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FACTORS ASSOCIATED WITH BRAIN TUMOR RISK

*WITH FOCUS ON FEMALE SEX HORMONES
AND ALLERGIC CONDITIONS*

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Större och mindre

Vi upptäckte mer och mer
och jorden blev större och större.
Upptäckte ändå mer
och jorden blev bara en prick,
en liten leksaksballong
i oändligheten.

Grubbel

Det är så erbarmligt lite
en människa kan förstå.
Man skulle ej grubbla och tänka
men tänker och grubblar ändå.
Och dagarna fogas till veckor,
veckorna fogas till år.
Man skulle ej snärjas av grubbel
så hastigt som livet går.

Nils Ferlin

ABSTRACT

Every year approximately 1200 people in Sweden are diagnosed with a brain tumor. The two main histological types of brain tumors, gliomas and meningiomas, differ in terms of their localization, histology, prognosis, and probably etiology. Exposure to ionizing radiation and a few rare genetic syndromes are the only unequivocally established risk factors.

The overall aim of this thesis was to look at some specific factors that potentially could be associated with glioma and meningioma risk, and to characterize and compare demographic and socioeconomic factors among participants and non-participants in a case-control study of brain tumors. Data from an international population-based case-control study of brain tumors formed the base for the papers included in the thesis. In papers I and IV only Swedish participants were included. Papers II and III included participants from Denmark, Finland, Norway, Sweden, and England.

We found an increased risk of meningioma associated with use of hormone replacement therapy. We found no association between use of oral contraceptives and meningioma risk, but results indicated an increased risk associated with use of other hormonal contraceptives. No associations were found between use of exogenous female sex hormones and glioma. Increasing number of pregnancies leading to a live birth was associated with an increased meningioma risk among women < 50 years of age, but not among older women. Ever having been pregnant was associated with a decreased glioma risk. Among parous women longer duration of breastfeeding and older age when giving birth for the first time was associated with an increased glioma risk.

Allergic conditions (asthma, eczema, hay fever, other allergy) were associated with a reduced glioma risk, OR=0.70 (95% CI: 0.61-0.80), which is in accordance with previously published studies. We showed that the inverse association was primarily related to current allergic condition and was not influenced by anti-allergy treatment. Allergic conditions were not associated with meningioma risk, except for a decreased risk associated with eczema.

Records were linked to registries at Statistics Sweden to gather information on socioeconomic status, income, and education, for all participating and non-participating cases and controls in the Swedish part of the study. Working status and income level were positively associated with participation among both cases and controls. A high income level was associated with a slightly increased risk of glioma, but not related to meningioma risk.

Conclusions: Our findings imply that female sex hormones influence the occurrence of meningioma and glioma. The results also indicate that immunological factors are of importance for glioma tumorigenesis. Non-participation related to socioeconomic factors should always be acknowledged as a potential source of selection bias, but the influence was not large in our study due to the fact that the level of participation was comparable between cases and controls and participation was similarly influenced by socioeconomic factors among cases and controls.

Keywords: Glioma, meningioma, case-control study, contraceptives, hormone replacement therapy, allergy, pregnancy, participation, selection bias

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1 LIST OF PUBLICATIONS

The thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. **Wigertz A**, Lönn S, Mathiesen T, Ahlbom A, Hall P, Feychting M, and the Swedish INTERPHONE Study Group.
Risk of Brain Tumors Associated with Exposure to Exogenous Female Sex Hormones
Am J Epidemiol 2006; 164:629-36
© Oxford University Press
- II. **Wigertz A**, Lönn S, Hall P, Auvinen A, Collatz Christensen H, Johansen C, Klæboe L, Salminen S, Schoemaker M, Swerdlow A, Tynes T, Feychting M.
Reproductive factors and risk of meningioma and glioma
Cancer Epidemiol Biomarkers Prev. Accepted for publication
- III. **Wigertz A**, Lönn S, Schwartzbaum J, Hall P, Auvinen A, Collatz Christensen H, Johansen C, Klæboe L, Salminen S, Schoemaker M, Swerdlow A, Tynes T, Feychting M.
Allergic Conditions and Brain Tumor Risk
Am J Epidemiol 2007; 166:941-50
© Oxford University Press
- IV. **Wigertz A**, Lönn S, Hall P, Feychting M.
Non-participant characteristics and the association between socioeconomic factors and brain tumor risk
Submitted

2 LIST OF ABBREVIATIONS

CI	confidence interval
CT	computerized tomography
EF	etioloical fraction
FSH	follicle stimulating hormone
GP	general practitioner
hCG	human chorionic gonadotrophin
HRT	hormone replacement therapy
IARC	the International Agency for Research on Cancer
ICD-10	International Classification of Diseases - tenth revision
ICD-O-2	International Classification of Diseases for Oncology - second edition
LH	lutheinizng hormone
MEN-1	multiple endocrine neoplasia type 1
MRI	magnetic resonance imaging
NF1	neurofibromatosis type 1
NF2	neurofibromatosis type 2
OR	odds ratio
PNET	primitive neuroectodermal tumor
RR	relative risk
SCB	Statistics Sweden (Statistiska centralbyrån)
SES	socioeconomic status
SV40	simian virus 40

3 AIMS OF THE THESIS

The general objective of this thesis is to examine the association between some specific risk factors and the occurrence of glioma and meningioma.

3.1 SPECIFIC AIMS

- To assess the association between the use of exogenous female sex hormones and the risk of glioma and meningioma. (Paper I)
- To assess the association between reproductive factors and the risk of glioma and meningioma. (Paper II)
- To assess the association between allergic conditions and the risk of glioma and meningioma, with specific consideration of the influence of current and past condition and the influence of anti-allergy treatment. (Paper III)
- To identify and compare characteristics of participants and non-participants in a Swedish population based case-control study of brain tumors and to assess the association between socioeconomic factors and glioma and meningioma risk. (Paper IV)

4 INTRODUCTION

4.1 BRAIN TUMORS

4.1.1 Incidence

Each year, 1100-1200 people in Sweden are diagnosed with a primary brain tumor (including the meninges). This is equivalent to 12-13 cases/100.000 per year (1). Less than one hundred of the yearly cases of brain tumors affect children and adolescents. An increase in the incidence rates have been observed both in Sweden and internationally during the last 30 years. The increase mainly occurred in the beginning of the 1980's when the introduction of computerized tomography (CT), magnetic resonance imaging (MRI), and the development of stereotactic biopsy technique improved diagnostic methods. Most of the increase was also seen in older age groups. Over the last 15 years the incidence rates in Sweden have been stable and even shown a slight decline (1-3). Factors that can affect the incidence must always be considered when comparisons are made among countries or for time-trends. Adjustments (standardization) for differences in the age structure must be made. Changes in diagnostic and coding practices, difference in completeness of reporting, histologic types included, autopsy frequency and screening activities must be considered to assure validity of the contrasts.

4.1.2 Tumor types

Primary brain tumors are a heterogeneous group of tumors which vary by the tissue of origin and they are classified according to histopathological evaluation. The two most common types are glioma (~ 50%) and meningioma (~25%) (4).

4.1.2.1 Glioma

Within the brain there are nerve cells (= neurons) and cells that support and protect the neurons. The supporting cells are called glia cells and tumors of these cells are called gliomas. Gliomas are subdivided into astrocytomas, oligoastrocytomas, oligodendrogliomas, and ependymomas. Based on histologic grading criteria the tumors are also divided into four grades, I-IV, depending on the degree of malignancy. The incidence of gliomas is approximately 1.5 times greater in men than in women (3, 4). Figure 1 shows the incidence of glioma in Sweden 2006.

Grade I astrocytic tumors, pilocytic astrocytomas, are seen as benign and have a good prognosis if treated surgically. They are most common in children and rare in adult age (5).

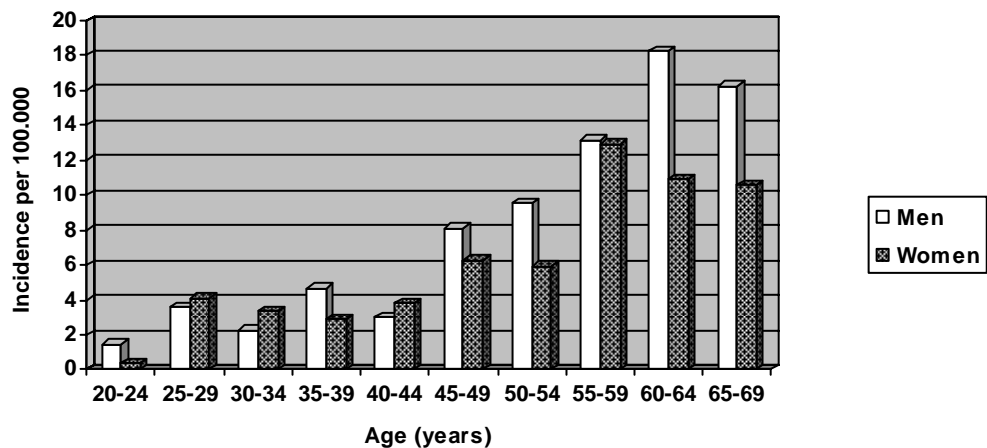
Grade II gliomas grow slowly and are fairly well differentiated. Most tumors, however, gradually turn into more malignant forms. The majority are found in young adults between age 30 and 40 (5). There is a considerable individual variation in the prognosis. Young age (<40 years), tumor less than six cm in diameter, no neurological deficit before surgery and oligodendroglioma subtype have been shown to be favorable prognostic factors for survival (6).

Grade III tumors or anaplastic tumors, have greater levels of dysplasia and more mitoses than do tumors of lower grades. The peak incidence is in early middle age (5).

Median survival time from diagnosis is 2-3 years for anaplastic astrocytomas and 3-7 years for anaplastic oligodendrogliomas (5, 7, 8).

Grade IV astrocytomas, glioblastoma multiforme, are the most malignant form of gliomas. Approximately half of gliomas are glioblastomas. They are called primary glioblastomas when there is no evidence of a previous glioma of a lower grade, otherwise they are called secondary glioblastomas. Approximately 5% of all glioblastomas have been reported to be secondary tumors (8), although some low grade gliomas with a rapid progression from low grade to glioblastoma might have been misclassified as primary glioblastoma. The tumor can occur at any age, even in utero (9), but the peak incidence is seen between 45 and 70 years of age (5). Glioblastomas have a poor prognosis and are usually rapidly fatal with a median survival of 12-15 months (10).

Figure 1. Incidence of glioma by age and sex in Sweden 2006 *



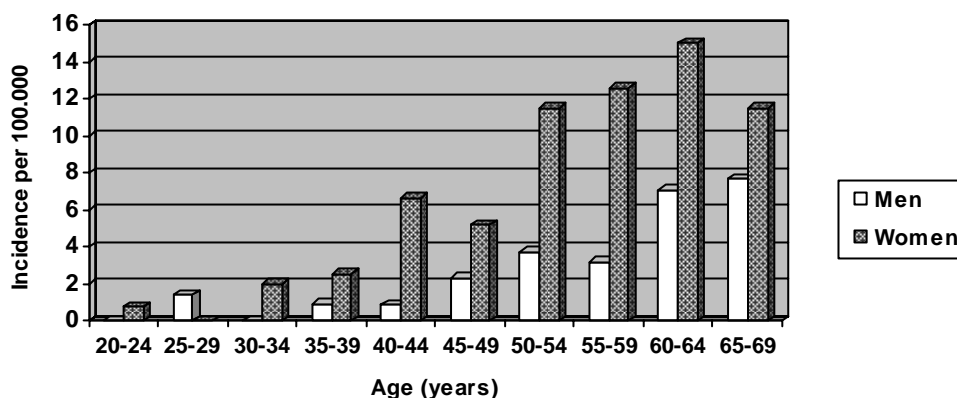
* from the Cancer Registry kept by the National Board of Health and Welfare

4.1.2.2 Meningioma

Meningiomas originate in archnoidal cells in the meninges, the membrane that encloses the brain. Most meningiomas are benign ~90% (grade I), 5-7% are atypical (grade II), and 1-3% anaplastic (grade III) (11). Meningiomas are rare before the age of 30 and the incidence increases with age. They are more common in women than in men, with the highest ratio (2-3:1) during the female reproductive period (2, 4). In figure 2 the incidence of meningioma by age and sex in Sweden 2006 is shown.

It has been estimated that 1-2% of the adult population has incidental asymptomatic meningiomas (12, 13). Asymptomatic meningiomas found incidentally can be left untreated and just monitored until symptomatic or growing (14, 15). Although most often benign the tumor can cause severe clinical symptoms because of its critical location, and can substantially influence the quality of life (16). Surgery is the primary treatment. Grade I meningiomas have a recurrence rate of 7-20%, grade II recur in 29-40% of cases, and grade III meningiomas in 50-78% of cases (5). The presence of progesterone receptors and a low proliferative index have been shown to predict a better outcome (17, 18).

Figure 2. Incidence of meningioma by age and sex in Sweden 2006 *



* from the Cancer Registry kept by the National Board of Health and Welfare

4.1.3 Clinical presentation

The initial clinical presentation is notably similar for gliomas and meningiomas, although the progression of symptoms varies with type and malignancy grade. The symptoms can be categorized as generalized or focal. Generalized symptoms are due to an increased intracranial pressure and consist of headache, and with progression of the disease, nausea and vomiting, and sixth cranial nerve palsy. Hemiparesis, visual field loss, and aphasia are focal symptoms that reflect the location of the tumor. Personality changes are also frequently seen. Seizures are common, and most often the first sign of a low-grade (I-II) glioma. Typically the seizures are focal, but may become generalized (19).

4.1.4 Etiology

The etiology of brain tumors is essentially unknown despite tremendous efforts to identify risk factors. Apart from a few rare genetic disorders, the only unequivocally established risk factor is ionizing radiation (4, 20).

4.1.4.1 Genetic disorders associated with brain tumors

There are a few rare genetic disorders that are associated with an increased risk of brain tumor development. These disorders however, account for less than 5% of brain tumor occurrence (21). The major disorders are listed in table 1. Meningiomas have also been shown to be a possible component tumor of Multiple Endocrine Neoplasia Type 1, MEN-1 (22). Findings of familial aggregation of glioma in first degree relatives suggests that other genetic factors than the known genetic disorders can be of importance (23, 24). A familial aggregation of course may be due to the effect of exposure to the same environmental factors. A study showing that first degree relatives and not spouses of brain tumor patients have an increased risk of brain tumors indicates genetic origin of the familial aggregation (25).

Table 1. Genetic disorders associated with brain tumors*

Disorder	Gene	Chromosome	Brain tumor
Neurofibromatosis 1	NF1	17q11	Astrocytomas, optic nerve gliomas
Neurofibromatosis 2	NF2	22q12	Meningiomas , astrocytomas, acoustic neuromas
Tuberous sclerosis	TSC1	9q34	Subependymal giant cell astrocytoma
	TSC2	16p13	
Li-Fraumeni	TP53	17p13	Astrocytomas, PNET
Turcot	APC	5q21	Medulloblastoma
	hMLH1	3p21	Glioblastoma
	hPSM2	7p22	

* Modified from Kleihues P, Cavenee W. Pathology & Genetics of tumours of the nervous system. World Health Organization classification of tumours. Lyon, France: IARC Press, 2000, p 215.

4.1.4.2 Ionizing radiation

Exposure to therapeutic doses of ionizing radiation is a recognized risk factor for brain tumor development. A large Israeli cohort with people who received scalp irradiation as treatment for tinea capitis (ringworm of the scalp) in childhood had a relative risk (=RR) of 9.5 (95% CI 3.5-25.7) for development of meningiomas and a RR of 2.6 (95% CI 0.8-8.6) for gliomas (26). A Swedish study of two cohorts of children who had been treated with radiation for skin hemangiomas reported a dose-response relationship between the absorbed dose in the brain and the risk of developing an intracranial tumor and the risk was higher among those exposed at younger ages (27). A study of childhood cancer survivors concluded that exposure to radiotherapy is the most important risk factor for the development of a new primary neoplasm in the central nervous system (28). The subsequent tumors occurred 5-28 years following the original cancer diagnosis and most commonly occurring were meningiomas and gliomas. Gliomas tended to occur earlier relative to the time of radiation exposure than did meningiomas. Diagnostic medical ionizing radiation has not been found to be associated with glioma risk (29-31). One study has reported of an increased risk of meningioma associated with diagnostic x-rays (29), but others have not (31, 32). Two studies concerning dental x-rays have observed an increased meningioma risk, but the increased risk was related to full-mouth x-rays (33, 34).

In conclusion radiotherapy treatment to the head increases the risk of development of both gliomas and meningiomas with the risk for meningioma higher than the risk for glioma and with meningiomas occurring later than gliomas. For both tumor types exposure at younger ages seems most detrimental. Results from diagnostic ionizing radiation are less convincing for an increased risk. Large epidemiological studies of CT-scans of the skull and brain are still needed. These studies will be methodologically challenging since confounding by indication will be a problem.

4.1.4.3 Other risk factors

Numerous environmental factors have been suggested as possible risk factors for brain tumors, but none has been convincingly linked to the risk.

Occupational exposure

A number of industries and occupations have been inconsistently associated with brain tumor risk. Employment in the petroleum industry (35, 36), occupational exposure to mercury (36), lead (36, 37), or electromagnetic fields (38) have each been implicated as a potential source of increased risk of brain tumors. In addition, farmers (39, 40), butchers (40), firemen (35), pulp mill workers (41), asphalt and welding workers (42) are among occupational groups that have shown an increased risk of brain tumors in at least one study. Overall evidence for associations between industries, occupations and brain tumors are inconclusive.

Epilepsy

Both case-control (43) and cohort studies (44-47) have reported associations between epilepsy and glioma or meningioma risk. Seizures are, however, a common initial symptom of both gliomas and meningiomas and a positive association with a later brain tumor is therefore difficult to interpret, especially prior to the use of CT or MRI. The seizures may actually be early signs of an undiagnosed brain tumor. The fact that studies have found that the brain tumor risk decreases with increasing duration of epilepsy corroborates the idea of reverse causality.

There has also been a debate as to whether long term use of antiepileptic drugs can increase the risk of cancer, but the carcinogenicity of these drugs has not been established (48).

Head trauma

Head trauma has been suggested as a possible risk factor for both glioma and meningioma. In case-control studies there might, however, be a problem with differential recall among cases and controls when reporting prior head trauma. Studies reporting only serious head trauma or head trauma resulting in hospitalization might therefore be more reliable; supposing these are less prone to differential recall or that the exposure could be measured through hospital registrations. There is, however, a problem with more serious traumas since subsequent medical attention and examinations might reveal an already existing tumor. Except for case-reports of gliomas developing in scars of old head traumas (49, 50), studies of glioma have not found an association (30, 51, 52). Studies of meningioma have reported a positive association (52, 53), but if only serious traumas is included the excess risk disappears.

Diet

The International Agency for Research on Cancer (IARC) has recently stated that “ingested nitrate or nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans” (54). Most interest has been focused on cured meat. A meta-analysis from 2003 of cured meat and adult glioma risk including nine studies concluded that they found an increased risk associated with cured meat overall, but that available data did not provide clear support for a causal relation (55). Aspartame, an artificial sweetener, has also been hypothesized to be a potential risk factor for gliomas based on animal studies, however, this association has not been confirmed in epidemiological studies (56).

Tobacco

Tobacco use is a well established risk factor for many cancers (57, 58), but smoking has not emerged as a strong risk factor for brain tumors. A recent study from 2007 comprising data from three large cohorts in the United States found no association between baseline or updated smoking status, intensity, duration, or age at smoking initiation among men or women and glioma risk (59). Studies of smoking and meningioma risk are sparse and results are contradictory and inconclusive (29, 60, 61).

Mobile phones

The use of mobile phones has increased dramatically during the last two decades. The mechanism for a potential carcinogenic effect is, however, unclear (62).

Epidemiological studies of the association between glioma and meningioma risk and mobile phone use have not found an increased risk with overall use, but the effect after long-term (>10 years) use cannot be evaluated until the number of long-term users increases (63, 64).

Extremely low frequency electromagnetic fields

Electromagnetic fields are produced whenever electric power is transmitted. These fields have not been shown to be able initiate cancer, but are hypothesized to act as cancer promoters. Epidemiological studies, mostly of occupational or residential exposure and brain tumor risk have not been able to find support for an association (65, 66).

Infections

In the 1950's the polio vaccine was prepared in cultures of monkey kidney cells. It was later revealed that a lot of these preparations were unintentionally infected by a monkey virus, SV40. The virus has been shown to have oncogenic properties in animal studies by binding to tumor suppressors and brain tumors have been induced after intrathecal administration (67). SV40 DNA has also been detected in human brain tumor tissue (68). There are reports of increased rates of ependymomas among those exposed to contaminated vaccines compared to unexposed birth cohorts (69), whereas others have found no association (70). Whether SV40 is a causal factor for brain tumors in humans is still under debate (71).

The JC-virus and the BK-virus are two human viruses similar to SV40. They cause a normally asymptomatic and latent infection. More than 70% of young adults in Sweden are seropositive (72). Both viruses can induce brain tumors in experimental animals and have been reported to be associated with brain tumors in humans in some studies but not in others making the evidence for a causal association is weak (73).

Other viruses including varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus have also been implicated as potentially oncogenic in relation to brain tumors and especially gliomas, but studies trying to detect occurrence of viruses in tumor tissue have reported contradictory results (74-76), and from a case-control study an inverse association with varicella-zoster virus and glioblastoma risk has been reported (77).

Allergies

An inverse association between allergic conditions and glioma risk has been reported in several epidemiological studies (29, 43, 78-85). A complicating factor in studies of

brain tumors is the use of proxy-respondents and the potential inaccuracies associated with that source of information. Schwartzbaum et al. (83) have shown that the inverse association in relation to allergies was strongest in past studies with the highest proportion of proxy-respondents, suggesting that proxies may underreport cases' allergic conditions. In most studies no association has been found between meningioma and allergic conditions (29, 43, 81, 86).

The biological mechanism behind the alleged reduced risk is not fully understood. According to the immune surveillance theory, the immune system is supposed to continuously recognize tumor cells as foreign and destroy them (87, 88). An enhanced tumor immunosurveillance in allergic individuals can be hypothesized. The idea of better surveillance owing to an active immune system is also supported by the opposite condition, with an impaired immune system leading to an increased risk of cancer (89-91). A biomarker for allergy has previously been studied. Wiemels et al. found a reduced level of IgE, the antibody related to atopic allergic diseases, among glioma patients compared with controls (92), but reversed causality could not be excluded since the level of IgE was measured after diagnosis.

Hormones

There is some evidence implying that sex hormones may play a role in brain tumor etiology. The higher incidence of meningioma in women than men, with the highest ratio (2-3:1) during the reproductive years (2, 4) and an observed growth stimulation during pregnancy and the luteal phase of menstruation (93, 94) support this hypothesis. An association between breast cancer and meningioma has also been reported, with an elevated risk of meningioma among women with a previous diagnosis of breast cancer and an elevated risk of breast cancer among women with a previous diagnosis of meningioma (95, 96), suggesting common genetic or environmental risk factors. The incidence of glioma is, in contrast, approximately 1.5 times greater in men than women (3, 4). The higher incidence of glioblastoma in men has in one study been shown to become evident around the age of female menarche, reaching a maximum around the age of menopause and diminishing thereafter (97). Progesterone, estrogen and androgen receptors are expressed in meningiomas (98-100) and gliomas (101, 102) in various degrees. Proliferation of a human meningioma cell line after exposure to estrogen and progesterone has also been observed, although not all cell lines expressing receptors did proliferate (103).

The few prior studies of exogenous hormones and brain tumor risk have shown contradictory results. Elevated risks for meningioma among postmenopausal women associated with use of hormone replacement therapy have been reported (104, 105), as well as no association or reduced risks (106-109). Oral contraceptive use has been reported to be associated with a decreased meningioma risk (106, 109), an increased risk (108) and not associated with meningioma risk (104, 107).

Studies of exogenous hormone use and glioma have reported of reduced risk (107) and of no association (110, 111) related to oral contraceptives and reduced risks (107, 110) and no association (111) for HRT.

Current knowledge based on epidemiological studies of how reproductive factors, including age at menarche, menopausal status, age at menopause, number of pregnancies and breast-feeding, influence the risk of glioma and meningioma is also conflicting and inconclusive (29, 43, 80, 104, 106-115). One explanation for this could be that with the exception of a register based study (115) the studies have not been large and have therefore not had enough power to produce stable results.

Socioeconomic factors

Previously published studies on socioeconomic factors and glioma risk have reported an increased risk associated with higher socioeconomic status (36, 116-119). Results from studies looking explicitly at meningioma risk and socioeconomic factors are conflicting, with highest incidence among the lowest social class reported (116), as well as a report of an increased risk with increasing household income (118), and with a higher socioeconomic status in women (36). Interpretation of the reported associations and possible underlying factors has been difficult, as issues such as non-participation possibly related to socioeconomic status, study design (type of control group), health care system, availability of care, and health seeking patterns might have influenced the observed associations.

4.2 FEMALE SEX HORMONES

4.2.1 Endogenous hormones

The female sex hormones are lipophilic molecules derived from cholesterol. The main types are estrogen and progestin and they are primarily produced in the ovaries. The clinically relevant estrogens are estradiol, estrone, and estriol. Progesterone and 17 α -OH-progesterone are the endogenously produced progestins. The hormones are mainly metabolized in the liver and then excreted in the urine.

4.2.1.1 Menarche and fertile life

At puberty the production of hormones starts and makes the breasts grow and creates all the other female sex characteristics. Eventually, also the periods start (menarche). The initial periods are usually anovulatory. Regular ovulations begin approximately one year after menarche (120). During the fertile part of a woman's life hormones rise and fall regulated by follicle stimulating hormone (FSH) and luteinizing hormone (LH) at different times in the menstrual cycle (121).

4.2.1.2 Pregnancy

At the start of a pregnancy human chorionic gonadotrophin (hCG), produced by the developing placenta, stimulates the ovaries (corpus luteum) to produce the higher levels of estrogen and progesterone that are needed to maintain a pregnancy. The growing placenta gradually then takes over as the main producer of estrogen and progesterone (121). The levels of estradiol and estrone increase more than hundredfold over the normal levels and estriol more than thousand fold during a pregnancy. The progesterone level increases steadily during pregnancy and at the end the level has increased 10 fold or more (121).

4.2.1.3 Breast feeding

After childbirth the levels of estrogen and progesterone fall sharply. The level of the hormone prolactin increases during the pregnancy and remains high if breast feeding is initiated and maintained. Prolactin is important for initiation of the milk secretion and maintenance of milk production (lactogenesis). Oxytocin stimulates contraction of myoepithelial cells, causing milk to be ejected into the ducts and cisterns of the breasts.

Full time breast-feeding can delay the reestablishment of normal ovulation by 6-9 months (122).

4.2.1.4 Menopause

During the 3-5 years leading up to the last menstrual period, the normal functioning of the ovaries begins to weaken. Finally, the ovaries produce so little estrogen that the periods stop. The level of progesterone thereafter is very low and depends on adrenal secretion. Low levels of estrogens are also produced in the adrenal glands and through peripheral conversion of androgens. The peripheral conversion mainly occurs in the adipose tissue and consequently heavy women have been shown to have higher conversion rates than slender women (123, 124).

4.2.2 Exogenous hormones

4.2.2.1 Oral contraceptives

Oral contraceptives, with a combination of estrogen and progestins, were introduced in Sweden in 1964. The “pills” at that time contained 10-20 times the level of progestins and 2-5 times more estrogens than do preparations used today (125).

In all combined oral contraceptives used in Sweden the synthetic estrogen etinylestradiol is used in combination with different progestins. Noretisteron, levonorgestrel and desogestrel are examples of commonly used progestins. These have similar but not identical effects and side-effects.

Low-dose progestin preparations were introduced in the 1970’s, so called “mini-pills”. These preparations do not contain any estrogens (125).

4.2.2.2 Other hormonal contraceptives

Medroxyprogesteronacetat has been used for intramuscular injections since the 1970’s. In 1985 subcutaneous implants (“p-stavar”) containing progestins were introduced and in the beginning of the 90’s a progestin releasing intra-uterine device (“hormonfrisättande spiral”) came into use (125).

4.2.2.3 Hormones for gynecological problems

Irregular menstruations and other bleeding problems can be treated with hormones and although contraception is not the primary indication, most often these problems are treated with oral contraceptives.

4.2.2.4 Hormone replacement therapy

Estrogen replacement was introduced in the 1960’s to reduce menopausal symptoms. It became progressively more popular during the second half of the 1980’s and was believed to be of benefit for women as a life-long supplement after menopause (126). Estrogen replacement was, however, shown to increase the risk of endometrial cancer, but this risk could be reduced or avoided if progestins were added to the estrogen (127, 128). In 1999 a Swedish study by Magnusson et al. reported an increased breast cancer risk associated with use of hormone replacement therapy (HRT) (129). Two large studies a few years later, one from the Women’s Health Initiative (130) and one from

the Million Women Study (131), also found an increased risk of breast cancer. The randomized controlled study from the Women’s Health Initiative also concluded that overall health risks exceeded benefits from use of HRT and treated women had not only an increased risk of breast cancer, but also of coronary heart disease, stroke and pulmonary embolism (130), and the use of HRT started to decline. Estrogen in combination with progestin has been shown to confer a higher risk of breast cancer than estrogen alone (131).

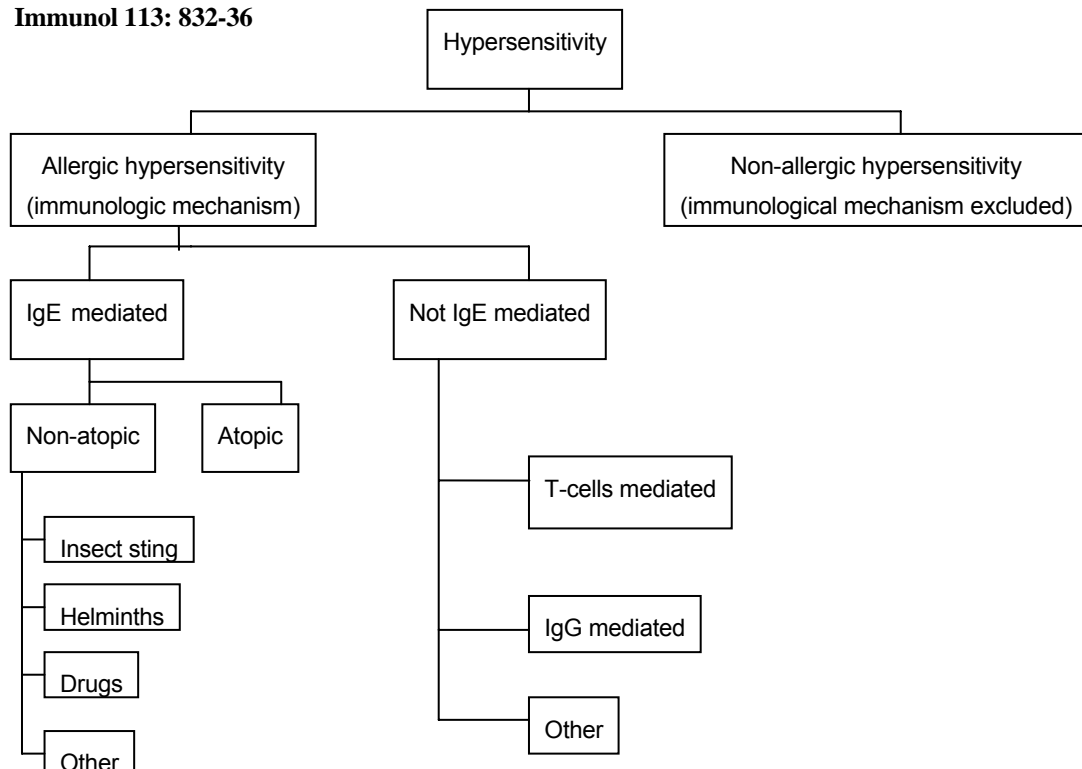
4.3 ALLERGIC CONDITIONS

Sweden and most other Western industrialized countries have experienced an increasing occurrence of allergic conditions (asthma, rhinoconjunctivitis, and eczema) since the 1950s, although this increase has leveled off in recent years (132).

One of the most popular explanations for this secular trend is called the “hygiene hypothesis”, and attributes a clean environment in early life, with little exposure to microbial components, that may predispose individuals to develop allergies (133, 134). This development has been thought to be due to a missing immune deviation from a T-helper lymphocyte type 2 (Th2) response towards a T-helper lymphocyte type 1 (Th1), but recently the role of regulatory T cells (Treg) has also been highlighted (135, 136). The Th2 response is associated with increased release of certain cytokines, e.g. IL-4, IL-5 and IL-13 (137).

Figure 3 shows the nomenclature of hypersensitivity and allergy revised in 2003. The nomenclature is based on the mechanism initiating the reaction. Allergy is defined as a hypersensitivity reaction initiated by specific immunologic mechanisms. The term atopy is often referred to and is used to describe a genetic predisposition to become IgE-sensitized to allergens commonly occurring in the environment which everyone is exposed to but to which the majority do not produce an IgE response (138).

Figure 3. Classification of hypersensitivity – based on Johansson, SG et al. 2004, J. Allergy Clin Immunol 113: 832-36



5 MATERIALS AND METHODS

The papers in this thesis are based on data from an international case-control study of brain tumors called the INTERPHONE-study (139). The primary focus of the study was to examine the association between mobile phone use and brain tumor risk. During the planning of the study a close collaboration between the Nordic countries (Denmark, Finland, Norway and Sweden) and the study centre in Southeast England, United Kingdom was formed and several additional questions were added to the INTERPHONE core protocol. A number of different issues were covered by detailed questions, including questions related to reproductive factors, use of exogenous female sex hormones, and allergic conditions.

5.1 STUDY PERIOD AND POPULATION

Eligible cases were diagnosed with glioma or meningioma during the study period, September 2000 to February 2004, although the exact dates within this period varied by country (table 2).

Table 2. Study period and population

	Denmark	Finland	Norway	Sweden	United Kingdom
Population	Nationwide	Excluding northern Lapland and Åland	The southern and middle regions	The regions of Stockholm, Göteborg, Umeå and Lund	The Thames regions of Southeast England
Period	Sep 2000 - Aug 2002	Nov 2000 - Sep 2002	Jan 2001 - Dec 2002	Sep 2000 - Aug 2002	Dec 2000 – Feb 2004

5.2 CASE ASCERTAINMENT

Eligible cases were all individuals diagnosed during the study period with intracranial glioma or intracranial meningioma (table 3). The age range for inclusion differed slightly between the countries: 20-69 years of age in the Nordic countries and 18-59 years of age in the UK.

Cases were identified continuously during the study period through collaboration with the treating clinics. The completeness of case ascertainment was verified through search in appropriate population-based cancer registries, and extra cases found during the study period were included in the study, except in Finland where the cancer registry was only checked afterwards for completeness without enrolling any additional patients. Medical records were examined to confirm the diagnosis and to establish the

date of diagnosis, defined as the first medical examination leading to diagnosis, usually the first radiological examination. This date was used as the reference date for cases. Since the first papers based on the Swedish part of the INTERPHONE have been published an additional linking to the cancer register has been done to update diagnostic information on patients without a confirmed histopathological diagnosis at the time when the medical records initially were reviewed. As a consequence a few cases (n=8) received a different diagnosis and therefore the number of cases differs slightly between studies.

Table 3. Codes of tumors eligible for inclusion

Tumor	ICD-10*	ICD-0-2†
Glioma	C71	9380-9384, 9390-9394, 9400-9401, 9410-9411, 9420-9424, 9430, 9440-9443, 9450-9451, 9460, 9480-9481, 9505
Meningioma	C70, D32	9530-9539

* International Classification of Diseases - tenth revision

† International Classification of Diseases for Oncology - second edition

5.3 CONTROL SELECTION

Controls were selected continuously throughout the study period. Controls from the Nordic countries were randomly selected from a population register of the total population of the study area, stratified on age (in 5-year groups), sex, and geographical region. In the UK, where there is no such population register, controls were randomly selected from the general practitioners' (GP) patient lists. This is a representative source of population-based controls as it has been estimated that 98% of the UK population is registered with a GP (140).

A reference date, corresponding to the reference date for cases, was constructed for each control. The controls were on average identified and interviewed later than the cases and it was important to construct the reference date for controls adjusting for this since time of exposure was calculated related to the reference date. Exposures that have dramatically changed in the general population the years prior or during the study period, as with mobile phone use, made it important to, as far as possible, make the time of potential exposure equal for cases and controls.

For paper I, only including Swedish data, the reference date was constructed from the date when the control was identified, adjusted for the average time difference between date of diagnosis and date of identification of the cases.

For paper II-III when the full Nordic-UK dataset was used a slightly different method to construct the reference dates was applied because the date of identification of the control was not available from all countries. The reference dates for controls were instead constructed from the interview date of the control, with adjustment for the mean interval between the diagnostic and interview dates of cases and the difference between the mean interview dates of cases and controls. The adjustments were done separately

for glioma and meningioma cases, since the time between diagnosis and interview differed for the different tumor types.

For both cases and controls, individuals were excluded if they were completely deaf prior to the reference date, had been diagnosed with an intracranial tumor previously, or did not possess the intellectual or language skill to complete an interview.

5.4 DATA COLLECTION

All contacts and interviews with cases and controls were made by persons employed for this purpose. Approval was sought from the attending physician to approach each case. Contact was sought as soon as possible after identification. An invitation letter was sent with information about the study, and thereafter a personal contact was tried to be established over the phone and a time for a personal interview was decided. The exact procedure used differed somewhat between countries. If the individual did not consent to a personal interview a phone interview was offered instead. If this was also declined individuals in Sweden were offered to fill out a short mailed questionnaire instead. If no contact was made a second letter was sent 2-4 weeks after the first letter, and a third letter after additional 2-4 weeks. In Sweden the third letter was sent together with the questionnaire to be filled out.

Data were collected through interviews using a computer program that guided the interview with questions read by the interviewer from a laptop computer screen. In Finland, however, answers were recorded on a paper copy of the questionnaire and later entered into the computer program. Almost half the interviews in Norway were conducted over the telephone, but only a small minority elsewhere (table 4). If a case had died the closest relative was contacted as a proxy-respondent when possible, except in the UK where ethical approval was only obtained for proxy interviews for too ill or deceased patients if a relative replied to the invitation letter on the patient's behalf (table 4).

Table 4. Type of interview (personal/telephone) and proxy interviews

	Denmark	Finland	Norway	Sweden	UK
Controls					
Personal/telephone (%)	100/0	99/1	54/46	94/6	99/1
Case/Proxy (%)	100/0	100/0	99.4/0.6	100/0	100/0
Glioma cases					
Personal/telephone (%)	100/0	99/1	48/52	95/5	100/0
Case/Proxy (%)	89/11	96/4	62/38	91/9	96/4
Meningioma cases					
Personal/telephone (%)	100/0	99/1	51/49	96/4	100/0
Case/Proxy (%)	98/2	99/1	98/2	97/3	99.6/0.4

5.5 EXPOSURE ASSESSMENT

Papers I-III

Participants were asked whether they had any biological children and if so when these children were born. Women were asked if they had breast fed the children and, for each child, for how long, how many pregnancies she had had including not completed ones, and whether she had used oral contraceptives, other hormonal contraceptives, hormones for gynecological problems, or hormone replacement therapy.

Information about allergic conditions was ascertained through questions that ascertained whether the person had ever been diagnosed with asthma, eczema, or hay fever, or suffered from any other allergy. Affirmative answers were followed by additional questions, such as the age at which the condition had started, and if and when symptoms of the condition had stopped. Individuals with hay fever were asked about use of anti-allergy treatment.

Paper IV

Through the personal identification number uniquely assigned to all Swedish residents a cross linkage was made to registries at Statistics Sweden (SCB) to gather information on socioeconomic factors such as the highest attained educational level, income, marital status, working status, and socioeconomic status for both participants and non-participants in the Swedish part of the INTERPHONE-study. The collected information refers to the years prior to brain tumor diagnosis of the cases, and the corresponding time period for the controls.

5.6 STATISTICAL ANALYSES

Papers I-III

Unconditional logistic regression models were used to estimate odds ratios (=OR) and their 95% confidence intervals (=CI) to study the associations between reproductive factors, use of exogenous female sex hormones, and allergic conditions and the risk of glioma and meningioma.

In all analyses adjustments were made for the stratifying variables; age, sex, and geographical region, and for highest educational level completed (compulsory school, vocational or secondary school, upper secondary school, and university). In paper I adjustments were moreover conducted for parity.

Analyses were also undertaken to investigate possible confounding from smoking (current, past, never), previous radiotherapy (papers I-III), marital status (papers I-II), ever use of hormonal contraceptives and hormone replacement therapy, and twin pregnancies (paper II). Results did not, however, change and these potentially confounding variables were therefore not included in the final models.

In papers II-III using data from five different countries tests were conducted for heterogeneity of the results between countries (defining heterogeneity, conservatively, as $p < 0.10$). No heterogeneity was identified in analyses of allergic conditions. In a few analyses in paper II heterogeneity was identified and we used a two-stage random effects method for the pooled analysis (141).

Paper IV

Odds ratios (OR) and 95% confidence intervals (CI) were estimated to compare participation for cases and controls separately using unconditional logistic regression. Differences in mode of participation among participants or reasons for not participating among non-participants were evaluated using contingency tables (Chi-squared test or Fisher's exact test).

Glioma and meningioma risk associated with socioeconomic factors were estimated by unconditional logistic regression and adjustments were made for sex, age and region. Analyses were also conducted separately for both sexes. Income categories were constructed based on the income distribution among controls.

6 RESULTS

6.1 PAPER I – EXOGENOUS FEMALE SEX HORMONES AND BRAIN TUMORS

We studied the association between use of exogenous female sex hormones and meningioma and glioma risk. This study was restricted to the Swedish part of the Nordic-UK material, so analyses were conducted on 178 meningioma cases, 115 glioma cases, and 323 controls. Participation rates were 84, 75 and 65 percent respectively.

There was no clear association between the use of oral contraceptives and meningioma. For the use of other hormonal contraceptives (subdermal implants, injections or hormonal intra-uterine devices), the odds ratio for meningioma was estimated to 1.5 (95% CI: 0.9-2.6). There was only a very small number of women who had used hormones for gynecological problems (such as irregular menstruations or other bleeding problems) and relative risk estimates for both meningioma and glioma were statistically unstable. Among postmenopausal women the use of hormone replacement therapy was associated with an elevated risk for meningioma for ever use, 1.7 (95% CI: 1.0-2.8), and for ten or more years duration of use the risk estimate was 1.9 (95% CI: 1.0-3.8). No clear dose- response relationship was noted, the p for trend = 0.13. The risk estimates for glioma were close to or below unity (table 5).

Table 5. Adjusted odds ratio for meningioma and glioma risk according to use of exogenous female sex hormones

Ever use of:	Meningioma cases (%)	Controls (%)	OR (95% CI)	Glioma cases (%)	Controls (%)	OR (95% CI)
Oral contraceptives	134 (75)	243 (76)	1.0 (0.6-1.6)	85 (74)	243 (76)	0.8 (0.5-1.4)
Other hormonal contraceptives	30 (17)	43 (13)	1.5 (0.9-2.6)	17 (15)	43 (13)	1.1 (0.6-2.1)
Hormones for gynecological problems	21 (12)	35 (11)	1.1 (0.6-1.9)	5 (4)	35 (11)	0.4 (0.2-1.1)
Hormone replacement therapy*	68 (63)	93 (50)	1.7 (1.0-2.8)	21 (45)	90 (49)	0.9 (0.4-1.7)

* Only postmenopausal women

The hormones given for gynecological problems (such as bleeding irregularities) are most often oral contraceptives (=OC) although the contraceptive property is not the primary requisite. Reanalyzing the data letting hormones for gynecological problems be included with oral contraceptives did not change the results for use of OCs. A multivariate model including both OC and other hormonal contraceptives did not give

different results. Adjustments for OC use and use of other hormonal contraceptives did not change the findings for HRT use among postmenopausal women.

6.2 PAPER II – REPRODUCTIVE FACTORS AND BRAIN TUMORS

We studied the association between reproductive factors and glioma and meningioma risk and used information from women in the full Nordic-UK dataset.

Participation rates were 61 percent (n=626) for glioma cases (range between countries 36-81 percent), 75 percent (n=907) for meningioma cases (58-88 percent), and 52 percent (n=1774) for controls (43-69 percent).

Women who had ever been pregnant had a lower risk of glioma OR=0.8 (95% CI: 0.6-1.0) than women who had never been pregnant. Ever having had a live birth and number of pregnancies resulting in a live birth were not associated with glioma risk, but after adjustment for breast-feeding duration a protective effect was found with a significant trend in decreasing risk for increasing number of pregnancies leading to a live birth (p for trend = 0.04). Among parous women increasing duration of breast-feeding increased the risk of glioma; women who had breast-fed for 36 months or more in total had an odds ratio of 2.2 (95% CI: 1.3-3.9) compared with women who had breast-fed \leq 3 months (p for trend = 0.003). An age of \geq 35 years when giving birth for the first time was associated with an increased glioma risk OR=1.8 (95% CI 1.0-3.4) compared with being less than 20 years. Menopausal status and age at menopause did not influence glioma risk. Excluding proxy answers from the analyses did not change the results except for the breast-feeding analysis where the OR changed from 2.2 (95% CI: 1.3-3.9) to 1.7 (95% CI: 0.9-3.1) for breast-feeding for 36 months or longer and the p-value for trend became 0.04.

Ever being pregnant or number of pregnancies was not related to meningioma risk. Stratifying the women according to age revealed an increasing meningioma risk associated with number of pregnancies leading to a live birth: p for trend among those ever having a live birth = 0.01, for women <50 years of age. This was not seen for older women. Menopausal status was not associated with meningioma risk, OR=1.0 (95% CI: 0.8-1.3). Excluding women who had ever used HRT from analyses of menopausal status did lower the point estimate, OR=0.8 (95% CI 0.6-1.1) for being postmenopausal compared with premenopausal. None of the other analyzed reproductive factors were associated with meningioma risk. Excluding proxy answers from the analyses did not alter the results.

6.3 PAPER III – ALLERGIC CONDITIONS AND BRAIN TUMORS

We evaluated the association between allergic conditions (asthma, eczema, hay fever and other types of allergy) and glioma and meningioma risk. We used the full Nordic-UK dataset and participation rates were 60 percent (n=1527) for glioma cases (range between countries 37-81 percent), 74 percent (n=1210) for meningioma cases (55-90 percent), and 50 percent (n=3309) for controls (42-69 percent).

An odds ratio of 0.70 (95% CI: 0.61-0.80) was estimated for glioma risk associated with diagnosis of any of asthma, hay fever, eczema, or other type of allergy. The risk

estimates for glioma were approximately 0.65 for each allergic condition (asthma, eczema, hay fever, and food allergy), with confidence intervals equally consistent, of approximately 0.55 to 0.80. For eczema, hay fever and any allergy the decreased risks for glioma were confined to current allergy, and did not vary appreciably with duration of current allergy. For asthma, on the other hand, a reduced risk was seen for both current and past disease (table 6). Results did not change when proxy answers were excluded from the analyses. In analyses of participants with hay fever the risks for glioma were similar or slightly reduced comparing ever with never use of anti-allergy treatments (oral antihistamines, nasal spray, eye-drops, and desensitization). No noteworthy associations were found for meningioma, except for a decreased risk associated with eczema, OR=0.74 (95% CI 0.60-0.91).

Table 6. Adjusted odds ratio for allergic conditions and glioma risk, Nordic-UK Brain Tumor Study, 2000-2004.

	Glioma cases (n=1527)	Controls (n=3309)	OR (95% CI)*
Reference (no allergy)	848	1637	
Asthma	118	325	0.65 (0.51-0.82)
<i>Status</i> [§]			
current	78	213	0.68 (0.51-0.91)
past	32	96	0.53 (0.34-0.80)
Eczema	196	592	0.65 (0.54-0.79)
<i>Status</i> [§]			
current	104	393	0.52 (0.41-0.66)
past	83	180	0.90 (0.67-1.19)
Hay fever	272	739	0.66 (0.56-0.78)
<i>Status</i> [§]			
current	199	629	0.56 (0.46-0.68)
past	57	80	1.25 (0.87-1.80)
Any allergy ^{**} , ††	574	1523	0.70 (0.61-0.80)
<i>Status</i> [§]			
current	440	1286	0.63 (0.55-0.73)
past	111	200	1.01 (0.78-1.30)
Number of allergic conditions ^{**}			
1 condition	374	918	0.76 (0.65-0.88)
2 conditions	148	419	0.65 (0.53-0.81)
≥3 conditions	52	186	0.52 (0.37-0.72)

* Adjusted for age, sex, geographical region and education

§ When divided into current or past, numbers do not add up due to missing information on if or when the allergy stopped

** Asthma, eczema, hay fever, or other types of allergy (including food allergy)

†† Numbers do not add up to the total numbers due to missing information or a don't know answer on one of the included variables

We had missing or don't know answers in questions concerning whether the individual ever had been diagnosed with any of the allergic conditions of interest. To determine whether missing data could have affected the results sensitivity analyses were

performed showing that missing data did not to substantially influence our findings (table 7).

Table 7. Odds ratio for glioma and meningioma associated with any allergy

	Missing data excluded	Missing data set to “no allergy”	Missing data set to “allergy”
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Meningioma	0.95 (0.82-1.10)	0.94 (0.82-1.08)	0.96 (0.83-1.10)
Glioma	0.70 (0.61-0.80)	0.68 (0.60-0.77)	0.75 (0.66-0.86)

6.4 PAPER IV – NON-PARTICIPANT CHARACTERISTICS AND THE ASSOCIATION BETWEEN SOCIOECONOMIC FACTORS AND BRAIN TUMORS

We compared demographic and socioeconomic characteristics between participants and non-participants in the Swedish part of the study by record linkage to official registries kept by Statistics Sweden. Information on socioeconomic status, income, education, and demographic variables for all participating and non-participating cases and controls was available. We also assessed the association between socioeconomic factors and glioma and meningioma risk and the influence of non-participation on this relationship.

During the study period 494 eligible glioma cases, 321 meningioma cases, and 955 controls were identified. 366 (74%) glioma cases, 274 (85%) meningioma cases, and 673 (70%) controls were interviewed or filled out a written questionnaire (table 8). 9% of glioma interviews and 3% of meningioma interviews were performed with proxy respondents.

Table 8. Number of eligible cases and controls and distribution of participants and non-participants, Brain Tumor study 2000-2002, Sweden.

	Meningioma cases	Glioma cases	Controls
Eligible	321	494	955
Participants (participation rate, %)	274 (85)	366 (74)	673 (70)
Personal interview	259	346	592
Telephone interview	12	18	40
Written questionnaire	3	2	41
Non-participants	47	128	282
Refusals	21	27	167
Failure of contact	4	11	101
No permission to contact*	7	31	-
Too sick or deceased†	15	59	14

* The attending physician did not give permission to contact the case

† No suitable relative to contact as proxy respondent

Working status and income level were positively associated with participation among both cases and controls. Compared with the lowest quartile of disposable income the odds for participation were 2-3 times higher for the second to fourth quartiles. Being married, having a high education and a non-manual employment were also associated with participation among controls (table 9).

Table 9. Odds ratio for participation associated with demographic and socioeconomic variables, Brain Tumor study 2000-2002, Sweden

	Glioma cases (n=494)		Meningioma cases (n=321)		Controls (n=955)	
	Participation rate (%)	OR (95% CI)	Participation rate (%)	OR (95% CI)	Participation rate (%)	OR (95% CI)
Sex						
Women	74	Ref.	84	Ref.	71	Ref.
Men	74	1.0 (0.7-1.5)	89	1.5 (0.7-3.1)	70	1.0 (0.7-1.3)
Age at inclusion (years)						
20-29	81	Ref.	75	Ref.	69	Ref.
30-39	77	0.9 (0.3-2.6)	76	1.1 (0.2-7.1)	65	0.8 (0.4-1.5)
40-49	81	1.2 (0.5-3.3)	89	2.8 (0.5-17.0)	73	1.2 (0.7-2.2)
50-59	73	0.7 (0.3-1.8)	89	2.8 (0.5-15.0)	72	1.2 (0.7-2.0)
60-	69	0.6 (0.3-1.6)	81	1.4 (0.3-7.6)	70	1.1 (0.6-1.9)
Marital status						
Single	73	Ref.	88	Ref.	64	Ref.
Married	76	1.1 (0.7-1.9)	88	1.0 (0.4-2.6)	75	1.7 (1.2-2.3)
Divorced	71	0.9 (0.5-1.8)	81	0.6 (0.2-1.7)	68	1.2 (0.8-1.8)
Widowed	82	1.7 (0.3-8.2)	77	0.5 (0.1-2.2)	65	1.0 (0.5-2.3)
Education						
Compulsory	69	Ref.	81	Ref.	61	Ref.
Secondary school						
≤ 2 year	73	1.2 (0.7-2.1)	85	1.3 (0.6-2.9)	70	1.5 (1.0-2.2)
3 year	79	1.6 (0.8-3.3)	95	4.4 (1.0-20.8)	71	1.5 (1.0-2.4)
Higher education	77	1.5 (0.9-2.6)	86	1.4 (0.6-3.1)	80	2.6 (1.7-3.9)
Working status						
Not working	66	Ref.	77	Ref.	60	Ref.
Working	78	1.8 (1.2-2.8)	90	2.8 (1.5-5.4)	76	2.1 (1.6-2.9)
Socioeconomic status [†]						
Manual workers	71	Ref.	86	Ref.	68	Ref.
Non-manual employees	75	1.2 (0.7-1.9)	90	1.6 (0.7-3.5)	79	1.8 (1.3-2.6)
Employees-not classified	79	1.5 (0.5-4.8)	69	0.4 (0.1-1.4)	80	1.9 (0.9-3.9)
Self-employed	83	2.0 (0.7-6.2)	92	2.0 (0.2-16.6)	67	0.9 (0.4-2.2)
Income year 2000*						
< 110.000	61	Ref.	72	Ref.	57	Ref.
110.000-150.000	76	2.1 (1.1-3.6)	90	3.3 (1.4-7.6)	65	1.4 (1.0-2.0)
>150.000-190.000	79	2.4 (1.3-4.4)	93	4.8 (1.7-13.5)	82	3.4 (2.2-5.2)
>190.000	79	2.4 (1.4-4.2)	90	3.4 (1.4-8.3)	82	3.4 (2.3-5.3)

* Disposable income, Swedish kronor (SEK)

[†] Based on occupation and type of employment in the census 1990

Among the controls the mode of participation (personal interview, telephone interview, or questionnaire) differed according to sex, with more women participating in telephone interviews or filling out written questionnaires. Non-married and non-working controls participated to a higher extent in telephone interviews. Having a disposable income in the highest quartile was more common among those with a personal interview compared with telephone interview or questionnaire.

Non-participation reasons among controls were also influenced by demographic and socioeconomic factors. Failure of contact was more common among individuals who were younger, single or divorced, or had a lower income level compared with those who refused to participate.

Having a family income level in the highest quartile was associated with an increased glioma risk, OR=1.5 (95% CI: 1.1-2.1) compared with a family income in the lowest quartile. This risk increase diminished when only participating individuals were included in the analysis, OR=1.2 (95% CI: 0.8-1.8). The individual level of disposable income was associated with a slightly increased glioma risk for the highest quartile of income compared with the lowest in the overall result including all eligible persons, OR=1.3 (95% CI: 1.0-1.8), but was only found for men. Socioeconomic factors were not associated with meningioma risk, except for an increased risk associated with higher education among women.

7 DISCUSSION

7.1 MAIN FINDINGS

7.1.1 Paper I

Meningioma

We found an elevated meningioma risk associated with use of hormone replacement therapy, although with no consistent dose-response relationship. We found no association between use of oral contraceptives and meningioma risk, but results indicated an increased risk associated with use of other hormonal contraceptives. The findings correspond with the hypothesis of a late acting hormonal influence on meningioma risk.

Six other studies have reported of oral contraceptive use and meningioma (table 10). Four of these studies found no statistically significant difference in risk between never and ever users, with both increased and decreased risks reported (104, 107, 108, 142). In the study by Custer et al. surprisingly an increased risk was found for tumors expressing progesterone receptors in 0-25% of cells, but no association for tumors with higher expression of progesterone receptors (108). The findings were, however, based on small numbers. One study has reported a significantly decreased meningioma risk associated with OC use, but due to their choice of control group (only married women and this restriction not required for cases) the results are probably biased (109). This study is described further in section 5.2.1.1.

One cohort study based on data from the nurses health study found an elevated risk of meningioma among postmenopausal women who used HRT (104), similar to the results in our study. Risk increase was confined to current HRT users, whereas no association was found among past users. In our study we were not able to make the distinction between current and past use. If increased risk is in fact restricted to current users our results may be diluted. Another recent cohort study of HRT and meningioma has also reported an increased risk for ever use. The study has, however, a potentially serious limitation as it is based on retrospective reviews of medical records to establish HRT users among all female patients at the Mayo Clinic Jacksonville. There is a possibility that patients with meningioma have a more complete historical documentation of HRT use than patients seeking care for minor medical conditions. This may create an incomplete register of HRT use among non-meningioma cases, which could lead to a spurious association between HRT use and meningioma, something that the authors acknowledge in their paper (105). Three studies have found no association between HRT use and meningioma risk (107-109). One of these studies stratified the analyses on progesterone receptor status and found no associations regardless of whether there were progesterone receptors present or not (108). A study of spinal meningiomas has reported of a decreased meningioma risk associated with current use of estrogen replacement therapy, however that study was based on only 4 exposed cases (106).

In conclusion, results from available studies are inconsistent and interpretation is difficult due to unstable estimates and because of limitations in the design of two of the studies (105, 109). At present the evidence points towards no association between meningioma risk and oral contraceptive use. Our study was the first study to publish

results on use of long-acting hormonal contraceptives and these results need to be evaluated in future studies. For HRT and meningioma risk further research is needed before definitive conclusions can be drawn. The findings for HRT-use are, however, especially interesting in the light of an increasing incidence of meningioma among women but not among men, as shown by an increasing female: male ratio from the 1980's to the late 1990's (2). This time period coincides with the increased use of HRT. If this is indeed a causal association the meningioma incidence among women and the female: male ratio is expected to be reduced within the near future as the use of HRT has recently declined (assuming that other risk factors have remained stable during the same period).

As to whether women already diagnosed with a meningioma should use HRT, the precautionary principle with avoidance of use still might be advisable or at least use with close monitoring would be reasonable.

Table 10. Studies of oral contraceptive use and hormone replacement therapy and meningioma risk

Study	Oral contraceptive use			Hormone replacement therapy			Comments
	No. exposed cases	RR (95% CI)	OC use	No. exposed cases	RR (95% CI)	HRT use	
Preston-Martin 1995	10	0.6 (0.2-1.9)	< 3 yrs	4	0.3 (0.1-1.8)	Current	Population based, case-control
	5	0.3 (0.1-1.0)	>3 yrs	24	1.2 (0.6-2.4)	Past	
Jhawar 2003	1	1.3 (0.2-10.0)	Current	33	1.9 (1.1-3.2)	Current	Spinal meningioma Population based, prospective cohort study
	55	0.8 (0.5-1.1)	Past	11	1.0 (0.5-2.1)	Past	
Hatch 2005	6	1.3 (0.4-4.1)	Current	32	0.9 (0.5-1.6)	Current	Hospital based, case-control
	67	0.9 (0.6-1.3) *	Past	16	1.0 (0.5-1.9) †	Past	
Lee 2006	2	0.2 (0.0-0.8)	Current	48	0.7 (0.4-1.2)	Ever	Hospital based, case-control
	70	0.5 (0.4-0.8)	Past				
Wigertz 2006	134	1.0 (0.6-1.6)	Ever	68	1.7 (1.0-2.8)	Ever	Population based, case-control
Custer 2006	5	2.5 (0.5-12.6)	Current	23	1.0 (0.4-2.2)	Current	Population based, case-control
	90	1.5 (0.8-2.7)	Past	40	0.7 (0.4-1.3)	Past	
Blitshteyn 2008				156	2.2 (1.9-2.6)	Ever	Retrospective cohort study
Benson 2008	219	1.1 (0.9-1.4)	Ever				Prospective cohort study

* Pooled result of the categories 1-9 years and 10-19 years and 20 or more years in the past

† Pooled result of the categories 1-9 years and 10 or more years in the past

Glioma

We did not find any associations between exogenous hormonal use and glioma. Odds ratios for oral contraceptive use were reduced as were odds ratios for use of hormones for gynecological problems, the latter was, however, based on very small numbers. Other studies of exogenous hormone use and glioma have reported a reduced risk (107) or no association (110, 111, 142) related to oral contraceptive use and reduced risks (107, 110) or no association (111) for HRT use (table 11). Additional and preferably larger studies are needed to draw definitive conclusions on the association between use of exogenous female sex hormones and glioma risk.

Table 11. Studies of oral contraceptive use and hormone replacement therapy and glioma risk

Study	Oral contraceptive use			Hormone replacement therapy			Comments
	No. exposed cases	RR (95% CI)	OC use	No. exposed cases	RR (95% CI)	HRT use	
Huang 2004	72	0.8 (0.6-1.2)	Ever	46	0.7 (0.5-1.1)	Ever	Population based, case-control
Hatch 2005	18	1.6 (0.7-3.6)	Current	33	0.7 (0.4-1.2)	Current	Hospital based, case-control
	76	0.6 (0.4-0.8) *	Past	13	0.5 (0.2-1.0) †	Past	
Wigertz 2006	85	0.8 (0.5-1.4)	Ever	21	0.9 (0.4-1.7)	Ever	Population based, case-control
Silvera 2006	65	1.0 (0.7-1.5)	Ever	27	0.9 (0.6-1.6)	Ever	Prospective cohort study
Benson 2008	323	0.9 (0.7-1.1)	Ever				Prospective cohort study

* Pooled result of the categories 1-9 years and 10-19 years and 20 or more years in the past

† Pooled result of the categories 1-9 years and 10 or more years in the past

7.1.2 Paper II

We found associations between reproductive history and glioma and meningioma risk that support the hypothesis that sex hormones play a role in the occurrence of glioma and meningioma. However, our results do not provide a totally coherent picture.

Meningioma

If indeed female sex hormones increase the risk of meningioma, as the higher incidence in women compared with men implies, the assumption would be that an early menarche and a late menopause would increase the risk, something we did not find. Being postmenopausal would (under the same hypothesis) be protective as two previously published studies (104, 113) have reported. We did not observe an effect of menopausal status and three other studies have also reported of no significant effect (43, 107, 109) and two studies found (106, 108) an increased risk. For analyses of menopausal status it might, however, be important to consider use of HRT since the difference between being premenopausal and postmenopausal might be diluted if a lot of women in the postmenopausal group use HRT. Excluding women who had ever used HRT from analyses in our study did lower the point estimate OR=0.8 (95% CI 0.6-1.1). Two studies have reported results comparing premenopausal status with postmenopausal and not using HRT and one reported an increased risk and the other a protective effect (104, 108). Supporting the hypothesis of an increased risk of meningioma associated with female sex hormones is our finding of an increased risk as the number of pregnancies leading to live births increases. This was only found for younger women. These results could indicate an effect of hormones on tumor growth rather than tumor initiation. If this is indeed true then our finding of no association with age at menarche would be expected since almost no meningiomas are found at that young age, and certainly not in our study with the youngest age for inclusion being 18.

An association between breast cancer and meningioma has been reported, with an elevated risk of meningioma among women with a previous diagnosis of breast cancer and an elevated risk of breast cancer among women with a previous diagnosis of meningioma (95, 96), suggesting common genetic or environmental risk factors.

The overall effect of giving birth is a reduced risk of breast cancer, but a transient increased risk of breast cancer is present approximately 10 years after a childbirth (143-

145). This transient increased risk has been explained by a growth stimulating effect of malignant cells of preclinical cancers induced by the pregnancy related hormonal changes. This corresponds well with our findings of an increasing risk of meningioma for increasing number of births in women < 50 years of age.

The long-term protective-effect of childbirth on breast cancer risk on the other hand may at least in part be due to the final differentiation of the breast gland tissue during full-term pregnancy and lactation (146).

Glioma

For glioma the hypothesis works in the opposite direction, and an early menarche and late menopause would be assumed to be protective. We found an increased glioma risk associated with increasing age at menarche, but this was only found among women aged < 50 years. No association was found for menopausal status. Excluding women, who had ever used HRT increased the point estimate a little but not significantly. Increasing number of pregnancies was inversely related to glioma risk. Four previously reported studies have also observed a decreased glioma risk associated with ever being parous and decreasing risks by number of pregnancies (107, 112, 114, 115).

We found no association between ever having a live birth or the number of live births and glioma risk, which is not in agreement with the results for the number of pregnancies. However, as we found an increased risk of glioma associated with duration of breast feeding, this might have confounded the results observed for number of live births. Duration of breast feeding should be more closely related to number of live births than to number of pregnancies. When we adjusted for breast feeding we also found a reduced glioma risk for number of live births. Five other studies have reported no association between parity and glioma risk (29, 80, 110, 111, 113); these studies did not adjust for breast-feeding.

We found an increased risk of glioma associated with longer breast-feeding among parous women. The result was to some extent influenced by proxy answers, but after exclusion of these the odds ratios were still increased. Breast-feeding duration has not been studied much previously in relation to glioma risk. One study (110) has, however, also reported an increased glioma risk associated with breast-feeding, whereas another (107) found no association. The biological mechanism explaining how breast-feeding could increase glioma risk is unclear and it is difficult to separate the effect of breast-feeding from other aspects of pregnancy. The hormones prolactin and oxytocin are increased during breast-feeding. They have been shown to have opposite effects on human glioma cells, with prolactin inducing cellular growth and mitogenesis (147) and oxytocin being able to inhibit cell proliferation (148). Prolactin levels, however, have been reported to be lower in parous women (post-lactational) than in nulliparous women and this lower level has been shown to be associated with a reduced breast cancer risk (149, 150). The post-lactational prolactin level is primarily lowered by the first full-term pregnancy and not by following pregnancies and has been reported to be determined by breast-feeding duration of the first child (149). Reanalyzing our data for breast-feeding duration of the first child and glioma risk, however, showed the same pattern of increasing glioma risk associated with longer breast-feeding duration. Breast-feeding can delay the reestablishment of normal ovulation by 6-9 months (122), and thereby reduce the cumulative time of hormone exposure. An increased glioma risk was also found associated with older age when giving birth for the first time. These findings however, need to be further evaluated before any firm conclusions can be drawn and the findings should be interpreted with caution.

7.1.3 Paper III

We found a decreased risk of glioma associated with allergic conditions. The risk estimates did not vary substantially by age at onset of the allergic conditions, age at reference date or between glioblastoma and non-glioblastoma glioma cases. For eczema, hay fever and any allergy the reduced risks were primarily confined to current disease. No noteworthy associations were found for meningioma except for a decreased risk related to eczema.

Our results are consistent with most prior case-control studies of the association between allergic conditions and glioma and meningioma risk (29, 43, 78-82, 84). Prior cohort studies have shown inconsistent results, but generally included very small numbers of cases (83, 151-153). In a recent meta-analysis in the Journal of the National Cancer Institute it is concluded that “there is a strong relationship between atopic disease and glioma that is unlikely to be explained by methodological bias alone” (85). Our study is the largest published thus far of the association between allergic conditions and glioma and meningioma risks. We showed that the association was unaffected when proxy-answers were excluded and we also addressed the question of timing of allergy, showing that the reduced risks were primarily confined to current disease. The results for asthma were, however, different from the other allergic conditions with decreased risk also for past disease.

The biological mechanism explaining the alleged reduced glioma risk is not fully understood. Anti-allergy treatment can be supposed to influence the protective effect if the protection is dependent on specific mediators of the allergic reaction such as histamine, whose effect can be suppressed by oral antihistamines. We could not find any substantial effect of treatment when comparing glioma risk among those with hay fever. Treatment (nasal spray and eye-drops) was even associated with slightly reduced risks. The most likely explanation for that finding is that treatment is an indicator of being truly allergic. A recent paper, however, has reported an increased glioma risk among allergic individuals who had used antihistamines compared with those who had never used antihistamines, although based on only 21 exposed cases. Similar to most previous studies, they also found a decreased glioma risk associated with being allergic (154).

Glioma patients have been shown to suffer from an impaired immunity (155). Whether the immunosuppression is evident before the diagnosis of the tumor is not known, as studies of patients in the early phases of tumorigenesis are hard to conduct. If the reduced risk associated with allergies was an effect of immunosuppression induced by the tumor or its treatment, current allergic disease would be expected to be associated with a decreased risk and the observed association would, at least to some extent, be a result of reversed causation. This would mean that the tumor at some time made an existing allergy disappear and consequently that the allergy would be reported as a past allergy. The risk associated with past allergic conditions would accordingly increase and be greater than for current conditions. But for reverse causality to explain the entire risk reduction associated with any allergic condition, glioma also needs to suppress the first occurrence of allergic symptoms in more than 10 percent of non-allergic glioma cases, as well as make earlier allergic symptoms disappear. When we reanalyzed the data putting the time-point for measurement of allergic conditions and current disease to 5 years prior to the reference date the results did not substantially change speaking in favor of another explanation for our results than reverse causation.

7.1.4 Paper IV

Population-based case-control studies are often questioned and criticized for low participation rates. Indeed low participation rates are a problem reducing the precision and power of a study. When case-control studies are questioned the reason for non-participation is most often also assumed to differ between cases and controls and thereby possibly causing biased results. To cause a bias, non-participation, however, must be related to both the exposure and the outcome (case-control status) of interest either directly or indirectly, for example through socioeconomic status. Our analyses of participants and non-participants in the Swedish part of the case-control study showed participation to be positively associated with income level and working status for both cases and controls. The possible influence of selection bias related to socioeconomic factors is thereby reduced, but may still influence the possibility to find small risk increases. Comparing results from different studies of factors influencing participation and non-participation can be difficult since the type of study, mode of participation, exposures of interest, geographical setting and time period might influence the results. Many studies, however, have reported non-participation to be related to young age and/or old age (156-163), male sex (156, 158, 162-164), being single (158, 160, 162, 165, 166), and related to low educational level, low socioeconomic status, or low income (157-160, 162, 163, 165-169). The results of our study were similar to previously reported findings although we did not find sex and age associated with participation.

Among non-participating controls the group that could not be contacted (who did not respond to the mail invitation and were not reached over the phone) differed more from the participating controls than did the non-participating controls that actively refused to participate. It might therefore, in the conduct of future studies, be worthwhile to make extra effort to contact this group.

We found that a high disposable income was associated with a slightly increased glioma risk. This association disappeared when analyses were restricted to persons participating in the personal interview, although the resulting smaller sample size might also have influenced the results.

Other studies have found similar association between an increased glioma risk and high socioeconomic status although with other measured socioeconomic factors such as place of residence (116, 119) income and education (117, 118), and occupational sectors (36). The underlying risk factors explaining these associations are unknown and need to be further evaluated.

Previously reported studies of meningioma risk and socioeconomic factors are scarce and results are conflicting (36, 116, 118). We found no associations between socioeconomic factors and meningioma risk except for an increased risk associated with higher education compared with compulsory schooling among women. Finding one significant association in a subgroup analysis could be a chance finding.

7.2 METHODOLOGICAL CONSIDERATIONS

All studies are more or less prone to errors. The errors can be divided into two categories: systematic errors and random errors.

7.2.1 Systematic errors

Systematic errors give estimates that are either above or below the true values depending on the error. Internal validity is high if systematic errors are few.

Systematic errors can be divided into selection bias, information bias, and confounding.

7.2.1.1 Study design and selection bias

The papers included in this thesis are all based on a population-based case-control study. For studies of rare diseases case-control studies usually have the most efficient study design. One of the foundations for valid case-control studies is unbiased selection of controls. The controls should represent a random sample of the population that gave rise to the cases and thereby correctly reflect the distribution of different exposures in the study population (170). We randomly selected population-based controls chosen consecutively during the study period. Controls were frequency matched on sex, age, and geographical region to increase efficiency.

The use of hospital controls is common in countries without available registers of the total population and perhaps also for the reason that hospital patients tend to be more willing to participate than people in the community. Nonetheless, for hospital based studies to be valid the distribution of exposure among hospital controls must be the same as that in the study population. Therefore two conditions must be fulfilled; individuals that are admitted to the hospital as cases would have been admitted to the same hospital for the control disease and *visa versa* and secondly the exposures of interest should be unrelated to the reason for admission of the control (170). In a study of reproductive factors and meningioma risk Lee et al. (109) used hospital controls. They tried to avoid the potential problem of the exposure being related to hospital admission by using female spouses of male back pain patients admitted to the same hospital as the meningioma cases. They found a decreasing meningioma risk associated with number of children and with use of oral contraceptives. However, all controls were married/cohabitating and this restriction was not applied to the cases. It is therefore likely that their results could have been biased, since living in a relationship most certainly could be assumed to be associated with having children and contraceptive use. To assess how a restriction of the control group to married women would affect our results we reanalyzed our data excluding any control who was not married or cohabitating. With this restriction we found a decreased meningioma risk associated with parity, which is opposite to the results we observed when the entire control group was used, and the originally observed increased risk among women <50 years disappeared.

Selection bias might be a problem in population-based studies too if participation is related to both case-control status and exposure, a problem that we address in paper IV. If selection bias is known to be or believed to be related to socioeconomic factors the effect of selection bias can be reduced if these factors can be adjusted for in the analyses. If the exposures of interest are known by the eligible study persons when they decide on whether to participate, selection bias might be created if this influences the decision to participate differently between cases and controls. In our studies the interest in allergic conditions, reproductive history and hormone use was not mentioned in the

invitation letter so the risk of this particular type of selection bias was therefore reduced. The interest in mobile phone use was on the other hand mentioned in the invitation letter and it was shown in a non-participant follow up of the Swedish part of the study that among potential controls who refused to participate regular mobile phone use was lower than among participating controls (171). This type of selection bias could explain observed risk estimates below 1, and could hamper the possibility to detect increased risks.

The results for meningioma and glioma risk differed in our studies of allergic conditions and reproductive and hormonal factors, which argues against a major problem of control selection bias as selection bias among controls would be expected to affect both tumor types similarly.

Non-response connected to specific questions might also cause bias if related to case-control status. In the study of allergic conditions 7 % of glioma cases, 6 % of meningioma cases, and 5 % of controls provided insufficient answers to allow them to be classified as allergic or not allergic. Sensitivity analyses, however, showed that missing data did not substantially change the results.

7.2.1.2 Information bias

Information bias is a type of systematic error that relates to misclassification of data, exposure and/or outcome. Misclassification of exposure is called differential if it is dependent on the outcome status, and non-differential if independent of outcome status. Non-differential misclassification leads to a dilution of the results with risk estimates closer to the null-value (OR=1). Differential misclassification can either cause an increased or decreased risk estimate compared to the true value depending on the misclassification at hand. The outcome can also be misclassified. If the misclassification is dependent on whether exposed or not there is a differential misclassification of outcome (disease), otherwise a non-differential misclassification.

Recall bias is one type of information bias that is differential when, for example, cases recall or try to recall exposures differently as a result of them having the disease under investigation than do controls. Such differential misclassification is probably more likely to occur when there is a common knowledge or concern in the general population about an association between the studied exposure and health outcome. For HRT the common knowledge through media exposure about its negative health effects is probably fairly well established and although there have not been reports linking the use of HRT to meningioma, knowledge of other risks might influence recall. This type of recall bias would probably influence recall of oral contraceptive use in the same manner. Our results for oral contraceptive use and HRT use and meningioma risk differed and this difference speaks against a major influence of differential recall bias.

The results for use of hormones may also be influenced by a non-differential recall bias simply by the difficulty to remember past use. OC use is more likely than HRT use to be influenced by such non-differential recall bias as the use is more distant in time for most of the participants.

The use of proxy respondents, who were in our study, a close relative participating instead of a deceased case, might bias results. There has been a concern that previously published studies on allergic conditions and glioma risk have been biased by proxy respondents and that the inverse association might be due to proxies underreporting cases' allergies. Schwartzbaum et al. have shown that the inverse association was strongest in past studies with the highest proportion of proxy respondents (83). We had a relatively low proportion of proxy respondents among participating glioma cases (13%) as compared with the studies reported in Schwartzbaum et al.'s paper having 20-43% proxy respondents. Excluding the answers from proxies in our study did not change the results.

Another concern in studies of brain tumors and especially studies of gliomas is the nature of this disease with an often rapid debilitating course and a disturbed brain function. Results of an inverse association as we found for allergic conditions could have been influenced by cases having an impaired memory. We tried to address that, as far as we could, by use of the interviewers' estimation of the quality of the interview. After completing the interview, the interviewer evaluated how he or she experienced that the interviewee could remember their own medical history. When we reanalyzed the data only including those who had been assessed as having remembered very well or well (79% of glioma cases and 88% of controls), the results did not change. The reduced risk estimates were confined to current allergy for hay fever, eczema, and any allergy. If memory disturbances in glioma cases are greater for more recent than distant events this could explain the restriction of observed effects to current allergy. To explore this further we estimated risk by duration of allergic condition among those who reported current allergy. The results were approximately equally reduced for both short (<10 years) and long (≥ 20 years) duration of hay fever and eczema, thus suggesting that the results are probably not explained by an impaired memory for recent events.

There are of course both pro and cons in using self-reported data compared to objectively gathered registry data. There is always the risk of recall bias, both differential and non-differential, in self-reports. On the other hand, it is often possible to get more detailed information compared with registry data where exposure information may be rather crude and limited in time.

7.2.1.3 Confounding

Confounding may be considered a mixing of effects, since the confounding factor is mistaken for or mixed with the actual exposure effect of interest (172). Depending on the direction of the associations that the confounding factor has with exposure and outcome confounding can lead to an overestimation or an underestimation of the true effect of the exposure factor. Confounding may cause biased results, but if identified and measured confounding can be adjusted and controlled for in the analyses. The factor should influence the risk of the outcome by itself and at the same time covary with the exposures of interest to be a confounding factor, but should not be an effect of the exposure (effect mediator). A factor can be a confounder in one study, but not in another study looking at the same exposure (173). In practice, likely confounders are

identified among known risk factors for the outcome and known covariates of the exposure. Their actual role in a particular study must, however, be assessed by comparing the estimates before and after adjustment for the suspected confounder.

The only established risk factor for meningioma and glioma apart from rare genetic syndromes is ionizing radiation. Adjustments for radiation therapy in our analyses did not change the estimates. Neurofibromatosis and tuberous sclerosis are two of the genetic syndromes that are associated with an increased brain tumor risk. Participants were asked if they had been diagnosed with either syndrome. In the full Nordic-UK material only six participants reported a diagnosis of neurofibromatosis and three participants a diagnosis of tuberous sclerosis. The possible influence as a confounder is therefore negligible.

In all studies and analyses we adjusted for the stratification variables (age, sex, and geographical region) and attained educational level. Analyses were also made to investigate possible confounding from smoking (current, past, never), marital status, previous radiotherapy, ever use of hormonal contraceptives and hormone replacement therapy, and twin pregnancies. Results did, however, not change and these variables were therefore not included in the final models.

Residual confounding is confounding from an unknown risk factor, or from an unmeasured risk factor, or from exposure misclassification of a measured confounder, or within categories of a confounder. To explain a substantially increased or decreased risk the confounder, however, must show a strong covariance with the exposure and have an association with the outcome that is stronger than the association that has been observed for the exposure (173). Our results can of course have been influenced to some extent by residual confounding including genetic factors.

7.2.2 Precision and random errors

Random errors result from the play of chance. The precision of a result is decided by the level of random errors. The precision can be improved by increasing the study size. The calculated risk estimates are equally likely to be above or below the true value as a result of random errors. The influence of random errors is shown by the width of the confidence intervals. The studies in this thesis that are based on the entire Nordic-UK dataset have large sample sizes; however the numbers in some subgroup analyses were low. The smallest study was the first one, which was restricted to Swedish female participants. It is a general problem in studies of rather rare diseases that the number of cases is low, even in case-control studies. The influence of random errors is therefore large which could give conflicting and contradictory results when comparing different studies. Due to the low statistical power the ability to find a true risk increase or decrease is reduced.

7.2.3 Etiological fraction

The etiological fraction (= population attributable fraction) is the proportion of disease occurrence that would disappear if the exposed group was unexposed (174).

$$\text{EF (etiologi\text{c}al fraction)} = f \cdot (\text{RR} - 1) / \text{RR} \quad f = \text{proportion of exposed cases}$$

Estimation of etiologi\text{c}al fraction is in principle only relevant if the exposure is causally associated with the outcome. Based on our findings and results from previously reported studies there is not enough evidence today to conclude that there is a causal relationship between HRT use and meningioma. It could nevertheless be interesting to estimate the impact HRT use could have on meningioma incidence under the assumption that our results reflect a causal relationship.

We found an increased meningioma risk associated with ever use of hormone replacement therapy (HRT) among postmenopausal women, OR = 1.7 and 63% of the cases reported that they had ever used HRT.

That would give an etiologi\text{c}al fraction of: $0.63 \cdot (1.7 - 1) / 1.7 = 26\%$. Meaning that in our population among postmenopausal women 26% of cases could have been avoided if no one had used HRT assuming a causal relationship.

7.3 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Survival from cancer and treatment options for cancer has in recent decades been greatly improved, but the prognosis for glioma and especially for glioblastoma patients is still dismal. Little is known about the causes of brain tumors. To be able to prevent new tumors it is essential to identify factors that may increase or decrease the risk of tumor formation.

There is a need for future studies further evaluating the influence of exogenous female hormones on the occurrences of meningioma and glioma. These studies should be able to relate the findings to hormone receptor status, to distinguish between estrogen and/or progesterin use, and current and past hormone use. The studies could be designed as case-control studies and preferably be international collaborations to be able to include enough cases to have adequate statistical power.

Of course large cohort studies also are of interest. The problem is, however, that these have to be very large and/or have long follow up periods as brain tumors are relatively rare. Repeated measures of hormone use are also needed.

Since 2005 there is a new national registry kept by The Swedish National Board of Health and Welfare (Socialstyrelsen, Epidemiologiskt Centrum), where all prescribed medicines being sold at pharmacies are registered and records are kept for each individual. In the future this registry could be used and linked with the cancer registry.

The findings of an increased glioma risk associated with a high income level and as reported by others related to other measurements of a high socioeconomic status (SES) need to be further evaluated and possible underlying factors need to be identified. Factors like smoking or alcohol use does not seem to explain the SES-glioma association.

The inverse association between allergic conditions and glioma risk has been consistently reported in case-control studies. To further evaluate this association

biological markers of allergy measured before tumor-formation are needed and the biological process explaining how an immune system prone to an allergic response can prevent the genesis of tumors has to be understood to substantiate a causal relationship. Recently polymorphisms in cytokine genes associated with allergic conditions have been reported related to the risk of glioma (175-178), although different polymorphisms were identified in the studies and the findings by one study could not be replicated by the others, so further studies are needed. Blood samples have been collected from the INTERPHONE-study participants and genetic and environmental interactions are possible to study. Whole genome association studies can identify genetic differences between cases and controls and thereby identify susceptible individuals. Genetic differences usually have a low impact on a person's risk but a combination of a few slightly altered genes together with environmental exposure might impose a major risk.

8 CONCLUSIONS

- Use of hormone replacement therapy was associated with an increased risk of meningioma. No association was found between use of oral contraceptives and meningioma risk, but results indicated an increased risk associated with use of other hormonal contraceptives. The findings support the hypothesis of a late acting hormonal influence on meningioma risk. No associations were found between use of exogenous female sex hormones and glioma risk.
- Increasing numbers of pregnancies leading to a live birth were associated with an increased meningioma risk among women < 50 years of age, but not among older women. The findings support the hypothesis of pregnancy hormones acting as tumor promoters stimulating growth of meningiomas. Ever having been pregnant was associated with a decreased glioma risk. Among parous women longer duration of breast-feeding and older age when giving birth for the first time were associated with increased glioma risk. These findings support the hypothesis that hormonal changes associated with pregnancy influence glioma risk.
- Allergic conditions were associated with a reduced glioma risk in accordance with previously published studies. We showed that this association was primarily related to current allergic condition. Anti-allergy treatment did not substantially change the inverse association. Allergic conditions were not associated with meningioma risk, except for decreased risk associated with eczema. The results indicate that immunological factors are of importance in glioma tumorigenesis.
- Non-participation was associated with socioeconomic factors with higher participation among those working and those having a high income. This was found for both cases and controls, and the possible influence of selection bias due to non-participation related to socioeconomic factors was thereby diminished.
- A high income level was associated with a slightly increased risk of glioma but not associated with meningioma risk.

9 SAMMANFATTNING (SUMMARY IN SWEDISH)

Varje år drabbas ca 1200 personer i Sverige av en primär hjärntumör. Gliom och meningiom är de två vanligast förekommande typerna av hjärntumör. Mycket lite är känt om varför tumörerna bildas. De enda riskfaktorer som med säkerhet bundits till en ökad hjärntumörrisk är joniserande strålning och några ovanliga genetiska syndrom. Målsättningen med avhandlingsarbetet var att studera sambandet mellan några specifika faktorer och risken att insjukna i gliom och meningiom, med fokus på kvinnliga könshormoner och allergiska tillstånd. Vi avsåg också att studera bortfallet i en fall-kontrollstudie av hjärntumörer, och framförallt hur detta bortfall var relaterat till socioekonomiska faktorer, vilket skulle kunna introducera selektionsfel.

Arbetet baseras på en stor internationell fall-kontroll studie av hjärntumörer hos vuxna, ”INTERPHONE-studien”. Vi hade tillgång till data från Sverige, Norge, Danmark, Finland och England. Samtliga vuxna som nyinsjuknat med ett gliom eller meningiom under studieperioden 2000-2002(-2004, England) och slumpvis från studiepopulationen utvalda kontroller inkluderades i studien. De intervjuades om bland annat allergier, barnafödande och bruk av preparat innehållande kvinnliga könshormoner.

Delarbete I

I studien ingick endast svenska data. Hormonanvändning hos 178 kvinnor med meningiom, 115 kvinnor med gliom och 323 kvinnliga kontroller analyserades. Vi fann ett samband mellan användande av hormonersättningsmedel i klimakteriet (=HRT) och en ökad risk för meningiom. Vi fann inget samband med användning av p-piller, men resultaten indikerade en ökad risk för meningiom vid användning av andra hormonella preventivmedel. Inga tydliga samband sågs mellan bruk av något av de hormonella medlen och risken för gliom.

Delarbete II

I studien ingick data från alla fem inkluderade länder och vi hade intervjudata från 626 kvinnor med gliom, 906 kvinnor med meningiom, och 1774 kvinnliga kontroller. Vi studerade sambandet mellan olika reproduktionsfaktorer, såsom ålder vid menstruationsstart, menopausal status, antal graviditeter, antal fullgångna graviditeter, samt amning och risken för gliom och meningiom. Vi fann att de som någon gång varit gravida hade en minskad risk för gliom jämfört med dem som aldrig varit gravida. Bland kvinnor som fött barn sågs en ökad risk för gliom bland dem som var äldre när de fick sitt första barn samt för dem som ammat länge. Risken för meningiom ökade med antalet fullgångna graviditeter. Det senare sambandet kunde endast ses för kvinnor som var yngre än 50 år, vilket kan tyda på att graviditetshormoner stimulerar tillväxten av en redan existerande tumör.

Delarbete III

I studien ingick data från alla fem inkluderade länder. 1527 personer med gliom, 1260 personer med meningiom och 3309 kontroller intervjuades om tidigare och nuvarande allergiska tillstånd, såsom astma, eksem och hösnuva. Risken för gliom var 30 % lägre hos allergiker. Detta samband sågs framförallt för en aktuell allergi, men inte för en

tidigare ej pågående allergi. För astma sågs emellertid även en skyddande effekt för tidigare astma.

Allergibehandling (antihistaminer, nässpray, ögondroppar och desensibilisering) förändrade inte sambandet påtagligt. Inga tydliga samband sågs mellan allergier och meningiom förutom en sänkt risk associerad med eksem.

Resultatet ger stöd åt att immunologiska processer är av betydelse vid uppkomsten av gliom.

Delarbete IV

Alla personer som väljs ut att delta i en studie kan eller vill inte vara med. Detta bortfall minskar studien precision och kan i värsta fall också orsaka fel i resultaten, så kallat urvalsfel (selektions bias). Detta sker om sambandet mellan exponering och sjukdom skiljer sig mellan de som deltagit i studien jämfört med dem som inte deltagit. För att undersöka hur bortfallet i den svenska delen av studien såg ut inhämtades data från SCB (statistiska centralbyrån) om civilstånd, utbildning, inkomst och socioekonomisk status för samtliga identifierade fall och kontroller. Insamlade data gällde tiden innan fallens insjuknande. Vi kunde jämföra de som deltagit i studien med dem som ej deltagit och kunde visa att en hög inkomst, samt att vara yrkesarbetande var vanligare bland dem som deltagit. Detta gällde dock både fall och kontroller varför den möjliga effekten av selektionsfel relaterat till bortfall och socioekonomiska faktorer minskar.

I analyser av socioekonomiska faktorer och risken för gliom och meningiom såg vi en något ökad risk för gliom (men ej för meningiom) associerat med en hög inkomst. Bakomliggande faktorer till detta samband måste utvärderas i framtida studier.

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