Norway and Sweden) with over 5,000 VS cases. The population-based Nordic cancer registries are considered a benchmark in cancer registry quality. Notification legislations have remained consistent in all countries throughout the period. The registration is based on a unique personal identification number assigned to all inhabitants in the Nordic countries eliminating the possibility of duplicate registration. In addition, public health care systems provide comprehensive coverage of the population, minimising differences in access to care, and in the quality of services.

In conclusion, our study shows an increase in VS incidence, mainly before mid-1990's. Increase occurred mostly in old (65+ years) population and the increase was relatively similar for men and women. The increasing trend was highest in Denmark (with initially the highest rates), whereas the increase was not seen in Finland, and was not pronounced in Sweden.

These changes could be attributable to increasing risk or improvements in diagnostics and registration.

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**III**

**LARJAVAARA S, MÄNTYLÄ R, SALMINEN T, HAAPASALO H, RAITANEN J, JÄÄSKELÄINEN J and AUVINEN A (2007): Incidence of gliomas by anatomic location. Neuro Oncol 9:319–325.**

# Incidence of gliomas by anatomic location

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**The anatomic location of a glioma influences prognosis and treatment options. The aim of our study was to describe the distribution of gliomas in different anatomic areas of the brain. A representative population-based sample of 331 adults with glioma was used for preliminary analyses. The anatomic locations for 89 patients from a single center were analyzed in more detail from radiologic imaging and recorded on a three-dimensional $1 \times 1 \times 1$–cm grid. The age-standardized incidence rate of gliomas was 4.7 per 100,000 person-years. The most frequent subtypes were glioblastoma (47%) and grade II–III astrocytoma (23%), followed by oligodendroglioma and mixed glioma. The gliomas were located in the frontal lobe in 40% of the cases, temporal in 29%, parietal in 14%, and occipital lobe in 3%, with 14% in the deeper structures. The difference in distribution between lobes remained after adjustment for their tissue volume: the tumor:volume ratio was 4.5 for frontal, 4.8 for temporal, and 2.3 for parietal relative to the occipital lobe. The area with the densest occurrence was the anterior subcortical brain. Statistically significant spatial clustering was found in the three-dimensional analysis. No differences in location were found among glioblastoma, diffuse astrocytoma, and oligodendroglioma. Our results demonstrate considerable heterogeneity in the anatomic distribution of gliomas within the brain.** *Neuro-Oncology 9, 319–325, 2007 (Posted to Neuro-Oncology [serial online], Doc. D05-00016, May 23, 2007. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-016)*

Keywords: brain neoplasms, diagnostic imaging, glioma, incidence

The incidence of gliomas has increased worldwide since the late 1970s.[1–5] There are several possible causes for this increase, including improved diagnostic methods, such as modern radiologic imaging, and better access to neurosurgical services.[2,3,6–8] Incidental findings of brain neoplasms increased with the introduction of CT and MRI technology in the 1980s.[4,8,9] However, it has also been suggested that the overall increase in incidence is leveling off,[3] whereas the increasing trend continues in the older age groups.[2,3]

The anatomic topographic location of a glioma affects treatment options and prognosis.[8,10–13] However, few large-scale studies have been published on the detailed anatomic locations of gliomas.[12]

To date, it has been widely believed that gliomas develop in different lobes with frequencies relative to the volume of glial tissue, reflected in the ratio of gray and white matter. Revealing differences in the anatomic distribution of gliomas may provide further insight into the etiology and pathogenesis of gliomas. It may, for instance, give clues about the role of highly local external exposures such as trauma or electromagnetic radiofrequency fields from mobile phones. Another possibility is that the anatomic structures provide physiologic stimuli to adjacent glial tissue, which affects the susceptibility to malignant transformation. A third possibility is the effect of functional differences among cells and tissues in different areas of the brain on the development of gliomas. Several studies have also shown differences in

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biologic characteristics (molecular alterations) in subsets of gliomas arising from different locations.[14–16]

The aim of our study was to describe the anatomic distribution of gliomas, using a representative case series with detailed localization based on radiologic imaging.

## Materials and Methods

The cases were identified from the neurosurgery clinics of all five university hospitals (Helsinki, Turku, Tampere, Kuopio, Oulu) in Finland. We retrieved the records of all patients diagnosed with any glioma at these hospitals during the period from November 2000 to September 2002. (In addition to these five hospitals, glioma is treated surgically at only one neurosurgery clinic in Finland; only 10 incident gliomas were diagnosed there during the study period, and these cases were not included in our study.) Two criteria were used to determine eligibility for inclusion in our study. First, all patients were required to be Finnish citizens residing in Finland. Second, those in the study cohort were required to be between the ages of 20 and 69 years. For the latter inclusion criterion, an age limit was imposed because these data were also used in the international INTERPHONE study, which assessed the possible effect of mobile phones on intracranial tumors.[17] Patients were approached for recruitment into the study immediately after surgical resection of the neoplasm and pathologic confirmation of the glioma diagnosis ($n$ = 328, 99%). In 1% of cases ($n$ = 3), the diagnosis was based on a radiologic finding (CT and/or MRI) indicating glioma as the tumor type rather than biopsy of a surgical specimen.

The study protocol was approved by the National Ethical Review Board of the Ministry of Health and Social Welfare (ETENE/TUKIJA). The study subjects or their relatives gave written informed consent. Of all the glioma patients diagnosed during the study period, 81% ($n$ = 267) gave their consent for participation. The remaining 61 patients (18%) were not willing to participate for various reasons, mainly poor general condition. Three patients died of their disease soon after diagnosis prior to enrollment and therefore could not participate. For the patients who did not give consent, additional information on the histologic type of the tumor was obtained from the Finnish Cancer Registry, a nationwide, population-based cancer registry with practically complete coverage of cancer cases in Finland.[18] However, the specific anatomic location of the tumors was not obtained at the Finnish Cancer Registry.

All cases were classified with a morphologic code according to the third edition of the International Classification of Diseases in Oncology (ICD-O-3).[19] For this study, all histologic specimens of the participants were reviewed afterward independently by an experienced neuropathologist (H.H.). Those originally classified by him were reviewed by one of the two other neuropathologists. The gliomas of the patients who did not give consent were reviewed by the study neuropathologist (H.H.). The gliomas were classified into the following groups: pilocytic astrocytoma (grade I; ICD-O-3 code 9421), diffuse astrocytoma (grade II; 9400, 9410, 9411, 9420), anaplastic astrocytoma (grade III; 9401), glioblastoma (grade IV; 9440–9442), all other astrocytomas (9384, 9424), oligodendrocytic gliomas (9450, 9451), mixed gliomas (9382), ependymal tumors (9383, 9391–9394), and choroid plexus tumors (9390).

The tumor location was specified by using radiologic imaging. Thus, all the tumors were assigned a topographic location according to the International Classification of Diseases, version 10 (ICD-10):[20] structures of cerebrum other than cortical lobes (ICD-10 code C71.0), cerebrum by lobe (frontal lobe C71.1, temporal lobe C71.2, parietal lobe C71.3, occipital lobe C71.4), ventricles (C71.5), cerebellum (C71.6), brainstem (C71.7), and other anatomic sites (C71.8, C71.9). Gliomas originally assigned to two lobes (with two topographic codes, e.g., frontotemporal) were treated differently from those with some overlap (e.g., predominantly frontal glioma with minor involvement of the temporal lobe). The former were recorded as occurring in two lobes, whereas in the latter case the overlap was ignored and the tumor was classified into one location. If the tumor had some overlap with several areas of the brain, the anatomic site was assigned systematically as the more superficial site versus deeper anatomical structure (e.g., frontal lobe for a tumor close to the sphenoidal wing). In the same fashion, the tumor was given a more anterior location versus posterior (e.g., frontal lobe for frontotemporal cases). A total of 181 gliomas (68%) were found to be located in only one anatomic site, whereas 86 (32%) were overlapping two or more sites.

More detailed analysis of 89 patients 30–69 years of age from Helsinki University Central Hospital was conducted based on radiologic imaging (CT and/or MRI). A neuroradiologist (R.M.) recorded the midpoint of each tumor from the CT/MR images on a 1 × 1–cm grid, separately in three projections (sagittal, coronal, and axial), using software (GridMaster computer program, Vompras, Düsseldorf, Germany) designed for this purpose for the INTERPHONE study.[17]

The world standard population was used in the age standardization.[21] Confidence intervals (CIs) for the incidence rates were calculated under the assumption that the observed numbers of cases follow a Poisson distribution.[22] In the analysis of the number of tumors in cerebral lobes, the number of tumors was related to the tissue volume of each lobe. Previously published estimates of the tissue volume in each lobe relative to the occipital lobe were used: frontal lobe, 3; temporal lobe, 2; parietal lobe, 2; occipital lobe, 1.[23] The ratio was used to adjust for different sizes of anatomic structures and to estimate incidence corrected for tissue volume.

In the analysis of heterogeneity of tumor distribution by lobe, the statistical significance was evaluated using the chi-square test, with expected frequencies calculated as the mean number of cases per lobe, assuming a uniform distribution across the lobes (in further analysis with adjustment for tissue volume of the lobe).

In the analysis of tumor localization with the three two-dimensional projections, simulation was used to obtain the statistical significance. The midpoint of each tumor was assigned to a square within the projection (i.e., each tumor constituting one observation for

the analysis). The observed value of the chi-square test statistic was compared with that obtained by randomly allocating a hypothetical location (square) for 89 tumors in the two-dimensional grid (relevant projection), based on a uniform distribution across the squares. This was repeated 999 times to obtain sufficient precision. The statistical significance was obtained by comparing the observed value of the chi-square statistic with the simulated ones (49 simulations with similar or larger chi-square values corresponding to a significance level of $p = 0.05$).

Three-dimensional analysis of spatial clustering was evaluated by using a chi-square test. Each glioma was assigned a single midpoint within a cube in the three-dimensional grid. There were four multifocal gliomas with midpoint assigned to the larger tumor. The test statistic was obtained by comparing the observed number of gliomas in the three-dimensional grid with 890 cubes, $1 \times 1 \times 1$ cm in size (some partial), to the expected frequency, obtained by assuming a uniform (random) distribution of tumors across cubes (0.1 tumors per cube). Owing to the small expected frequency, a conventional interpretation based on the chi-square distribution could not be used. Instead, statistical significance was assessed by simulations, randomly assigning a similar number of tumors to the grid. This simulation was repeated 999 times, and the observed chi-square value was compared with those obtained from simulations. A two-sided hypothesis was used, based on the frequency of simulations with similar or higher chi-square statistic (e.g., 49 simulations with chi-square value larger than the observed corresponding to a $p$ value of 0.05). In addition, the mean distance between the midpoints of gliomas was calculated as a summary descriptive measure.

For comparison of the location of histologic types, gliomas were grouped into three morphologic categories: diffuse and anaplastic astrocytomas (grades II and III, $n = 19$), glioblastomas ($n = 34$), and a combined group of mixed gliomas and oligodendrogliomas ($n = 30$).

## Results

A total of 331 incident gliomas were diagnosed during our study period. The majority (47%) were glioblastomas. Diffuse astrocytomas accounted for 14%, anaplastic astrocytomas for 9.4%, pilocytic astrocytomas for 5.1%, and all other astrocytomas for 0.6% of the gliomas. Oligodendroglial tumors comprised 11%, mixed gliomas 9.7%, and ependymomas 3.0% of the gliomas (Table 1). In addition, one choroid plexus tumor and one dysembryoplastic neuroepithelial tumor were diagnosed (0.3% each). No substantial differences in histology were found between patients who gave consent to participate and those who did not give consent ($p = 0.17$). For the former, the average patient age was 49.2 years (median = 51; range = 20–69) and 51.7% were men, whereas for those who did not give consent, the average age was 52.4 years (median = 54.5; range = 26–68) and 54.7% were men.

The age-standardized incidence rate was 4.67 per 100,000 person-years (95% CI, 4.2–5.2), with a slightly higher rate for men than women (4.90 compared with 4.47 per 100,000 person-years).

Most of the gliomas were located in the cerebral lobes (86%). Gliomas in the frontal lobe accounted for 40%, temporal lobe for 29%, parietal lobe for 14%, and occipital lobe for 3.0% of the cases. In addition, 6.4% were located primarily in the deep structures of the cerebrum, 2.2% in the ventricles, 1.5% in the cerebellum, and 4.1% in the brainstem.

The crude incidence rate of gliomas (per 100,000) was 1.68 (95% CI, 1.36–2.00) for the frontal lobe, 1.21 (95% CI, 0.94–1.48) for the temporal lobe, 0.58 (95% CI, 0.39–0.77) for the parietal lobe, and 0.13 (95% CI, 0.04–0.21) for the occipital lobe.

Gliomas were located more frequently in the right hemisphere (51%) than in the left (40%). Eleven gliomas were in the center of the brain. Of the 267 gliomas in the study for which the specific anatomic locations

**Table 1.** Number and incidence of gliomas by histologic type

| Histologic Type | No. of Cases (%) | | | Incidence (/100,000) |
|---|---|---|---|---|
| | Participants | Nonparticipants[a] | All[b] | |
| Glioblastoma | 116 (43) | 37 (61) | 154 (47) | 2.0 |
| Diffuse astrocytoma | 38 (14) | 8 (13) | 46 (14) | 0.7 |
| Anaplastic astrocytoma | 24 (9) | 5 (8) | 31 (9) | 0.5 |
| Pilocytic astrocytoma | 14 (5) | 3 (5) | 17 (5) | 0.3 |
| All other astrocytomas | 2 (<1) | 0 (0) | 2 (<1) | 0.03 |
| Oligodendroglioma | 34 (13) | 3 (5) | 37 (11) | 0.5 |
| Mixed glioma | 29 (11) | 3 (5) | 32 (10) | 0.5 |
| Ependymoma | 8 (3) | 2 (3) | 10 (3) | 0.2 |
| Choroid plexus | 1 (<1) | 0 (0) | 1 (<1) | 0.01 |
| All other gliomas | 1 (<1) | 0 (0) | 1 (<1) | 0.02 |
| Total | 267 | 61 | 331 | 4.7 |

[a]Nonparticipants refers to patients who did not give consent. For these patients, information was obtained from the Finnish Cancer Registry.

[b]Total number (331) includes three persons who died of their disease soon after diagnosis (prior to enrollment) and who are therefore not counted among participants or nonparticipants.

**Table 2.** Number and frequency of gliomas relative to tissue volume by cerebral lobe

| Location of Glioma | Frequency (No. of Gliomas) | Relative Volume[a] | Frequency/ Volume[b] | Frequency: Volume Ratio Relative to Occipital Lobe[c]* |
|---|---|---|---|---|
| Frontal lobe | 107 | 3 | 36 | 4.5 |
| Temporal lobe | 77 | 2 | 39 | 4.8 |
| Parietal lobe | 37 | 2 | 19 | 2.3 |
| Occipital lobe | 8 | 1 | 8 | 1.0 |

[a]Burger et al.[23]

[b]Number of cases relative to tissue volume.

[c]Frequency adjusted for tissue volume, with occipital lobe as the reference (assigned a value of 1).

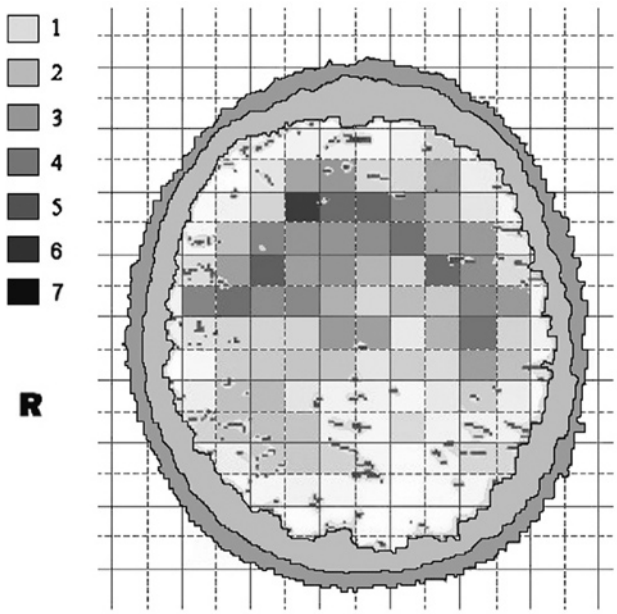
*$p$ value for difference between lobes $< 0.001$.

of the tumors were available, 13 (4.9%) were bilateral: eight were glioblastomas (ICD-O-3 code 9440), one was a diffuse astrocytoma (9400), two were anaplastic astrocytomas (9401), and two were mixed gliomas (9382). Seven of these bilateral gliomas were located primarily in the frontal lobes. The location of one glioma was unknown.

There were substantial differences in the tumor frequencies between lobes (Table 2). Even after accounting for tissue volume, the frequency was highest for the frontal lobe, followed by the temporal, parietal, and finally the occipital lobe ($p < 0.001$). The volume-adjusted frequency in the frontal and temporal lobes was roughly four times higher than in the occipital lobe.

More detailed analyses were performed based on the 89 cases with assessment of CT/MR images. The age distribution of these cases was similar to that for the other cases (average age, 49.2 years compared with 50.3 years, respectively). Also, distribution of histologic type was comparable (47.6% compared with 45.7% of the gliomas were glioblastomas). The tumor localization was characterized using a two-dimensional 1 × 1–cm grid in three projections. In the axial projection, there was some evidence for heterogeneity, that is, uneven distribution across squares with borderline significance (Fig. 1; $p = 0.06$). The tumors arose most frequently in the anterior subcortical part of the brain. In the coronal projection, there was an inverted U-shape distribution of tumors (Fig. 2; $p < 0.001$ for difference between squares). In the sagittal projections, the neoplasms were in the anterior areas of the brain and around the sellar region on both the left hemisphere (Fig. 3A; $p = 0.007$) and right hemisphere (Fig. 3B; $p = 0.02$).

In the three-dimensional analysis, the observed mean distance between the gliomas was 5.17 cm (SEM = 0.09 cm; median = 5.02 cm). There were 11 cubes with two gliomas, providing a chi-square test statistic of 1,021 with 889 degrees of freedom. The frequency of similar or higher chi-square values in the simulations was 7/999, corresponding to a statistical significance of 0.007. The observed mean coordinate was similar to the simulations in the axial and sagittal axes (mean observed and simu-



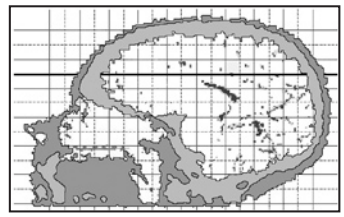



Fig. 1. The anatomic site distribution of gliomas in an axial projection of the brain (anterior at top). The colors represent the number of gliomas in each 1 × 1–cm square, with smoothing based on adjacent squares. The inset shows the section plane.

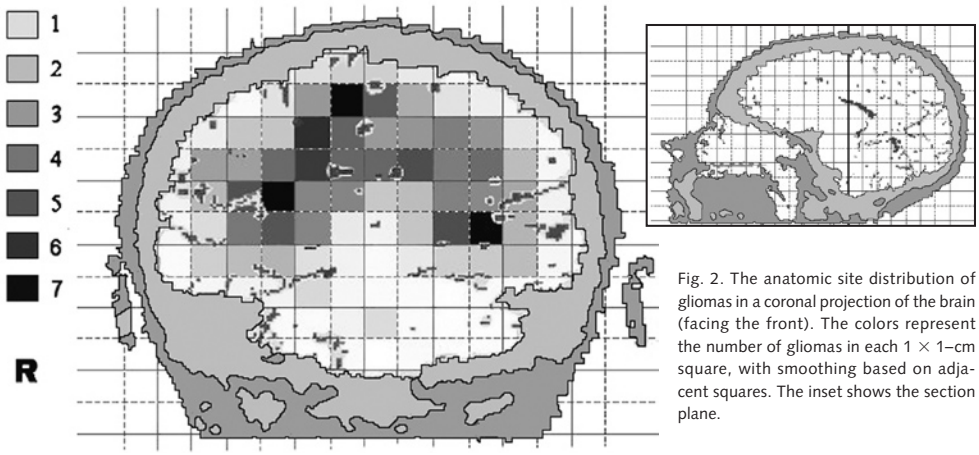



Fig. 2. The anatomic site distribution of gliomas in a coronal projection of the brain (facing the front). The colors represent the number of gliomas in each 1 × 1–cm square, with smoothing based on adjacent squares. The inset shows the section plane.

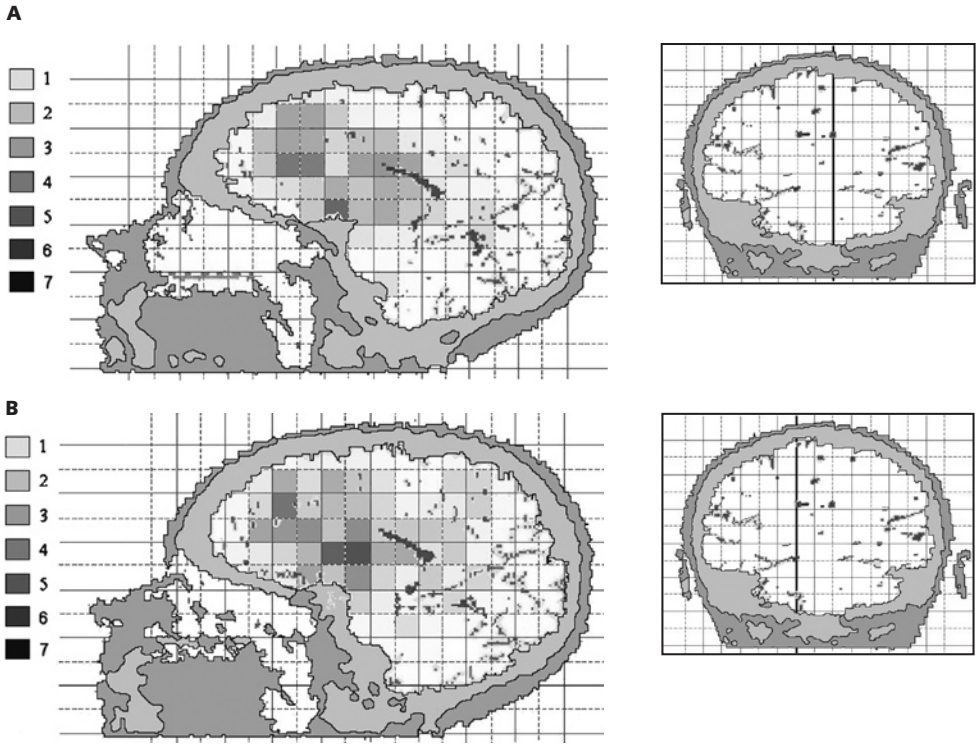



Fig. 3. The anatomic site distribution of gliomas in a sagittal projection of the brain from the left (A) and from the right (B). The colors represent the number of gliomas in each 1 × 1–cm square, with smoothing based on adjacent squares. The inset shows the section plane.

lated values of 8.6 vs. 8.3 in axial and 6.5 vs. 6.6 in sagittal axis) but slightly different for the coronal axis (10.0 vs. 11.8), indicating a tendency toward upper (superior) parts of the brain.

There were no statistically significant differences in the location of gliomas (based on assessment on the three-dimensional grid) between the three major histologic subtypes. In the three-dimensional analysis, the distances between group-specific midpoints were 1–2 cm (diffuse astrocytoma vs. glioblastoma, 1.2 cm; diffuse astrocytoma vs. oligodendroglioma/mixed glioma, 0.6 cm, glioblastoma vs. oligodendroglioma/mixed glioma, 1.2 cm), indicating closer proximity between the subgroups than with the simulation (2.3 cm for diffuse astrocytoma, 1.4 cm for glioblastoma, and 2.4 cm for oligodendroglioma/mixed glioma).

## Discussion

Our results demonstrate considerable differences in distributions of gliomas, with the densest occurrence in the frontal lobe and a higher frequency in the right hemisphere than in the left hemisphere.

The incidence rate (4.67/100,000) of gliomas in our study was comparable with that in a previous report from Finland.[24] However, it was relatively high compared with findings in other countries.[2,25] The fairly high incidence compared with most other populations is consistent with findings from other Nordic countries.[2,4,26] This may be attributable to completeness of registration and rate of histologic confirmation. However, compared with other forms of cancer, brain tumors do not show substantial international variation.[27]

The incidences of different histologic types of gliomas in this study were comparable with those in previous studies, with astrocytic tumors accounting for more than three quarters of gliomas.[25,27] According to the data from the Central Brain Tumor Registry of the United States,[25] glioblastomas account for 51%, anaplastic astrocytomas for 8%, and oligodendrogliomas for 10% of all primary brain and CNS gliomas.

The anatomic distribution of gliomas was irregular, with the number of tumors substantially higher for the frontal and temporal lobes than for other lobes, even after adjustment for tissue volume. Furthermore, statistically significant clustering was found in the three-dimensional analysis. No differences were found in distributions of the three major categories of gliomas. These results are consistent with a previous study, which found that 43% of glioblastomas were located in the frontal lobe, 28% in the temporal, 25% in the parietal, and 3% in the occipital lobe.[10] The occurrence of bilateral gliomas was toward the frontal lobes, because most gliomas involving both hemispheres are bifrontal.[28] Also, the more frequent involvement of the right hemisphere has been reported in a previous study.[29] A study of the anatomic distribution of low-grade gliomas found the highest tumor frequency in the secondary functional areas.[12] In these studies, however, assessment of tumor location was not as detailed as here.

In more detailed analyses, the tumors were distributed toward frontal subcortical areas. The cortical areas consist of gray material, whereas the subcortical areas contain more glial cells. As gliomas develop from the glial cells, the difference between the cell types in separate areas may explain partly why tumors arise preferably from the subcortical sites. The nonuniform anatomic distribution of gliomas with frontal and temporal predominance may reflect the involvement of developmental, neurochemical, or functional factors in the pathogenesis of gliomas. In one study, allelic loss was most common in oligodendrogliomas located in the same anatomic areas (frontal lobe) where we found the highest tumor frequency.[16] It has also been suggested that tumors in different parts of the brain arise from different precursor cells or that differences in the extracellular environment may account for the differences between lobes.[14] Furthermore, involvement of structural and functional differences between brain regions, including energy metabolism, architectonic tissue arrangements, and interaction between neuronal and glial cells, has been postulated.[12]

The topographic location (ICD-10 code) obtained from the medical records and cancer registry for the nationwide material was not always specified with sufficient detail. A simplified classification was used in summarizing the anatomic locations, with preference for lateral (i.e., cortical) and anterior structures. This overestimated slightly the tumor frequency in the superficial and frontal sites. The frequency of gliomas in certain lobes may be slightly overestimated, because some tumors in the unspecified or deep cerebrum were coded into the lobes. For example, the sphenoidal wing can be considered a part of the cerebrum other than the lobes as well as a part of the frontal lobe. However, these issues cannot explain the inhomogeneous distribution of gliomas between cerebral lobes. This limitation in classification did not affect the more detailed analyses. Also, some information was lost in the more detailed analysis, because only the midpoint of the tumor was considered.

The distribution of gliomas by anatomic site differs between adults and children.[3] Pilocytic astrocytomas in children occur typically in the cerebellum and brainstem,[6,30] whereas in adults diffuse supratentorial astrocytomas predominate.[2] Thus, the findings of this study apply to gliomas in adults.

Our study has several advantages. A single neuroradiologist evaluated the location of all gliomas, and histologic subtype was verified by a panel of neuropathologists. We had a representative data set owing to a well-defined source population in addition to a high coverage and a high participation rate. Furthermore, the dropout analysis showed no major differences in tumor types between the patients who gave consent to participate and those who did not give consent. Finally, although the radiologic data for tumors about which detailed location were known came from a single center (Helsinki University Central Hospital), there were no major differences in histologic tumor types or age distribution of patients between Helsinki and the other hospitals.

In conclusion, our findings indicate that gliomas arise mainly from the anterior subcortical structures of the brain, with an excess in the frontal and temporal lobes that is not accounted for by tissue volume alone. These findings, based on a detailed analysis of a large representative case series, consolidate the knowledge regarding localization of gliomas and may provide some insights into the development of gliomas.

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**IV**

**LARJAVAARA S, SCHÜZ J, SWERDLOW A, FEYCHTING M, JOHANSEN C, LAGORIO S, TYNES T, KLAEBOE L, TONJER SR, BLETTNER M, BERG-BECKHOFF G, SCHLEHOFER B, SCHOEMAKER M, BRITTON J, MÄNTYLÄ R, LÖNN S, AHLBOM A, FLODMARK O, LILJA A, MARTINI S, RASTELLI E, VIDIRI A, KÄHÄRÄ V, RAITANEN J, HEINÄVAARA S and AUVINEN A: Location of gliomas in relation to mobile phone use: a case-case and case-specular analysis. Am J Epidemiol (In press)**

# Location of gliomas in relation to mobile phone use: a case-case and case-specular analysis

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**Abstract:** The energy absorbed from the radiofrequency (RF) fields of mobile phones depends strongly on distance from the source. The objective of the study was to evaluate whether gliomas occur preferentially in the areas of the brain having the highest RF exposure. We used two approaches: in a case-case analysis, tumor locations were compared with varying exposure levels; in a case-specular analysis, a hypothetical reference location was assigned for each glioma and the distance from the actual and specular location to the handset was compared. The study included 888 gliomas from seven European countries

with tumor mid-points defined on a three-dimensional grid based on radiologic images. The case-case analyses were carried out using unconditional logistic regression, whereas in the case-specular analysis, conditional logistic regression was used. In the case-case analyses, tumors were located closest to the source of exposure among never-regular and contralateral users, but not statistically significantly. In the case-specular analysis, the mean distances between exposure source and location were similar for cases and speculars. Our results do not suggest gliomas in phone users being preferentially located in the parts of the brain with the highest RF fields from mobile phones.

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Mobile phone use has become common worldwide since the beginning of the 1990's (1). Mobile phones emit radiofrequency (RF) electromagnetic fields; those fields have not been shown to be tumorigenic (2), but research is still ongoing to investigate whether low-level RF fields have adverse health effects.

Several studies have been conducted on the association between mobile phone use and brain tumors, with unclear results. There is no clear evidence for increased risk of gliomas related to mobile phones, but the exposure and latency times analyzed have been limited (3–5). However, recent reviews have concluded that, to date, there was no consistent support for a causal effect of mobile phone use on glioma risk even with use of over 10 years (2,6).

Two previous studies have evaluated the location of glioma in relation to mobile phone use (7,8), but with very small sample sizes (approximately 100 cases). Because the RF field emitted by the phones penetrates the brain in a highly localized fashion, occurrence of tumors in the part of the brain closest to the handset would be expected if there is an etiological effect. The absorbed RF energy transmitted to the tissue from a mobile phone depends primarily on the distance from the source, decreasing to one tenth in 5 cm (9).

The current analysis is based on data from seven European centers within the Interphone study, an international collaborative case-control study whose main objective was assessing whether mobile phones increase the risk of brain tumors (10).

The aim of this analysis was to investigate whether gliomas among mobile phone users are located closer to the presumed position of the mobile phone handsets (the source of the RF field) than gliomas among non-users.

## MATERIALS AND METHODS

### Materials

Eligible cases were all glioma cases diagnosed in seven countries (or areas within the country) (Denmark, Finland, Germany, Italy, Norway, Sweden and the Southeast of England) between September 2000 and January 2004 (the study periods varied between countries), with mid-point(s) of the tumor in three dimensions defined by neuroradiologists based on computerized tomography (CT) or magnetic resonance imaging (MRI) images. A specific location (mid-point(s)) was assigned to 912 cases, i.e. 63% of all glioma cases diagnosed during the study period that fulfilled the study inclusion criteria. The inclusion criteria were age at diagnosis between 18 – 69 years (with some variation between countries), no prior diagnosis of brain tumor and a histological confirmation (N = 910) or diagnostic imaging allowing unambiguous classification of the tumor type (N = 2). The case selection is described in further detail elsewhere (10).

All gliomas were assigned a mid-point(s) by neuroradiologists, blind to the data on mobile phone use, in each center. The coordinates for the mid-point were recorded using a software program (GridMaster) designed for the Interphone study. In GridMaster, three projections (axial, sagittal, and coronal) form a three-dimensional (3D) grid ($1 \times 1 \times 1$ cm). Cases with no clear single mid-point (i.e. irregularly shaped tumors, N = 116) were assigned several mid-points (thus also several sets of coordinates). Multifocal cases (with non-adjacent mid-points) were excluded from the study (N = 24). For each case with multiple mid-points, the mean of the tumor mid-points was defined (for calculating the distance to the exposure source).

All cases were interviewed (83% personally, 17% via proxies) about their mobile phone use. Phone use in the eighteen months prior to glioma diagnosis was excluded from the analyses, and use of hands-free-devices. Use of cordless phones (DECT) was not included. Regular use was defined as at least one call per week for a period of six months or more.

The study protocols were approved by local ethical review boards in each center.

### Statistical methods

Two types of analyses were used to evaluate the anatomic distribution of gliomas within the brain in relation to mobile phone use. A case-case analysis was based on comparing exposed and unexposed cases using dichotomous exposure indicators. A case-specular analysis contrasted the actual location of the case with a hypothetical (specular) assigned for each case as a mirror image on the opposite side of the same hemisphere in terms of axial and coronal axes (*Figure 1*).

The main exposure indicator in the analyses was the shortest estimated distance from the mid-point of the glioma to the putative source of exposure, i.e. typical location of the phone. A line from the external orifice of the ear canal to the corner of the mouth was assigned to represent the position of the phone. The entire phone was regarded as the source

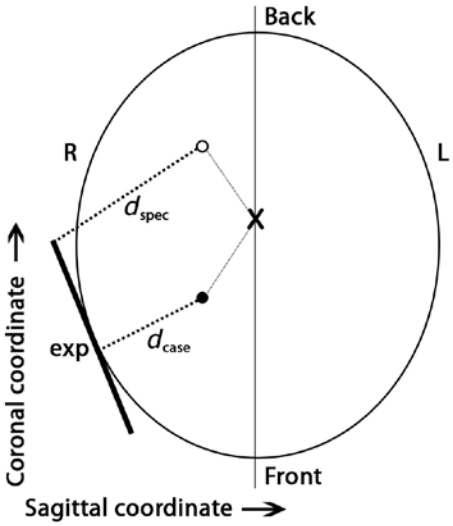


**FIGURE 1. A schematic representation of the assignment of the coronal coordinates for the specular analysis. In the axial projection, x-axis sagittal and y-axis coronal the mid-point for a case is indicated with a solid circle and the corresponding specular location with an open circle. The distance from the source of exposure (exp) is denoted by d separately for the case ($d_{case}$) and for the specular location ($d_{spec}$). Axial coordinates were obtained in a similar fashion using a coronal projection. R = right, L = left.**

of exposure, as most GSM phones have an integrated antenna with the whole body of the phone emitting an RF field.

The exposure line (approximately 6.7 cm) was divided into a hundred segments of similar length. The distance from the mid-point of the glioma was calculated separately to each of the 101 points and the shortest was used as the main exposure indicator.

To avoid potential recall bias, distance was calculated to the nearest source of exposure on the same side as the glioma was located, irrespective of the patient's reported typical side of use.

In the case-specular analysis, 3D coordinates were defined for the specular cases representing a hypothetical control location symmetrically reflecting the location of the actual case across the mid-point of the axial and coronal planes. In accordance with the rationale of the case-specular study design, the specular location was representing the exposure if the tumor had been located in another location (11). This counterfactual 'control' was contrasted in the analysis with the actual case.

We constructed the specular locations (from which the distance was calculated similarly to the actual cases) using a geometrical 'mirror reflection' through a center-point. This center-point was defined as the point that resulted in a similar distance from the exposure line for unexposed cases (i.e. never-regular users) and their specular controls. The anatomical center-point of the brain could not be used, because gliomas are not symmetrically distributed within the brain and therefore using the zero point of the anatomic coordinate axes would have led to an asymmetrical distribution of the specular locations (and hence bias). Thus, the center-point used was based on the mean coordinates of cases among never-regular users (the unexposed group). The procedure for the axial coordinate is illustrated in *Figure 1*. The same procedure was used for coronal projection. For the sagittal projection, an identical coordinate on the sagittal axis was used (i.e. the specular location had identical distance to the falx cerebri as the actual case).

The specific locations of gliomas are presented in four projections to demonstrate the heterogeneous distribution of gliomas (which restricted the use of the anatomic mid-point

of the brain as the origo). These figures are shown using an axial projection of the brain, a coronal projection, and right and left sagittal projections (*Figure 2*).

In the analyses of differences in distances of glioma from the exposure line, the statistical significances were evaluated using the Mann-Whitney test. When analyzing differences of glioma distribution by lobe and by increasing level of intensity or duration of mobile phone use, chi-square tests were used.

In the case-case analysis, unconditional logistic regression was used with distance between the mid-point of the glioma and the presumed source of exposure as a binary outcome (≤ 5 cm, > 5 cm). The cut-point was chosen because the energy from RF field is predominantly absorbed by the tissue within 5 cm of the phone (9). Exposure indicators analyzed included regular use, cumulative call-time, laterality (preferred side of use) and duration of use (years). Never regular use of a mobile phone was considered as the unexposed reference category in all analyses. Phone users were divided into tertiles by cumulative call-time (0.001 – 46 hours, 47 – 339 h and > 339 h, with a median of 133 hours and maximum of 20,000 hours). Similarly, duration of use was categorized into three groups, with cut-points chosen to correspond to those in previous studies (1.5 years to 4 years, 5 to 9 years and 10 or more years of use). All analyses were adjusted for country, sex, age group and socioeconomic status.

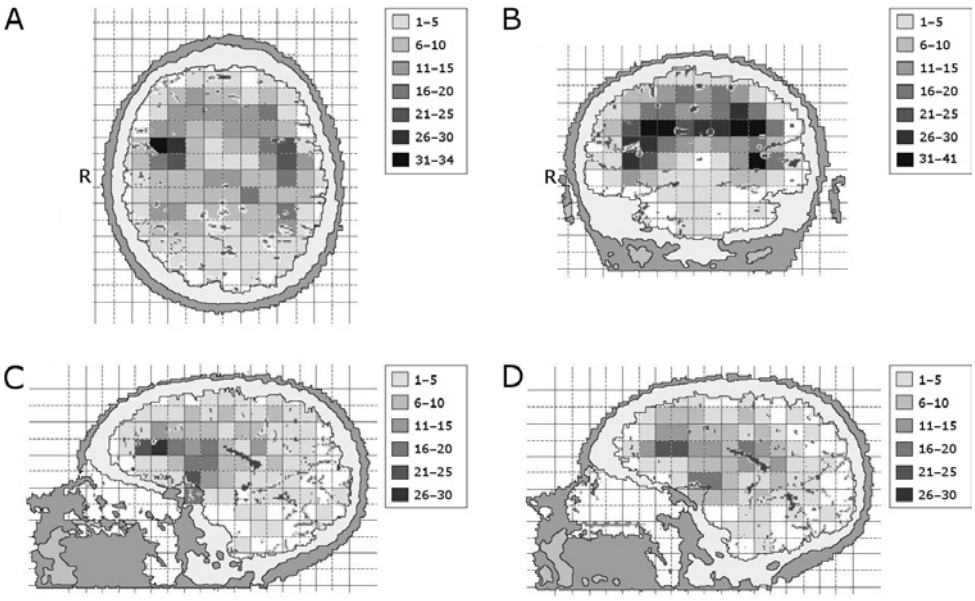


**FIGURE 2. The anatomic distribution of gliomas in different projections of the brain. The shades of grey represent the number of gliomas in each 1 x 1-cm square, smoothing based on adjacent squares. Number of gliomas indicated in the legend. R = right. A) Axial projection (frontal part at top), B) Coronal projection (facing the front), C) Sagittal projection (right hemisphere), D) Sagittal projection (left hemisphere).**

Case-specular analyses were conducted using conditional logistic regression. The odds ratios (OR) were calculated with distance as the exposure variable and case/specular status as the outcome. The explanatory variables included regular phone use, cumulative call-time and duration of use in years.

The statistical software Stata 8.2 (StataCorp, Texas, USA) was used in all analyses.

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## RESULTS

A total of 912 cases fulfilled the inclusion criteria, with one or more mid-points of glioma recorded. Of these, 24 cases (3%) were excluded as they had several non-adjacent mid-points. Of the remaining 888 cases, 116 (13%) had two or more mid-points (range 2 to 21, mean 3.6, median 2).

Altogether 518 (58%) gliomas were in men and 370 (42%) in women. Information on mobile phone use was obtained from 873 cases (98%), with 57% regular mobile phone users and 43% reporting no regular use. The median cumulative call-time among regular users was 133 hours, while the mean call-time was 917 hours.

Preferred laterality of use was known for 490 cases (99% of all regular users). Of these, 59% were using the phone on the right side, 28% on the left side and 13% on both sides. The reported side of use and the brain hemisphere where the glioma was located are presented in *Table 1*.

**TABLE 1. Location of glioma in the hemispheres in relation to the side of self-reported mobile phone use.[a]**

| | | Laterality of use | | |
|---|---|---|---|---|
| | | **Right** | **Left** | **Total** |
| **Side of glioma** | Right | 160 | 47 | 207 |
| | Left | 123 | 86 | 209 |
| | **Total** | 283 | 133 | 416 |

[a] Statistical significance for heterogeneity evaluated based on Fisher's exact test, $p < 0.001$.

Regular mobile phone use was most common in the youngest ages, among men and subjects with the highest level of education (*Table 2*).

There were no differences in phone use (regular vs. never-regular) among cases with only one glioma mid-point and those with several (14% of never-regular users had several mid-points vs. 12% of regular users, $p = 0.65$).

Tumors were located in the right hemisphere in 46% of cases, in the left in 46% of cases and in a central location in 7% of cases. Glioma cases included in the present study were most

**TABLE 2. Demographic characteristics of regular users and never-regular users.**[a]

| | Regular, N(%) | Never, N(%) | Total | Statistical significance for heterogeneity |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 329 (65) | 180 (35) | 509 | |
| Female | 166 (46) | 198 (54) | 364 | p < 0.001 |
| **Age (years)** | | | | |
| 18–39 | 149 (71) | 60 (29) | 209 | |
| 40–49 | 145 (64) | 82 (36) | 227 | |
| 50–59 | 171 (50) | 173 (50) | 344 | |
| 60–69 | 30 (32) | 63 (68) | 93 | p < 0.001 |
| **Education**[b] | | | | |
| Compulsory | 77 (46) | 91 (54) | 168 | |
| Secondary | 161 (56) | 129 (44) | 290 | |
| Upper secondary | 135 (61) | 86 (39) | 221 | |
| University | 120 (63) | 71 (37) | 191 | p = 0.01 |
| **Country** | | | | |
| Denmark | 53 (37) | 89 (63) | 142 | |
| Finland | 78 (79) | 21 (21) | 99 | |
| Germany | 52 (40) | 77 (60) | 129 | |
| Italy | 76 (72) | 30 (28) | 106 | |
| Norway | 100 (62) | 62 (38) | 162 | |
| Sweden | 97 (56) | 77 (44) | 174 | |
| UK | 39 (64) | 22 (36) | 61 | p < 0.001 |

[a] Information on usage missing in 15 cases (N = 873).
[b] Information on education missing in 3 cases.

**TABLE 3. Distribution of gliomas in the cerebral lobes among regular and never-regular users.**

| All gliomas | Total, N(%)[a,b] | Regular, N(%)[b] | Never, N(%)[b] | Statistical significance for heterogeneity |
|---|---|---|---|---|
| Frontal | 293 (40) | 175 (43) | 115 (37) | |
| Temporal | 220 (30) | 113 (28) | 104 (33) | |
| Parietal | 169 (23) | 91 (22) | 75 (24) | |
| Occipital | 51 (7) | 31 (8) | 19 (6) | p = 0.23 |
| **Total in the lobes** | 733 (100) | 410 (100) | 313 (100) | |

[a] The numbers of regular and never-regular users do not add to total, as information on mobile phone use is missing in some cases.
[b] Percentages shown as distribution in the cerebral lobes.

frequently located in the frontal lobe (40% of 733 gliomas with a cerebral lobe assigned), followed by the temporal (30%). There were no major differences in the distribution of gliomas by cerebral lobes between regular phone users and never-regular users (*Table 3*). The distribution by lobe was also comparable between regular and never-regular users when gliomas were subdivided into glioblastomas and other gliomas.

The mean distance did not vary substantially by the indicators of mobile phone use being somewhat shorter among cases who had never used phone regularly or reported a preferred

**TABLE 4. Distance between glioma and source of exposure, in relation to exposure variables.**

| | mean (cm) | ≤5 cm, N (%) | >5 cm, N (%) | Statistical significance for heterogeneity |
|---|---|---|---|---|
| **GLIOMA CASES** | 6,25 | 200 (23) | 688 (77) | |
| **Regularity of use** [a] | | | | |
| Regular | 6.29 | 107 (22) | 388 (78) | |
| Never-regular | 6.19 | 91 (24) | 287 (76) | p = 0.39 |
| **Cumulative call time (hours)** [b] | | | | |
| 0.001 – 46 | 6.29 | 33 (21) | 125 (79) | |
| 47 – 339 | 6.27 | 38 (25) | 114 (75) | |
| > 339 | 6.36 | 30 (19) | 129 (81) | p = 0.41 |
| **Duration of use (years)** [c] | | | | |
| 1.5 – 4 | 6.31 | 65 (21) | 239 (79) | |
| 5 – 9 | 6.28 | 30 (21) | 112 (79) | |
| ≥ 10 | 6.38 | 10 (24) | 32 (76) | p = 0.82 |
| **Laterality** [d] | | | | |
| Ipsilateral | 6.37 | 51 (21) | 195 (79) | |
| Contralateral [e] | 6.29 | 37 (22) | 133 (78) | p = 0.80 |
| **SPECULARS** | 6.24 | 166 (19) | 722 (81) | |
| Ipsilateral speculars | 6.26 | 47 (19) | 199 (81) | |
| Contralateral speculars [e] | 6.36 | 30 (18) | 140 (82) | p = 0.71 |

[a] Information missing on 15 cases.
[b] Cumulative time below 0.001 h, never-use or information missing on 419 cases.
[c] Regular use <1.5 yrs, never-use or information missing on 400 cases.
[d] Use on both sides, glioma located centrally or information missing on both sides on 472 cases.
[e] Distance calculated to the closest (ipsilateral) exposure line despite the knowledge of contralaterality.

side of use as contralateral to the tumor (in comparison to regular or ipsilateral users) (*Table 4*). The mean distance was slightly longer for those with the highest cumulative call-time and for those having used a mobile phone for more than ten years, but the differences were not significant. Also, the mean distances were relatively similar between countries (ranging from 6.08 cm to 6.51, p = 0.29).

In the case-case analysis, non-significantly decreased ORs for gliomas located within 5 cm of the presumed phone location were found in regular users compared with never-regular users (*Table 5*). All the ORs for the higher categories of intensity or duration of mobile phone use were below unity in these analyses, indicating no excess risk in the highly exposed parts among regular vs. never-regular users, although all the upper confidence limits were above one.

In the case-specular analysis, the average distance from the source of exposure was comparable for actual and specular glioma cases (6.25 vs. 6.24 cm, p = 0.49 with medians 6.34 cm (SD 1.60, range 2.42 – 10.7) and 6.26 cm (SD 1.38, range 2.98 – 11.0), respectively). The distribution of the distances of the actual glioma cases showed more kurtosis (p < 0.001, with a peak at 6 – 7 cm) than for the specular gliomas. The specular cases on the other hand,

**TABLE 5. OR (with 95% confidence interval) for distance ≤5 cm between glioma mid-point and typical source of exposure from case-case-analysis by exposure characteristics, all compared with never-regular users.**

| | Crude OR (95% CI) | Adjusted OR (95% CI) [a] |
|---|---|---|
| **Frequency of use** | | |
| Regular | 0.87 (0.63–1.20) | 0.80 (0.56–1.15) |
| **Cumulative call time (hours)** | | |
| 0.001–46 | 0.82 (0.52–1.29) | 0.82 (0.51–1.31) |
| 47–339 | 1.04 (0.67–1.60) | 0.97 (0.60–1.56) |
| >339 | 0.72 (0.46–1.15) | 0.58 (0.35–0.96) |
| **Laterality of use** | | |
| Ipsilateral | 0.82 (0.56–1.21) | 0.80 (0.52–1.22) |
| Contralateral | 0.87 (0.56–1.34) | 0.77 (0.47–1.24) |
| **Duration of use (years)** | | |
| 1.5–4 | 0.86 (0.60–1.23) | 0.85 (0.57–1.25) |
| 5-9 | 0.84 (0.53–1.35) | 0.71 (0.43–1.18) |
| ≥10 | 0.99 (0.47–2.08) | 0.85 (0.39–1.86) |

[a] Adjusted for age, education, sex and country.

**TABLE 6. Case-specular analysis: OR (95% confidence interval) for distance between glioma mid-point and typical position of mobile phone as a categorical (≤5cm) and a continuous variable, by exposure characteristics, all compared with speculars (case vs. specular).**

| | OR for case ≤5cm (95% CI) | OR for case with increasing distance (cm) from exposure (95% CI) |
|---|---|---|
| Case vs.specular | 1.22 (0.99–1.51) | 1.00 (0.95–1.07) |
| **Never-regular users** | | |
| Regular | 1.19 (0.89–1.59) | 0.99 (0.92–1.08) |
| Never-regular | 1.30 (0.95–1.80) | 1.01 (0.92–1.11) |
| **Cumulative call time (hours)** | | |
| 0.001–46 | 1.39 (0.81–2.38) | 1.00 (0.87–1.16) |
| 47–339 | 1.21 (0.74–1.97) | 0.99 (0.86–1.13) |
| >339 | 1.00 (0.59–1.69) | 1.01 (0.88–1.16) |
| **Duration of use (years)** | | |
| 1.5–4 | 1.15 (0.80–1.66) | 0.98 (0.89–1.09) |
| 5–9 | 1.04 (0.61–1.76) | 1.02 (0.89–1.18) |
| ≥10 | 2.00 (0.68–5.85) | 1.08 (0.82–1.42) |

showed some evidence for skewness ($p = 0.002$, two cases exceeding the expected range, i.e. $\mu + 3 \times 6$) not observed among the actual cases.

In the case-specular analyses with distance as a categorical variable, a slightly larger proportion of glioma cases than speculars were within 5 cm of the presumed typical phone location (*Table 6*). However, the confidence intervals covered unity. In addition, no significantly increased OR was found among regular users or those with highest exposure;

on the contrary, highest ORs were observed among never-regular users and among regular users with the lowest call-time**.** A two-fold OR was found in those having used mobile phone over ten years, but with a confidence interval including unity. With distance as a categorical variable, all ORs were above unity, also for the unexposed. In the analyses of distance as a linear variable, no increased ORs were observed.

Analyses of digital and analogue phones separately did not show substantially different results from the main analyses, nor did analyses by histological sub-groups of gliomas (glioblastomas and other gliomas separately). In addition, the analyses were relatively similar even with the exclusion of the cases with multiple (adjacent) mid-points or cases with only proxy respondents.

## DISCUSSION

Our results do not support the hypothesis of gliomas among users of mobile phones being preferentially located in the parts of the brain with the highest exposure. In the case-case analyses, gliomas among contralateral and never-regular users, representing lower RF exposures, had a shorter mean distance between tumor mid-point and the presumed source of exposure than ipsilateral and regular users. In the case-specular analysis, both exposed and unexposed glioma cases were non-significantly located within 5 cm from the phone more frequently than the hypothetical locations assigned for speculars, but no such pattern was found in analyses by amount of phone use. In both models glioma cases were closer to the exposure line in long-term users, but the differences remained non-significant.

We applied a novel approach for studying focal effects of RF fields emitted by mobile phones in the etiology of gliomas. Instead of concentrating on crude indicators of phone use as in most previous studies, the method utilizing tumor location enabled us to focus on risk in relation to the postulated distribution of the RF field within the brain. This offers a biologically and physically more meaningful and more specific measure of RF exposure compared with phone usage pattern.

The case-specular method has not been previously used in brain tumor studies, but was developed for studies on residential (extremely low frequency) electromagnetic fields from power lines and childhood cancer (12,13). In those analyses, the residential location was the exposure indicator, for which specular indices were obtained. In our case, hypothetical tumor locations were generated following the same principles. The analysis resembles a case-case study, but with the advantage of avoiding potential confounding.

The RF field decreases sharply in the brain tissue, with 90% of the energy to the head absorbed in the tissue within 5 cm range of the handset. Nearly all (97 – 99%) of the energy from a mobile phone is absorbed to the hemisphere on the side of the phone, with the highest exposure to the temporal lobe (50 – 60%) (9).

In our study, no excess of gliomas was found in the temporal lobe among regular users compared with never-users (28% vs. 33% of the locations in the cerebral lobes). Overall,

the distribution of anatomic locations in our study was similar to previously reported findings (14 – 17), with somewhat lower relative frequency of gliomas in the frontal lobe in our data (35% of all brain vs. previously reported 40 – 53%) and a higher frequency in the occipital lobe (6% vs. 2 – 3%).

Side of use was ignored in the case-specular analyses, and glioma cases were overall, both among regular mobile phone users and never-regular users, slightly closer to the source exposure than the hypothetical locations assigned for speculars, but the differences were not significant, and disappeared when exposure was analyzed in more detail. Yet, the only suggestion of an increased risk was related to long-term use in this analysis, but with a wide confidence interval. The ORs for different exposure indicators showed hardly any departure from unity, when distance was considered as a continuous variable, and in analyses among users, the point estimates for the higher exposure groups never exceeded those for less mobile phone usage.

Our localization approach was based on the 3D mid-point(s) of the glioma, as defined by neuroradiologists, for its unequivocal nature compared with the theoretically relevant point of origin, which is no longer identifiable at the time of diagnosis. The mid-point is a crude but robust measure. It has limitations particularly for large, irregularly shaped tumors close to the margin of the brain tissue. The size of gliomas has been reported being smaller in regular mobile phone users in one study, but with a relatively small number of glioma cases (18). However, vestibular schwannomas have been reported to be larger among regular than never-regular users, though no association with amount of use was reported (19). If a similar (unknown) mechanism was to influence also gliomas, they may be larger among phone users. Larger gliomas may not grow symmetrically around their point of origin, but e.g. towards the center of the brain, resulting in the mid-point being further from the cortex and thus the exposure. Larger tumor size among users could therefore potentially cause a bias towards the null. In our study gliomas with several mid-points were slightly further away from the exposure line than those with only one mid-point (6.44 cm vs. 6.22, $p = 0.15$).

In the case-specular analysis, the hypothetical alternative location in the coronal and axial axes of the 3D brain model was assigned symmetrically across the mid-point of the plane to reflect the location of the case. The center-points of the axes (in relation to which the specular coordinates were obtained) were chosen based on the medians observed among never-regular users, in accordance with the null hypothesis. The number of such cases was substantial (more than 370) and the precision should be adequate.

However, in the case-specular analyses the ORs are slightly above unity also for never-regular phone users (*Table 6*). This indicates that the reference is not necessarily located on an exact basis rendering the results of the case-specular analysis somewhat difficult to interpret.

Never-users were on average older and more commonly women and if these features affect the tumor location, bias could be introduced. Nevertheless, in our data, the average

distances from the exposure line did not differ significantly between age groups (ranging from 6.14 cm in those aged 50 – 59 years to 6.43 in those aged 40 – 49 years, p = 0.32), whereas there was a borderline significant difference between the sexes (6.16 cm in men vs. 6.37 in women, p = 0.051). This higher proportion of women among the unexposed may have driven the center-point somewhat further from the exposure line (as gliomas among women are located further from the line), which may accentuate the differences in distances when comparing all cases and all speculars.

We addressed the histological subtypes of gliomas in a very simplified fashion by dividing gliomas into two subgroups (glioblastomas and others), and the results for the two groups were largely similar to the main analyses. However, both etiological factors and preferential locations may vary by the molecularly defined subtypes of the tumor, which we could not investigate further in this study.

Due to the short penetrance of the RF field into the head, exposure emitted by a mobile phone is virtually confined to the brain hemisphere at the side of the phone. However, most people do not use the phone exclusively on one side. Several earlier studies have found an increased risk on the side of head where the user reported that the phone had predominantly been used (2). Frequently, however, this has been accompanied by a deficit on the contralateral side, giving rise to suspicion of recall bias (overestimation of use on the side of the tumor by the cases, with corresponding underreporting on the other side).

The only finding consistent with the study hypothesis was statistically significant excess of gliomas on the self-reported side of mobile phone (*Table 1*). However, the more detailed analyses failed to support it. The reported predominant side of use is prone to recall bias and in our interpretation such bias is a likely explanation for this specific result.

Case-case analysis overcomes the discrepancy of information between cases and controls. The results of our case-case analysis did not show differences by laterality of use in relation to tumor location.

As only cases were included in our study, selection bias arising from lower participation among controls, in particular non-users of mobile phones, was avoided (20,21).

Still, even if only cases were included, reported usage may be inaccurate. Slight underestimation of the number of calls and substantial overestimation of call duration have been demonstrated in short-term recall (22). Such overestimation would, however, distort the current results only if it were related to the location of the tumor.

The main limitation of the study is the relatively short time since first exposure. While a fifth of the cases (N = 184) had used phones for at least five years, only 5% (N = 42) had used phone for ten or more years, which adds considerable uncertainty to our results on long-term exposure. No statistically significant difference was found for gliomas among cases with five to nine years or over ten years of use in terms of mean distance to the typical phone location in our case-case or case-specular analyses. Even if in the case-specular analysis the OR was twofold for cases with over ten years of use, the

confidence intervals of the risk estimates for the increasing categories of duration of use remained wide.

This is the largest study on detailed glioma localization published to date, with 888 glioma cases from seven countries. Further research with similar methods, but a larger number of long-term users is warranted.

To conclude, the results do not indicate that gliomas are located in excess in the brain tissue presumably receiving the highest intensity electromagnetic field among regular mobile phone users. Cumulative call-time, duration of use and laterality were not consistently associated with the location of the gliomas.

## FUNDING

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